Antibiotic Exposure and Juvenile Idiopathic Arthritis: A Case–Control Study

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abstract

BACKGROUND AND OBJECTIVE: Recent evidence has linked childhood antibiotic use and microbiome disturbance to autoimmune conditions. This study tested the hypothesis that antibiotic exposure was associated with newly diagnosed juvenile idiopathic arthritis (JIA).

METHODS: We performed a nested case–control study in a population-representative medical records database from the United Kingdom. Children with newly diagnosed JIA were compared with age- and gender-matched control subjects randomly selected from general practices containing at least 1 case, excluding those with inflammatory bowel disease, immunodeficiency, or other systemic rheumatic diseases. Conditional logistic regression was used to examine the association between antibacterial antibiotics (including number of antibiotic courses and timing) and JIA after adjusting for significant confounders.

RESULTS: Any antibiotic exposure was associated with an increased rate of developing JIA (adjusted odds ratio: 2.1 [95% confidence interval: 1.2–3.5]). This relationship was dose dependent (adjusted odds ratio over 5 antibiotic courses: 3.0 [95% confidence interval: 1.6–5.6]), strongest for exposures within 1 year of diagnosis, and did not substantively change when adjusting for number or type of infections. In contrast, nonbacterial antimicrobial agents (eg, antifungal, antiviral) were not associated with JIA. In addition, antibiotic-treated upper respiratory tract infections were more strongly associated with JIA than untreated upper respiratory tract infections.

CONCLUSIONS: Antibiotics were associated with newly diagnosed JIA in a dose- and time-dependent fashion in a large pediatric population. Antibiotic exposure may play a role in JIA pathogenesis, perhaps mediated through alterations in the microbiome.

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WHAT'S KNOWN ON THIS SUBJECT: The etiology of juvenile idiopathic arthritis (JIA) is poorly understood. A recent study suggested a link between antibiotics and JIA but did not examine the potential for confounding from infections or the role of antibiotic timing.

WHAT THIS STUDY ADDS: Antibiotics were associated with newly diagnosed JIA in a dose- and time-dependent manner after adjusting for infection and other confounders. Antibiotics may play a role in the pathogenesis of JIA.

Juvenile idiopathic arthritis (JIA) is the most common rheumatic diagnosis in children, but its etiology remains unclear.[1] Despite the presence of known genetic risk factors, population-based studies suggest that genetics explains only 10% to 25% of disease incidence.[2,3] Environmental triggers such as viral infections have been suggested,[4–6] but other studies have not substantiated these findings.[7–10] One study found that hospitalization for infection in the first year of life was associated with an increased risk of developing JIA.[11] However, this study focused on hospital-based diagnoses and not on antibiotic use, thus limiting its interpretability.

Disturbance of the human microbiome has been implicated in the development of chronic pediatric diseases, including inflammatory bowel disease (IBD).[12,13] At least 1 category of JIA has been associated with distinct intestinal microbial populations.[14] Antibiotics can alter some subjects' intestinal microbiota for ≥6 months.[15–17] Correspondingly, anaerobic antibiotic use has been associated with incident pediatric IBD.[18] Another recent study suggested that childhood antibiotic exposure was associated with a subsequent diagnosis of JIA.[19] Of note, this study controlled for age, gender, and geography but did not differentiate the effects of antibiotic use from the effects of infection. Furthermore, the impact of antibiotic timing was not examined in detail. The present study tested the hypothesis that antibiotics were associated with incident JIA in a large pediatric population in a dose- and time-dependent fashion after adjusting for confounding from infection and other variables.

METHODS

Study Design and Data Source

A nested case–control study was performed by using The Health Improvement Network (THIN), a population-representative electronic medical records database from >550 practices of general practitioners across the United Kingdom.[20] This design was chosen for its computational efficiency and unbiased estimates of incidence rate ratios, including when studying common time-varying exposures and rare outcomes.[21,22] Data within THIN are collected during routine medical care by using Vision software (INPS, London, United Kingdom) and are anonymized for research purposes. These data contain information on demographic characteristics, diagnoses, specialist and hospital referrals, and outpatient prescriptions. The present study included data from 1994 through 2013. THIN has been validated for several diseases in pharmacoepidemiologic research,[23] including JIA.[24]

