Antibiotic use and inflammatory bowel diseases in childhood

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ABSTRACT

Background The composition of the intestinal microflora has been proposed as an important factor in the development of inflammatory bowel diseases (IBD). Antibiotics have the potential to alter the composition of the intestinal microflora. A study was undertaken to evaluate the potential association between use of antibiotics and IBD in childhood.

Methods A nationwide cohort study was conducted of all Danish singleton children born from 1995 to 2003 (N=577 627) with individual-level information on filled antibiotic prescriptions, IBD and potential confounding variables. Using Poisson regression, rate ratios (RRs) of IBD were calculated according to antibiotic use. Antibiotic use was classified according to time since use, type, number of courses used and age at use.

Results IBD was diagnosed in 117 children during 3 173 117 person-years of follow-up. The RR of IBD was 1.84 (95% CI 1.08 to 3.15) for antibiotic users compared with non-users. This association appeared to be an effect on Crohn's disease (CD) alone (RR 3.41) and was strongest in the first 3 months following use (RR 4.43) and among children with ≥7 courses of antibiotics (RR 7.32).

Conclusions Antibiotic use is common in childhood and its potential as an environmental risk factor for IBD warrants scrutiny. This is the first prospective study to show a strong association between antibiotic use and CD in childhood. However, as with any observational study, causality cannot be inferred from our results and confounding by indication—in particular, prescribing of antibiotics to children with intestinal symptoms of as yet undiagnosed CD—should also be considered as a possible explanation.

Significance of this study

What is already known about this subject?

- Antibiotics alter the composition of the intestinal microflora.
- The intestinal microflora is intimately linked to the gut immune system.
- Antibiotic use is more prevalent among patients with inflammatory bowel disease (IBD) than healthy controls.

What are the new findings?

- Children who use antibiotics are more likely to be diagnosed with IBD.
- This risk was temporal, was strongest for Crohn's disease and increased with the number of courses of antibiotics used.
- This is the first prospective study of this association.

How might it impact on clinical practice in the foreseeable future?

- The observed association suggests that antibiotics or their indications (infections) either increases the risk of developing IBD or can trigger IBD in susceptible individuals.
- Antibiotics are among the most important health interventions and, as such, decisions regarding their clinical use should be based on the strongest evidence possible.
- Further studies are needed to determine if and how use of antibiotics increases the risk of IBD before specific clinical directions can be given.

The intestinal microflora is intimately linked to the gut immune system and has been proposed as an important initiator and mediator in the chronic inflammatory processes in inflammatory bowel diseases (IBD).[1 2]

The composition of the microflora is determined early in life.[3] Immediately after birth, colonisation is initiated and it is thought that a wide range of early life environmental factors have the potential to influence this process and consequently influence the homeostatic microflora of later life.[4] Antibiotics are common early life exposures which can disturb the intestinal microflora. They can alter the composition of the intestinal microflora by reducing colonisation resistance against opportunistic microorganisms.[5] The extent of these effects depends on the spectrum of the agent, the pharmacokinetic and dynamic properties of the agent, and the dose and duration of treatment. In many cases these disturbances are only temporary, but exposures occurring early in life are more likely to have a lasting impact on the composition of the flora.[4] Consequently, the possible association between use of antibiotics (especially in infancy and early childhood) and IBD warrants scrutiny. Only a few studies have evaluated this association, but the use of antibiotics has consistently been found to be more prevalent among patients with IBD than controls.[6–9] We conducted a nationwide cohort study of the association between use of antibiotics and IBD in Danish children. The study is unique because it is the first prospective study and it provides detailed information on antibiotic exposure including age at exposure, type of agent used, number of exposures and time since use.

METHODS

The Danish Civil Registration System contains vital and demographic information on all people

living in Denmark.[10] This information is indexed by a unique personal identification number (the CPR number) which is also used in other nationwide registries. We constructed a cohort of all singleton children born in Denmark in the period from 1995 to 2003. Using the CPR number, we linked information on antibiotic use, IBD and potential confounding variables to the children in the cohort.

Antibiotic use

The nationwide Danish Drug Prescription Registry was established in 1994 and includes detailed individual-level information on all prescriptions filled at pharmacies and aggregated data on hospital use—the only places where prescription medications are legally available in Denmark.[11] Information on individual-level prescriptions includes the CPR number of the recipient, date of filling the prescription, anatomical therapeutic chemical code and number of daily defined doses in the prescription. The date of filling the prescription was considered the date of use for the purpose of this study. We obtained information on use of all systemic antibiotics (anatomical therapeutic chemical code J01) for the cohort children in the period 1995–2004. For some children (primarily in 1995–6), antibiotic use was not registered using their own CPR number but that of an accompanying adult, usually a parent. In this case a variable in the registry marked the recipient as a child with the corresponding age at the date of filling the prescription, and all antibiotic use initially ascribed to CPR numbers of mothers and fathers of cohort children with such a child marking, and the correct corresponding age at the date of filling the prescription, was re-ascribed to the relevant cohort children. Antibiotics were classified as follows: extended spectrum penicillins, penicillin V, macrolides and other systemic antibiotics. Use was quantified as courses, with all further use of the same class of antibiotics within 1 month of the first use considered as one course.

Inflammatory bowel diseases

Cases of IBD among cohort children in the period from 1995 to 2004 were ascertained through the Danish National Hospital Register.[12] Since 1994 this register contains diagnoses, coded using the International Classification of Diseases 10th revision, for all hospitalisations, emergency room visits and outpatient hospital visits in Denmark. We used the code K50 for Crohn's disease (CD) and K51 for ulcerative colitis (UC).

Potential confounding factors

Information on the following potential confounding factors was obtained from the Civil Registration System, the Danish Medical Birth Registry[13] and Statistics Denmark: child's sex, birth order (1, 2, 3, 4+), place of birth classified according to degree of urbanisation (Copenhagen, Copenhagen suburbs, area with >100 000 population, area with 10 000–99 999 population, area with <10 000 population), ethnicity of mother (Danish or not), mother's age at birth (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years), birth weight (<2500, 2500–2999, 3000–3499, 3500–3999, ≥4000 g), gestational age (<34, 34–36, 37–39, 40–41, ≥42 weeks), socioeconomic category of father in the year preceding the year of birth (outside labour market, employment with unknown qualifications, employment with basic or no qualifications, employment with medium-level qualifications, top management or employment with high-level qualifications, self-employed or co-working spouse) and educational level of mother in the year preceding the year of birth (primary school, secondary school, vocational training or short tertiary education, medium or long tertiary education). The percentages of missing values for the variables place of birth, birth weight, gestational age, ethnicity of mother, socioeconomic category and educational level were 0.03%, 1.20%, 0.99%, 0.46%, 1.77% and 5.38%, respectively.

Statistical analysis

The association between antibiotic use and subsequent IBD was analysed in a historically prospective cohort design with longitudinal classification of antibiotic use and IBD diagnosis. Children in our cohort were followed for IBD (CD and UC) from birth until death, disappearance, emigration, IBD or 1 January 2005, whichever occurred first. The resulting person-years of follow-up were aggregated together with counts of IBD according to antibiotic use and analysed using Poisson regression (log-linear regression of the counts using the logarithm to the follow-up time as offset).[14] This produced incidence rate ratios (RRs) according to antibiotic use. The number of courses of antibiotics was considered a time-varying variable. In the analysis of specific types of antibiotic use and specific ages of use, children with >1 course of antibiotics contributed person-time according to the most recent course. RRs according to antibiotic use were always adjusted for age (in 1-year intervals) and calendar period (in 1-year intervals). Variables described above as potential confounding factors were only included in the models if they were independently associated with IBD as indicated by p values <0.05 in univariate models. When adjusting for the potential confounding effect of variables with missing values, we used mode imputation. We calculated the attributable risk from antibiotic use as $RR - 1/RR \times$ prevalence of exposure among cases.