Subject Selection

Eligible subjects were aged 1 to 15 years, born after initiation of the Vision software, and registered within 3 months of birth to capture lifetime outpatient prescriptions. Cases were defined by using diagnostic Read codes (analogous to *International Classification of Diseases, Ninth Revision/Tenth Revision* codes) validated for JIA.[24] The study period spanned from registration to the date of the first JIA code (ie, the index date). Secondary case definitions were analyzed to improve the specificity of JIA diagnosis, consisting of the JIA code (same index date) plus: (1) anti-inflammatory prescription (nonsteroidal or glucocorticoid, 2 months before to 1 year after diagnosis) or disease-modifying antirheumatic drugs (postdiagnosis); (2) rheumatology referral; and (3) anti-inflammatory/disease-modifying antirheumatic drug prescriptions and/or rheumatology visits ≥3 months after diagnosis. Children with previous IBD, immunodeficiency, or non-JIA

systemic rheumatic diseases (eg, lupus, vasculitis) were excluded.

Ten control subjects without inclusion or exclusion diagnoses were matched according to age and gender to each case subject at the index date by using incidence density sampling. To limit practice-based confounding based on general practitioners' lack of awareness of JIA, control subjects were randomly selected from practices caring for at least 1 subject with JIA. Control subjects were not matched on practice (except sensitivity analyses) to capture variability in antibiotic prescribing across practices. Matching on practice can cause overmatching when the same prescribing physicians treat both case and control subjects.[25]

Exposure and Covariate Data

Exposures to systemic antibacterial antibiotics prescribed by general practitioners were examined, characterized according to type, date, and dose (courses or weeks prescribed). Prescriptions written on different days at any time before diagnosis were considered a new course. When course duration was unclear, the mode was imputed according to age and drug class. Additional analyses examined antibiotics categorized as antianaerobic versus non-antianaerobic or by individual antibiotic classes[18] (Table 1). Antibiotics were also stratified according to the presence of enterohepatic circulation, using biliary/fecal excretion as a proxy,[26–28] with the theory that such drugs might preferentially affect intestinal microbiota. Systemic nonbacterial (eg, antifungal, antiviral) antimicrobial agents were analyzed for comparison.

Potential confounders were demographic variables, comorbidities, previous infections, maternal autoimmunity, and other factors such as hospitalization (Table 1). Diagnoses including infections were