RESULTS

A total of 577 627 singleton children were included in our cohort. During 3 173 117 person-years of follow-up for IBD, we identified 50 cases of CD and 67 cases of UC. The mean (SD) age of first IBD hospital contact was 3.4 (2.8) years (range 9.8). The mean (SD) ages for CD and UC were 3.3 (2.6) years (range 9.7) and 3.5 (2.9) years (range 9.8), respectively. Follow-up was terminated prematurely for 13 471 children because of death (n=3095), emigration (n=10 084) or disappearance (n=292). A total of 489 946 children (84.8%) received at least one course of antibiotics. The average number of courses in children exposed to antibiotics was 4.3 courses (median 3, IQR 4).

The overall prevalence of use in the study cohort was 84.8%; 66.8% used penicillin V, 61.4% used extended spectrum penicillins, 24.5% used macrolides and 15.1% used other systemic antibiotics. In table 1 we present descriptive characteristics for all cohort participants and antibiotic users separately. The prevalence of use increased dramatically throughout the study period. This should be interpreted in the context of a cohort study design with forward inclusion of birth cohorts—initially only infants are included and become older throughout the study period. Prevalence of use was highest among older children, boys, children with Danish mothers, younger mothers, mothers with a lower educational level, mothers employed with basic or no qualifications, children with fewer older siblings, non-premature children with a birth weight >2499 g and children born in the suburbs of Copenhagen.

In table 2 the RRs of IBD according to antibiotic use are shown. Antibiotic users were 1.84 times more likely to be diagnosed with IBD than non-users. This corresponded to a 12% increase in IBD risk for each course of antibiotics used. The risk of IBD was greatest in the first 3 months following a course of antibiotics (RR 2.39).

Table 1 Descriptive characteristics of the study cohort of all Danish singleton children born 1995–2003 and followed from 1995 to 2004 (N=577 627)

	All		Antibiotic users (N = 489 946)		
	N	Person-years of follow-up	N	Person-years of follow-up	Prevalence (%)
Calendar year*					
1995	68112	34399	10731	2307	15.8
1996	133029	100155	51150	30924	38.5
1997	197822	165405	104521	76930	52.8
1998	260915	228797	159786	131657	61.2
1999	323961	291849	210248	184469	64.9
2000	387503	354714	264492	239032	68.3
2001	449042	417276	322211	294960	71.8
2002	508885	477573	381831	352742	75.0
2003	568949	536861	436540	409405	76.7
2004	566565	566088	485028	463727	85.6
Age*					
0	577627	574449	254230	91283	44.0
1	573049	541338	406721	332611	71.0
2	509612	478748	408090	367995	80.1
3	447395	416383	381427	346406	85.3
4	384435	352561	339921	307428	88.4
5	320238	289036	289825	259364	90.5
6	257021	225815	236350	206529	92.0
7	194214	162749	180693	150878	93.0
8	130062	98307	122026	91963	93.8
9	66341	33732	62450	31696	94.1
Sex					
Girls	296662	1543524	233984	1032179	78.9
Boys	280965	1629594	255962	1153973	91.1
Mother's origin					
Born in Denmark	497833	2768868	424889	1916099	85.3
Born abroad	79794	404249	65057	270053	81.5
Mother's age at birth					
≤19	10085	58548	8819	42123	87.4
20–24	81171	472613	71205	339334	87.7
25–29	213051	1186749	182492	827719	85.7
30–34	192120	1038639	161357	707703	84.0
35–39	70794	363716	57802	236114	81.6
≥40	10406	52852	8271	33159	79.5
Mother's educational level					
Primary school	139156	804623	122027	579974	87.7
Secondary school	79779	431542	66670	287958	83.6
Short tertiary education	236160	1303237	201686	908199	85.4
Medium or long tertiary education	122532	633715	99563	410021	81.3
Socioeconomic status					
Self-employed/co-working spouse	49455	279374	41721	189472	84.4
Employment with high level qualifications	80387	419817	65552	272073	81.5
Employment with medium level qualifications	66131	353862	55508	238830	83.9
Employment with basic or no qualifications	274276	1553996	237358	1099555	86.5
Employment with unknown qualifications	35884	183420	29866	124470	83.2
Outside labour market	71494	382649	59941	261751	83.8
Birth order					
1	249227	1366543	211412	930213	84.8
2	215251	1187702	183713	831463	85.3
3	83117	457247	69972	314980	84.2
≥4	30032	161625	24849	109496	82.7
Birth weight (g)					
≤2499	20494	107172	17089	76456	83.4
2500–2999	58155	319917	49760	222515	85.6
3000–3499	177409	978009	150564	674067	84.9
3500–3999	205859	1134611	174211	777225	84.6
≥4000	115710	633409	98322	435888	85.0

Continued

Table 1 Continued

	All		Antibiotic users (N = 489 946)		
	N	Person-years of follow-up	N	Person-years of follow-up	Prevalence (%)
Gestational age (weeks)					
≤33	7692	37312	6187	26813	80.4
34–36	20052	107374	17256	76258	86.1
37–39	215782	1159260	183488	801992	85.0
40–41	284761	1589549	240985	1088960	84.6
≥42	49340	279623	42030	192129	85.2
Place of birth					
Copenhagen	77443	407841	64292	273523	83.0
Copenhagen suburbs	84494	465368	73622	334469	87.1
Population ≥100 000	73561	401640	59850	261747	81.4
Population 10 000–99 999	156578	869793	133909	603745	85.5
Population ≤9999	185551	1028475	158273	712667	85.3

*Since each child can contribute follow-up in different age and calendar periods, the column numbers for age and calendar period sum to more than the total number of children.

Evaluating CD and UC separately, antibiotic users were 3.41 times more likely to be diagnosed with CD, corresponding to an increase of 18% in the risk of CD for each course used. No similar increased risk was observed for UC. The risk of CD was greatest in the first 3 months following a course of antibiotics (RR 4.43) and among children with ≥7 courses of antibiotics (RR 7.32).

In table 3 explorative RRs of CD according to type of antibiotics used and age at antibiotic use are shown. Evaluating antibiotic use according to type of antibiotics, we found the highest risks for CD were associated with use within 3 months of penicillin V and extended spectrum penicillins (RR 2.92 and RR 3.13, respectively). Evaluating antibiotic use according to age of use, we found the highest risks for CD were associated with use within 3 months at ages 3–11 months and 2–3 years (RR 3.32 and RR 3.73, respectively). For use more than 3 months previously, the highest risk for CD was associated with use at ages 0–2 months (RR 4.19).

Of the variables considered as potential confounding factors, no one proved to be a significant univariate risk factor ($p<0.05$) for IBD, so all analyses included adjustment for age and calendar period only. The univariate associations between the potential confounding factors and IBD with p values are shown in table 1 in the online supplement.

In a further analysis we included all the examined potential confounders together with age and calendar period, which resulted in a fully adjusted RR of IBD of 1.81 (95% CI 1.05 to 3.11), similar to the RR reported above with adjustment for age and calendar period only (RR 1.84).

Excluding children born in 1995–6, when antibiotic prescriptions are likely to have been registered through parents and misclassification might have occurred, had little impact on the effect measures (RR 1.90, 95% CI 1.01 to 3.58). Following the children for IBD from 1 year of age instead of birth magnified the effect (RR 3.30, 95% CI 1.32 to 8.26). Changing the definition of one course of antibiotics to only include use within 14 days instead of 30 days had little impact on the effect measures (increase in RR per course 1.12, 95% CI 1.04 to 1.20). Excluding never users when estimating the increase in RR per course had little impact (increase in RR per course 1.12, 95% CI 1.04 to 1.22).

Assuming causality, the attributable risk of CD from any use of antibiotics in childhood was 55% (95% CI 24% to 68%). The attributable risk of CD from any use in the last 3 months was 22% (95% CI 13% to 45%).