TABLE 1 Characteristics of the Study Population

Characteristic[a]	Case Subjects (n = 152)	Control Subjects (n = 1520)	P[b]	Exposed (n = 1280)	Unexposed (n = 382)	P[c]
Demographic variables						
Female gender	96 (63)	960 (63.2)	—	783 (61.2)	273 (69.6)	.002
Age, median (IQR), y	3 (2–6)	3 (2–6)	—	4 (2–7)	2 (1–4)	<.001[d]
Age category, y						<.001
1–5	107 (70)	1070 (70.4)	—	844 (65.9)	333 (85.0)	
6–10	35 (23)	350 (23.0)		342 (26.7)	43 (11.0)	
11–15	10 (7)	100 (6.6)		94 (7.3)	16 (4.1)	
Country of origin						
England	126 (82)	1301 (85.6)	.24[c]	1087 (84.9)	339 (86.5)	.26
Northern Ireland	7 (5)	48 (3.2)		48 (3.8)	7 (1.8)	
Scotland	11 (7)	120 (7.9)		101 (7.9)	30 (7.7)	
Wales	9 (6)	51 (3.4)		44 (3.4)	16 (4.1)	
Townsend index[e]			.73[c]			.44
1	40 (26)	389 (25.6)		337 (26.3)	92 (23.5)	
2	29 (19)	266 (17.5)		222 (17.3)	73 (18.6)	
3	29 (19)	305 (20.1)		258 (20.2)	77 (19.6)	
4	22 (14)	298 (19.6)		248 (19.4)	71 (18.1)	
5	23 (15)	213 (14.0)		171 (13.4)	65 (16.6)	
Missing	9 (6)	49 (3.2)		44 (3.4)	14 (3.6)	
Comorbidities						
Prematurity	5 (3)	26 (1.7)	.18	28 (2.2)	3 (0.8)	.07
Down or Turner syndrome	0	0	—	0	0	—
Personal AID[f]	4 (3)	2 (0.1)	.002[g]	6 (0.5)	0	.17
Psoriasis	3 (2)	2 (0.1)				
Uveitis	1 (1)	0				
Any infection[f]	141 (93)	1297 (85.3)	.01	1184 (92.5)	254 (64.8)	<.001
Upper respiratory tract	124 (82)	1129 (74.3)	.04	1071 (83.7)	182 (46.4)	<.001
Lower respiratory tract	37 (24)	392 (25.8)	.69	412 (32.2)	17 (4.3)	<.001
Gastrointestinal	29 (19)	251 (16.5)	.42	236 (18.4)	44 (11.2)	.001
Skin and soft tissue	35 (23)	294 (19.3)	.26	303 (23.9)	23 (5.9)	<.001
Urinary tract	6 (4)	61 (4.0)	.97	66 (5.2)	1 (0.3)	<.001
Bone and joint	0	0	—	0	0	—
Other	78 (51)	825 (54.3)	.47	774 (60.5)	129 (32.9)	<.001
No. of infections, median (IQR)	4 (1.5–8)	3 (1–6)	.02	4 (2–8)	1 (0–2)	<.001[d]
Antibiotic exposures						
Any antibiotic prescribed	133 (88)	1147 (75.5)	<.001	1280	0	—
Antianaerobic antibiotics[f]	126 (83)	1099 (72.3)	.004	1225 (95.7)	—	—
Penicillins	124 (82)	1082 (72.2)	.006	1206 (72.1)		
Broad-spectrum penicillins	14 (9)	115 (7.6)	.47	129 (7.7)		
Metronidazole	0	8 (0.5)	—	8 (0.6)		
Clindamycin	1 (<1)	0	—	1 (0.1)		
Other antianaerobic[h]	0	1 (0.1)	—	1 (0.1)		
Non-antianaerobic antibiotics[f]	64 (42)	469 (30.9)	.003	533 (41.6)		
Cephalosporins	18 (12)	143 (9.4)	.32	161 (12.6)		
Macrolides	49 (32)	329 (21.6)	.003	378 (29.5)		
Sulfonamides	25 (16)	130 (8.6)	.001	155 (12.1)		
Other non-antianaerobic[h]	0	9 (0.5)	—	9 (0.7)		
Antibiotics with enterohepatic circulation[f]					—	—
Yes	70 (46)	492 (32.4)	<.001	562 (33.6)		
No	126 (83)	1094 (72.0)	.003	1220 (73.0)		
No. of antibiotic courses prescribed						—
Unexposed	19 (13)	373 (24.5)	<.001[c]	0	392 (100)	
1–2 courses	41 (27)	497 (32.7)		538 (42.0)		
3–5 courses	46 (30)	342 (22.5)		388 (30.3)		
>5 courses	46 (30)	308 (20.3)		354 (27.7)		
Time between consecutive courses, median (IQR)	136 (64–295)	133 (68–280)	.99	134 (67–287)	—	—
Other antimicrobial exposure, any[i]	23 (15)	184 (12.1)	.28	182 (14.2)	25 (6.4)	<.001

TABLE 1 Continued

Characteristic[a]	Case Subjects (n = 152)	Control Subjects (n = 1520)	P[b]	Exposed (n = 1280)	Unexposed (n = 382)	P[c]
Maternal variables						
Maternal AID[f]	21 (14)	115 (7.6)	<.001[g]	114 (9.7)	22 (6.3)	.05[g]
Arthritis	2 (1)	4 (0.3)		5 (0.4)	1 (0.3)	
Connective tissue disease	1 (1)	3 (0.2)		4 (0.3)	0	
Diabetes	0	5 (0.3)		4 (0.3)	1 (0.3)	
IBD	1 (1)	4 (0.3)		4 (0.3)	1 (0.3)	
Multiple sclerosis	3 (2)	7 (0.5)		8 (0.7)	2 (0.6)	
Psoriasis	7 (5)	52 (3.4)		48 (4.1)	11 (3.1)	
Thyroid disease	10 (7)	38 (2.5)		43 (3.7)	5 (1.4)	
Uveitis	0	7 (0.5)		5 (0.4)	2 (0.6)	
Vasculitis	0	6 (0.4)		5 (0.4)	1 (0.3)	
Missing maternal data	13 (9)	137 (9.0)	.85	108 (8.4)	42 (10.7)	.001
Other variables						
Cesarean delivery	32 (21)	227 (14.9)	.07	197 (24.5)	62 (25.5)	.74
Missing delivery data	51 (34)	573 (37.7)	—	475 (37.1)	149 (38.0)	—
Hospitalization[f]	30 (20)	167 (11.0)	.002	177 (13.8)	20 (5.1)	<.001
Infection	14 (9)	69 (4.5)	.01	80 (6.3)	3 (0.8)	<.001
JIA	17 (11)	—	—	—	—	—
Other	18 (12)	116 (7.6)	.07	115 (9.0)	18 (4.6)	.10
No. of outpatient visits in last 2 y, median (IQR)[j]	7 (4–11.5)	5 (2–10)	<.001	6 (2–11)	4 (1–7.5)	<.001
Subsequent diagnoses after the study period						
Immunodeficiency	0	0	—	0	0	—
IBD	1 (1)	0	—	1 (0.1)	0	—
Vasculitis	0	2 (0.1)	—	2 (0.2)	0	—

AID, autoimmune disease; IQR, interquartile range.