DISCUSSION

In this study we evaluated the potential association between antibiotic use and IBD in childhood and observed an increased risk of IBD associated with antibiotic use (RR 1.84). This association appeared to be an effect restricted to CD which was strongest in the first 3 months following use, and among children receiving several courses of antibiotics.

Table 2 Rate ratios of inflammatory bowel diseases according to antibiotic use among Danish children born 1995–2003 followed from birth until 1 January 2005

	Inflammatory bowel diseases			Crohn's disease			Ulcerative colitis		
	Number of cases	RR*	95% CI	Number of cases	RR*	95% CI	Number of cases	RR*	95% CI
Antibiotic use									
No courses	33	1	Reference	11	1	Reference	22	1	Reference
At least 1 course	84	1.84	(1.08 to 3.15)	39	3.41	(1.45 to 8.02)	45	1.21	(0.61 to 2.38)
Use in last 3 months	26	2.39	(1.36 to 4.19)	14	4.43	(1.88 to 10.44)	12	1.49	(0.69 to 3.19)
Use >3 months previously	58	1.42	(0.79 to 2.53)	25	2.27	(0.88 to 5.84)	33	1.04	(0.50 to 2.16)
Number of courses									
1–2	32	1.63	(0.92 to 2.91)	14	2.94	(1.18 to 7.31)	18	1.11	(0.54 to 2.32)
3–4	21	2.07	(1.03 to 4.18)	11	5.12	(1.69 to 15.53)	10	1.12	(0.45 to 2.80)
5–6	15	2.76	(1.27 to 5.97)	6	5.30	(1.49 to 18.87)	9	1.86	(0.71 to 4.87)
7+	16	2.93	(1.34 to 6.40)	8	7.32	(2.14 to 24.99)	8	1.59	(0.57 to 4.39)
Increase in RR per course		1.12	(1.04 to 1.21)		1.18	(1.06 to 1.32)		1.08	(0.97 to 1.19)

*Adjusted for age and calendar period.

Table 3 Rate ratios of Crohn's disease according to age at antibiotic use and type of antibiotics used among Danish children born 1995–2003 followed from birth until 1 January 2005

	Crohn's disease					
	Antibiotic use in last 3 months			Antibiotic use >3 months previously		
	Number of cases	RR	95% CI	Number of cases	RR	95% CI
No courses	11			11		
At least 1 course	14	4.43	(1.88 to 10.44)	25	2.27	(0.88 to 5.84)
Type of antibiotics used†						
Penicillin V	8	2.92	(1.22 to 6.97)	22	1.50	(0.70 to 3.23)
Extended spectrum penicillins	8	3.13	(1.33 to 7.40)	22	1.42	(0.67 to 2.99)
Macrolides	1	0.97	(0.13 to 7.14)	11	1.38	(0.67 to 2.87)
Other systemics	0	NA		5	1.38	(0.52 to 3.62)
Age at antibiotic use*						
0–2 months	0	NA		5	4.19	(1.64 to 10.68)
3 –11 months	5	3.32	(1.15 to 9.56)	18	1.04	(0.53 to 2.04)
1 year	1	1.53	(0.15 to 15.46)	22	1.11	(0.52 to 2.35)
2–3 years	4	3.73	(1.02 to 13.60)	21	2.17	(0.87 to 5.42)
4+ years	4	2.34	(0.71 to 7.73)	7	1.35	(0.45 to 4.08)

*RRs adjusted for age, calendar period, use of other types of antibiotics and other times since use. Note that the number of cases do not sum to 14 and 25 respectively, since children can use multiple types of antibiotics at different ages.
†RRs adjusted for age, calendar period, other ages of use and other times since use. RR for systemic antibiotics could not be estimated owing to lack of cases.

Biological plausibility

Antibiotic use can alter the commensal intestinal microflora both in the short and long term,[4 5] and such alterations may be accompanied by overgrowth with potentially pathogenic microorganisms that may directly trigger IBD in susceptible individuals. A further consequence of a changed intestinal microflora is the potential indirect effects on the intestinal immune system.[1] The removal of beneficial populations of bacteria could interfere with immune system maturation and balance leading to immune dysfunction, manifesting in reduced tolerance to microorganisms and triggering IBD in susceptible individuals. If our finding of an increased CD risk shortly after an antibiotic course reflects a causal influence of antibiotic use, it would be more easily compatible with an IBD-triggering effect of a sudden change in the bowel microflora than with some as yet uncharacterised long-term immune dysfunction.