[a] All statistics are expressed as n (%) unless otherwise stated.

[b] All P values were obtained from univariable conditional logistic regression models.

[c] P value signifies overall χ^2 except as otherwise noted.

[d] P values were obtained by Wilcoxon rank-sum testing.

[e] Geography-based deprivation index; higher index score means more deprived.

[f] Some subjects had >1 type.

[g] P value represents comparison of main category.

[h] Other antianaerobic antibiotics: tetracyclines, glycopeptides (oral vancomycin), carbapenems, cefoxitin (all other cephalosporins categorized as non-antianaerobic). Other non-antianaerobic antibiotics: fluoroquinolones, all other antibiotic classes.

[i] Other antimicrobial agents, including antifungal, antiviral, and antimycobacterial drugs.

[j] Total outpatient visits during 2-year period starting 2.5 years before JIA diagnosis.

identified by using Read codes. Antibiotic courses and hospitalizations within ±1 week of an infection were attributed to that infection. Outpatient visits were tabulated over 2 years starting 2.5 years before the index date, excluding 6 months before diagnosis to limit biased ascertainment of this covariate. For the same reason, outpatient visits and hospitalizations for JIA symptoms (eg, joint swelling, limp) were excluded.

Subjects were matched with mothers by using an algorithm modified from a previous approach.[29] Briefly, family relationships are not explicit in THIN due to anonymization, but deidentified household numbers are recorded. Subjects were matched with female subjects from the same household who were aged 12 to 50 years at subjects' birth. If matches remained ambiguous, codes for pregnancy, labor/delivery, and postnatal period were identified within 270 days before to 90 days after subjects' birth dates, and eligible maternal age was restricted to 15 to 45 years. Only subjects matched to a unique female were analyzed in models with maternal data.

Statistical Analysis

The association between antibiotic prescription and JIA was determined by conditional logistic regression, accounting for matching. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). After unadjusted analysis, potential confounders were included in a multivariable model if associated with the outcome in univariate analysis with $P < .2$; they were retained if they changed the OR by ≥10% or had a P value <.05. Variables with >10% missing data were excluded from the multivariable analysis.

Antibiotic dose models (based on number of courses or weeks prescribed) examined dose as an ordinal or continuous variable, the latter to test for trend. The effect of timing of the first and last antibiotic exposure during the study period was examined. Primary and secondary analyses were repeated based on secondary case definitions. Additional secondary analyses were performed for each antibiotic category (antianaerobic versus other) and

class. To consider confounding by indication (whereby infections rather than antibiotics could be associated with JIA risk), we compared the risk of treated and untreated upper respiratory tract infections (URIs) because patients with these common conditions may or may not warrant and receive antibiotic treatment.

Multiple sensitivity analyses were performed (Supplemental Table 5). To further consider confounding by infection, analyses compared the rate of infection between case subjects and control subjects not prescribed antibiotics. Study periods ending 4, 8, and 12 months before the index date were examined to determine whether infections closer to diagnosis were more strongly associated with JIA. To address possible confounding by local environmental factors and practice patterns, analyses were repeated after matching case subjects and control subjects according to practice along with age and gender. Protopathic bias was explored, whereby antibiotics are given for early JIA symptoms, by using as the index date the first joint symptom (eg, stiffness, limp) or rheumatology visit that preceded diagnosis (if known). Because inpatient medications are not well captured in THIN, analyses assumed that antibiotics were received with infection-related or all hospitalizations. Finally, the role of unmeasured confounding was also examined by using the rule out method; this method tests whether a theoretical confounder could nullify results over a range of covariate prevalence and associations with exposure and outcome.[30]

All analyses were performed by using Stata version 12.1 (Stata Corp, College Station, TX). Hypothesis tests were 2-sided with a type I error of 0.05. P values were derived from regression models. There was no adjustment for multiple comparisons in secondary or sensitivity analyses. This study of anonymized data was exempted by the University of Pennsylvania

institutional review board and was approved by THIN's scientific review committee.

RESULTS

Characteristics of the Study Population

There were 152 cases of JIA diagnosed in 454 457 children meeting the inclusion criteria, within 3.1 million person-years of follow-up (Fig 1, Supplemental Table 6). These data yielded an incidence of 4.9 per 100 000 person-years (female subjects: 6.4 per 100 000; male subjects: 3.6 per 100 000) (Supplemental Table 7).
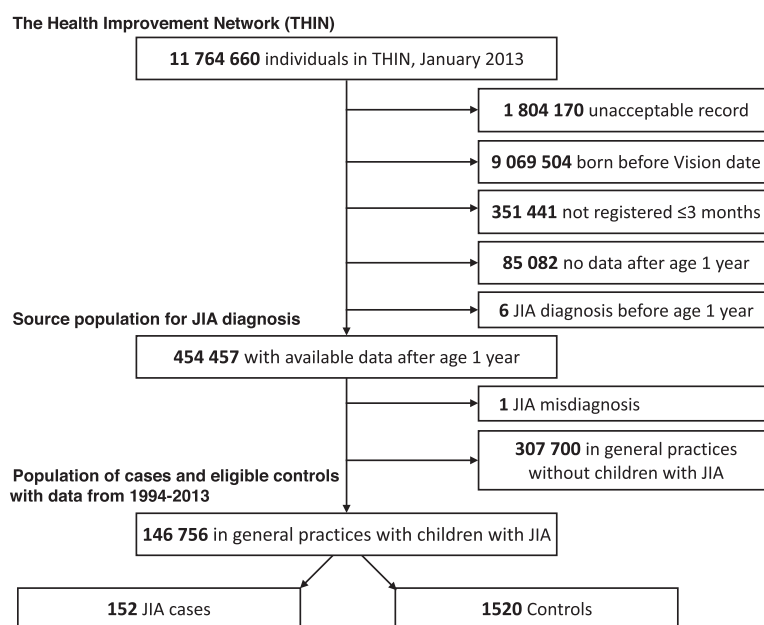
Because of matching, case subjects and control subjects did not differ in age or gender (Table 1). Previous autoimmunity, including psoriasis and uveitis, was more prevalent among case subjects (P = .002). Case subjects more commonly had a history of infection (P = .01) and hospitalization for infection (P = .01), and they had more infections (P = .03) than control subjects. Case

subjects also had more outpatient visits (P < .001). Mothers of case subjects were nearly twice as likely to have autoimmune diseases (P < .001). Cesarean delivery may have been more common among case subjects (P = .07), but this variable had considerable missing data (37%).

Association Between Antibiotics and JIA

After adjustment for matching, other autoimmune conditions, and previous infection, receipt of ≥1 antibiotic prescription was associated with an increased risk of developing JIA (adjusted OR: 2.1 [95% CI: 1.2–3.5]) (Table 2). Adjustment for specific infection types (eg, URI) or number of infections did not appreciably change this association (adjusted OR range: 2.0–2.5). The magnitude of the association increased with additional antibiotic courses (test for trend: P < .001) (Table 3). Models that analyzed dose in weeks prescribed produced a similar dose response.

In terms of timing of antibiotic exposure, age of first prescription did not significantly modify the

The Health Improvement Network (THIN)

11 764 660 individuals in THIN, January 2013

→ **1 804 170** unacceptable record

→ **9 069 504** born before Vision date

→ **351 441** not registered ≤3 months

→ **85 082** no data after age 1 year

→ **6** JIA diagnosis before age 1 year

Source population for JIA diagnosis

454 457 with available data after age 1 year

→ **1** JIA misdiagnosis

→ **307 700** in general practices without children with JIA

Population of cases and eligible controls with data from 1994-2013

146 756 in general practices with children with JIA

152 JIA cases   **1520** Controls

FIGURE 1
Flowchart of subject selection. The diagram displays the numbers of patients excluded from the THIN cohort and reasons for exclusion, leading to selection of case subjects with JIA and age- and gender-matched control subjects randomly selected (10:1) at the time of diagnosis.

TABLE 2 Association of Any Antibiotic Prescription With JIA

Variable	N	Exposed	Unadjusted OR	Adjusted OR[a]	95% CI	P
Primary model	1672					
Any antibiotic prescription	JIA 152	133	2.4	2.1	1.2–3.5	.007
	Control 1520	1147				
Any infection	JIA 152	141	2.3	1.8	0.4–3.4	.09
	Control 1520	1297				
Any personal AID	JIA 152	4	35.1	30.6	3.4–278	.002
	Control 1520	2				
Secondary case definitions (any antibiotic prescription)[b]						
JIA + drug for JIA	1221		2.3	2	1.1–3.6	.03
	JIA 111	97				
	Control 1110	843				
JIA + rheumatology referral	1100		3	2.5	1.2–6.1	.01
	JIA 100	90				
	Control 1000	763				
JIA + management ≥3 mo	1298		2.4	2	1.1–3.7	.02
	JIA 118	104				
	Control 1180	900				
JIA + any secondary definition	1474		2.6	2.1	1.2–3.8	.01
	JIA 134	119				
	Control 1340	1024				