Other studies

A number of previous studies have evaluated the association between antibiotics and IBD. Card and colleagues conducted a large case–control study in Britain including 587 cases of CD with a median age of 42 years.[6] The researchers observed an increased risk of CD associated with use of antibiotics 2–5 years prior to diagnosis (adjusted OR 1.32). Gilat and colleagues conducted a multicentre study including 499 cases of IBD diagnosed before 20 years of age.[7] In that study cases of CD reported antibiotic use more frequently than controls. However, this result was based on questionnaire data obtained after diagnosis and could therefore be subject to recall bias. In another study, Wurzelmann and colleagues observed that adult CD cases in the USA were more likely than controls to report frequent antibiotics use.[8] In Sweden, Hildebrand and colleagues conducted a large case–control study of the association between hospitalisation with infections where antibiotic treatment is likely and CD risk.[9] These researchers observed that both paediatric and adult-onset cases of CD were more likely to have been hospitalised with such infections prior to the time of diagnosis. In summary, previous evaluations of the potential association between antibiotic use and IBD are few and limited by either recall bias, restriction to adult-onset cases or the use of proxy variables for antibiotic use.

Strengths and limitations

In any observational study the results must be considered carefully in the context of potential bias and confounding. We relied on a nationwide hospital discharge register for ascertainment of IBD cases using International Classification of Diseases 10th revision coding. The validity of the CD and UC diagnoses in the Danish National Hospital Register has previously been estimated to be 97% and 90%, respectively, and the completeness of both IBD diagnoses have been estimated to be 94%.[15] We have previously used these data in epidemiological studies of IBD in Denmark.[16]

Exposure to antibiotics was determined through a nationwide prescription drug registry and we assumed that filling a prescription for antibiotics was interchangeable with use of the drug. Some divergence, both with respect to use and timing of use, is to be expected, and will bias our results towards no effect. In Denmark, antibiotic exposure occurs legally through hospitalisations and through prescriptions. A limitation of our study was our inability to take hospitalisation exposure into account. Exposure to antibiotics outside of hospital and pharmacy settings is likely to be limited, especially among children. In a study by Muscat and colleagues of self-medication with antibiotics in Denmark, only one out of 164 antibiotic uses in children was from self-medication (specifically, left-over antibiotics).[17]

We examined a wide range of potential confounders other than age and calendar period in our study. However, no confounders could be identified and fully adjusted results were almost identical to age- and calendar period-adjusted results, providing reassurance for the robustness of our findings.

Confounding by indication is a potential source of selection bias in this study as in any other observational study of this association. If antibiotics are indicated for conditions with an increased risk of IBD, this could lead to an apparent increased risk after exposure that is not attributable to the antibiotics themselves. However, while mycobacterial infections have long been discussed as possible risk factors for childhood CD, to our knowledge there is no firm evidence linking infections to risk of childhood IBD.[18] In adults, an increased risk of IBD has been associated with gastroenteritis.[19 20] Unfortunately, information on the underlying indications for antibiotic use was not available

in our study. Similarly, we cannot exclude the possibility that some children with as yet undiagnosed IBD presented with infection-like symptoms such as fever or diarrhoea, and that such non-specific symptoms could have led to the antibiotics being prescribed, a situation of reverse causality. The majority of CD cases occurred after exposure to penicillin V and extended spectrum penicillins. In Denmark, the indications for penicillin V in children are tonsillitis, otitis and pneumonia—penicillin V is highly unlikely to be prescribed in response to intestinal symptoms. Extended spectrum penicillins have similar indications to penicillin V. However, it is somewhat more conceivable that extended spectrum penicillins could be prescribed in response to intestinal symptoms. In Denmark, macrolides are prescribed for intestinal symptoms in children. For older children, ciprofloxacin—included in the category 'other systemics'—may also be prescribed. As such, the antibiotic type specific results do not support the notion that CD cases occur in children prescribed antibiotics in response to intestinal symptoms. Antibiotics are used in the treatment of IBD, and cases diagnosed initially outside the hospital setting could consequently be classified as occurring after antibiotic use in our study relying on hospitalisation diagnoses. However, as metronidazole and ciprofloxacin are the antibiotics of choice in the treatment of IBD, our results cannot be explained by antibiotic treatment.