[a] Models adjusted for matching, any infection, and any personal autoimmune disease (AID).
[b] Secondary case definitions used JIA Read code (analogous to *International Classification of Diseases, Ninth Revision/Tenth Revision* code) plus either JIA drug prescription (nonsteroidal anti-inflammatory drug, glucocorticoid, or disease-modifying antirheumatic drug), rheumatology referral, or evidence of JIA management after at least 3 months (eg, new JIA drug prescription, contact with a rheumatologist).

relationship between antibiotic use and JIA (test for interaction: $P = .50$). In contrast, timing of last exposure was important. Antibiotics prescribed within 1 year of diagnosis (and within 6 months of first joint symptom or rheumatology referral) showed the strongest association with JIA (Table 4). In contrast, untreated infections were not associated with JIA during any time period.

Secondary Analyses

Results of repeat analyses using secondary case definitions were similar (Tables 2 and 3). The association between antibiotics and JIA was also similar for antianaerobic and non-antianaerobic antibiotics, for drugs with and without enterohepatic circulation, and for individual drug classes, although the association for cephalosporins was weak and not significant (Supplemental Table 8). Notably, nonbacterial antimicrobial drugs lacked association with JIA. In exploring possible confounding by infections, having multiple antibiotic-treated URIs was strongly associated with JIA, but there was no association between JIA and multiple untreated URIs. An association with treated URIs persisted after excluding cases of acute otitis media, pharyngitis, and sinusitis.

Sensitivity Analyses

Number of infections was not associated with JIA among exposed (adjusted OR: 1.02 [95% CI: 0.98–1.05]) and unexposed (adjusted OR: 1.06 [95% CI: 0.80–1.42]) subjects. However, in an unmatched sensitivity analysis of unexposed subjects, URI was associated with JIA. This association weakened and was not significant when using an index date 4 to 12 months before JIA diagnosis.

When control subjects were matched on practice, the association between antibiotics and JIA was similar to the original data set, if modestly stronger (Supplemental Table 9). Results were also similar when the first joint symptom or rheumatology referral was used as the index date, and when hospitalization (for infection or otherwise) was considered equivalent to an antibiotic course. Based on the strength of the association (OR: 2.1), only prevalent (20%–60%) and strong (OR: 5–10 with exposure and outcome) unmeasured confounders could explain and nullify these results, calculated by using the rule out method.[30] Adjustment for noninfectious hospitalization alone and in combination with maternal autoimmunity and visits had minimal effect on the main results.

DISCUSSION

Previous studies indicate that antibiotic exposure may possibly predispose children to chronic diseases, including IBD[18] and JIA.[19] Our study supports the hypothesis that antibiotic exposure is associated with an increased risk of developing JIA. This effect was significant after adjusting for confounders such as infection. These findings were also dose dependent, strongest within 1 year of diagnosis, specific to antibacterial antimicrobial agents, and robust to numerous sensitivity analyses. Together, these results suggest a possible role for antibiotics in JIA pathogenesis. This public health finding is potentially important, considering that approximately one-quarter of antibiotics prescribed for children, and an estimated one-half of antibiotics for acute respiratory infections, may be unnecessary and potentially avoidable.[31,32]

The human microbiome plays important roles in immune regulation and self-tolerance.[33] Disturbance of the intestinal microbiome has been linked to several autoimmune diseases, including IBD,[34,35] rheumatoid arthritis,[36–40] and at least 1 category of JIA.[14] After antibiotic treatment, commensal microbial populations often recover within ~3 months, including in young children.[17,41] However, rates of microbial recovery are variable, and incomplete recovery of certain taxa may persist for ≥6 months, particularly after repeated antibiotic exposures.[15–17,42] Our finding that

TABLE 3 Association of Antibiotic Prescription Dose With JIA

Variable	N	Exposed	Unadjusted OR	Adjusted OR[a]	95% CI	P
No. of antibiotic courses	1672					
Unexposed (reference)	JIA 152	19				
	Control 1520	373				
1–2 courses		41	1.7	1.5	0.8–2.7	.16
		497				
3–5 courses		46	2.9	2.5	1.4–4.4	.002
		342				
>5 courses		46	3.5	3.0	1.6–5.6	<.001
		308				
Each additional antibiotic course[b]			1.10	1.09	1.05–1.13	<.001
No. of antibiotic weeks	1672					
Unexposed (reference)	JIA 152	20				
	Control 1520	392				
1–2 wk		40	1.7	1.5	0.9–2.7	.14
		470				
3–5 wk		43	2.8	2.4	1.3–4.3	.003
		324				
>5 wk		49	3.3	2.9	1.6–5.2	<.001
		334				
Each additional week of antibiotics[b]			1.07	1.06	1.03–1.10	<.001
Secondary case definitions (no. of antibiotic courses)						
JIA + drug for JIA	1221					
Unexposed (reference)	JIA 111	14				
	Control 1110	267				
1–2 courses		31	1.7	1.5	0.8–3.0	.23
		360				
3–5 courses		33	2.7	2.3	1.2–4.6	.02
		251				
>5 courses		33	3.2	2.7	1.3–5.5	.007
		232				
JIA + rheumatology referral	1100					
Unexposed (reference)	JIA 100	10				
	Control 1000	237				
1–2 courses		24	1.9	1.6	0.7–3.5	.22
		324				
3–5 courses		27	3.3	2.7	1.2–5.9	.01
		224				
>5 courses		39	5.6	4.6	2.1–10.0	<.001
		215				
JIA + management ≥3 mo	1298					
Unexposed (reference)	JIA 118	14				
	Control 1180	280				
1–2 courses		32	1.7	1.5	0.8–2.9	.24
		396				
3–5 courses		34	2.8	2.4	1.2–4.7	.01
		262				
>5 courses		38	3.8	3.1	1.6–6.4	.001
		242				
JIA + any secondary definition	1474					
Unexposed (reference)	JIA 134	15				
	Control 1340	316				
1–2 courses		38	1.9	1.6	0.9–3.1	.12
		443				
3–5 courses		38	2.9	2.4	1.2–4.6	.009
		305				
>5 courses		43	4.0	3.3	1.7–6.4	.001
		276				

[a] Models adjusted for matching, any infection, and any personal autoimmune disease.
[b] Numbers of total courses and weeks of antibiotics were truncated at the upper 2.5 percentile (18 courses and 25 weeks, respectively) to limit the influence of outliers.

TABLE 4 Effect of Timing of Exposure on the Association With JIA

Exposures			Any Antibiotic			Any Untreated Infection		
Timing of Exposure		N	Exposed	Adjusted OR (95% CI)[a]	P	Exposed	Adjusted OR (95% CI)[a]	P
Before JIA diagnosis		1672						
Unexposed (reference)	JIA 152		19			27		
	Control 1520		373			315		
>24 mo			24	1.0 (0.5–1.9)	.91	34	0.7 (0.4–1.3)	.25
			392			469		
12–24 mo			25	1.7 (0.9–3.2)	.11	32	1.1 (0.6–1.9)	.85
			243			284		
6–12 mo			30	2.9 (1.6–5.3)	.001	17	0.7 (0.4–1.5)	.37
			187			194		
0–6 mo			54	3.1 (1.7–5.5)	<.001	42	1.4 (0.8–2.4)	.24
			325			258		
Before JIA diagnosis or antecedent joint symptom or rheumatology referral		1672						
Unexposed (reference)	JIA 152		24			31		
	Control 1520		404			328		
>24 mo			22	1.0 (0.5–1.9)	.90	33	0.7 (0.4–1.3)	.31
			328			411		
12–24 mo			23	1.4 (0.8–2.6)	.27	27	0.8 (0.5–1.5)	.52
			250			281		
6–12 mo			23	1.7 (0.9–3.1)	.10	17	0.7 (0.4–1.4)	.31
			216			211		
0–6 mo			60	3.0 (1.8–4.9)	<.001	44	1.2 (0.7–2.0)	.43
			322			289		

[a] Models adjusted for matching and any personal autoimmune disease.

antibiotic exposure is most strongly associated with JIA within 1 year of diagnosis (and 6 months of first symptom/referral) supports the hypothesis that antibiotic-induced microbiome dysregulation could precipitate JIA in children predisposed to this disease.

In addition to a causal relationship, alternative explanations for this association are protopathic bias (treatment of early JIA symptoms with antibiotics) and confounding from infection. We found no evidence of protopathic bias in a sensitivity analysis that used first joint symptom or rheumatology referral as the index date. Unfortunately, we could not study or exclude subjects with systemic JIA, who present with symptoms including fever and rash that might initially be confused with infection and treated with antibiotics. However, systemic JIA usually presents acutely and only comprises ~5% to 10% of all JIA diagnoses.[43] This JIA category, therefore, is unlikely to fully explain the association with antibiotics, including

exposures 6 to 12 months before diagnosis.

Confounding from infection could occur if infections triggered JIA or if an inherited or acquired immunodeficiency preceded the diagnosis of JIA. We found a significant association between URIs and JIA among unexposed subjects in the months preceding diagnosis. For some subjects, this finding could represent an early predisposition to infection, a short-term infectious trigger, a process exacerbating subclinical arthritis, or an event that merely brought arthritis symptoms to medical attention. Antibiotic-untreated infections can also precipitate changes in children's microbiota.[41] JIA has rarely been reported in association with a definable immunodeficiency,[44] but children diagnosed with JIA are at higher risk for serious infection independent of disease treatment.[45] In our study, case subjects had more office visits than control subjects and were more likely to be hospitalized for infection. It is unclear whether more severe infections led to more

antibiotics, which then triggered autoimmunity in susceptible subjects, or whether JIA-associated immune dysfunction caused more severe illnesses beforehand, for which antibiotics were a marker. Because office visits and hospitalizations could be on the causal pathway between antibiotics and JIA, we did not adjust for these variables in the primary analyses. Of note, the lack of association of JIA with nonbacterial antimicrobial agents argues against the immunodeficiency hypothesis. Indeed, these findings, and the stronger association of JIA with antibiotic-treated URIs than with untreated URIs, support a causal model for antibiotics.

Our study has several strengths. Outpatient prescription data are comprehensive in THIN, and most antibiotics in general pediatrics are prescribed in the outpatient setting, ensuring near complete capture of antibiotic exposure in these children followed up from early infancy. The failure of some subjects to take some or all of the prescribed medication

would likely bias results toward the null, suggesting that our study may underestimate the true effect. Although inpatient prescription data were not available, models assuming inpatient antibiotic exposure were similar. Infections were important confounders in the relationship between antibiotics and JIA, and timing of last antibiotic exposure proved important. Our analyses incorporating these factors made this study unique compared with an earlier report.[19] JIA itself has previously been validated with 86% positive predictive value.[24] The incidence (overall and gender-specific) of JIA in our cohort was similar to earlier published estimates from other western European countries using current classification criteria.[46,47] Secondary case definitions designed to increase the specificity of JIA diagnoses yielded similar results. Finally, multiple sensitivity analyses were consistent and robust to a wide range of assumptions.

This study has several limitations. Although JIA has been validated, specific JIA categories have not been validated and are usually unspecified in THIN. This absence made it difficult to discern whether antibiotics were associated only with particular JIA categories. If this association were category-specific, then the true effect could be larger for certain forms of JIA and null for others. Similarly, race and ethnicity correspond to differences in JIA presentation[48] but are poorly captured by THIN data. The study's inclusion of children registered early in life also identified a relatively young cohort. This design limited the study's generalizability to older children and adolescents, and compromised our ability to study the interaction between age and antibiotic exposure on JIA risk, including age of diagnosis. In addition, we could not detect substantial differences across antibiotic classes, as was previously shown for pediatric IBD[18] and JIA in another study that reported relatively greater risk for cephalosporins and clindamycin[19]; our study was not powered to address this specific issue. Finally, despite our efforts to account for infection and our many analyses implicating antibiotics in the development of JIA, we cannot definitively rule out residual confounding from infections.

CONCLUSIONS

The present study found that treatment with antibiotics was associated with the development of JIA in a large general pediatric population. This relationship was dose dependent, strongest within 1 year of diagnosis, specific for antibacterial agents, persisted after adjustment for infection, and was robust to numerous assumptions. These findings suggest a potential role for antibiotics in the pathogenesis of JIA, perhaps mediated through changes in the microbiome. If this association is causal, antibiotics could be considered a potentially modifiable risk factor for JIA, especially in light of the overprescribing of antibiotics to children, particularly for respiratory tract infections. Children with JIA may also be at risk for more infections before diagnosis due to immune dysfunction, and a causal role for infections remains a possibility. Further research is necessary to confirm these findings in other populations; to determine whether this association depends on age, JIA category, and antibiotic drug class; and to investigate underlying mechanisms.

ACKNOWLEDGMENT

The authors thank Molly Collins, MD, for her critical review of the manuscript.

ABBREVIATIONS

CI: confidence interval
IBD: inflammatory bowel disease
JIA: juvenile idiopathic arthritis
OR: odds ratio
THIN: The Health Improvement Network
URI: upper respiratory tract infection

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