Detection bias, where children with indications for antibiotic use are diagnosed earlier with IBD, is also a potential explanation for at least some of the increased risk of IBD in the first 3 months following antibiotic use.

Our study has a number of strengths. First, it is population-based with prospective and independent ascertainment of antibiotic use and IBD diagnoses, reducing concern over selection and recall bias. Second, our study provides detailed individual-level information on antibiotics, enabling detailed analysis of IBD risk according to time since exposure, age at exposure, type of agent used and number of exposures. Finally, our results were unchanged by a number of sensitivity analyses and the large number of potential confounders examined had virtually no impact on the effect estimates.

Conclusion and perspectives

The incidence of IBD has risen in many countries. In Denmark, Jakobsen and colleagues compared the incidence of paediatric IBD in the periods 1962–1987 and 1998–2006,[21] reporting a 15-fold increase in the incidence of childhood CD between the two periods. Such a marked increase suggests that environmental factors play an important role in the aetiology of paediatric IBD. Antibiotic use is widespread in childhood, and its potential as an environmental risk factor for IBD deserves scrutiny. Our study is the first prospective study to show a strong and dose-dependent association between antibiotic use and CD in childhood. As with any observational study, causality cannot be inferred by our results. However, the possibility of a causal connection should not be dismissed and warrants serious attention in additional large-scale studies with individual-level information on both antibiotic use and the underlying reasons for their use.

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REFERENCES

1. **Shanahan F.** Inflammatory bowel disease: immunodiagnostics, immunotherapeutics, and ecotherapeutics. *Gastroenterology* 2001;**120**:622–35.
2. **Guarner F,** Malagelada JR. Gut flora in health and disease. *Lancet* 2003;**361**:512–19.
3. **Fanaro S,** Chierici R, Guerrini P, *et al*. Intestinal microflora in early infancy: composition and development. *Acta Paediatr Suppl* 2003;**91**:48–55.
4. **Bedford Russell AR,** Murch SH. Could peripartum antibiotics have delayed health consequences for the infant? *Br J Obstet Gynaecol* 2006;**113**:758–65.
5. **Sullivan A,** Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. *Lancet Infect Dis* 2001;**1**:101–14.
6. **Card T,** Logan RF, Rodrigues LC, *et al*. Antibiotic use and the development of Crohn's disease. *Gut* 2004;**53**:246–50.
7. **Gilat T,** Hacohen D, Lilos P, *et al*. Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. *Scand J Gastroenterol* 1987;**22**:1009–24.
8. **Wurzelmann JI,** Lyles CM, Sandler RS. Childhood infections and the risk of inflammatory bowel disease. *Dig Dis Sci* 1994;**39**:555–60.
9. **Hildebrand H,** Malmborg P, Askling J, *et al*. Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease. *Scand J Gastroenterol* 2008;**43**:961–6.
10. **Pedersen CB,** Gotzsche H, Moller JO, *et al*. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;**53**:441–9.
11. **Forskningsdatabaser.** *Databeredskab i Danmarks Statistik*. Danmarks Statistik, Copenhagen, Denmark, 2002.
12. **Andersen TF,** Madsen M, Jorgensen J, *et al*. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;**46**:263–8.
13. **Knudsen LB,** Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;**45**:320–3.
14. **Clayton D,** Hills M. Poisson and logistic regression. *Statistical Models in Epidemiology* 1st edn. In: Clayton D and Hills M, eds. Oxford, UK: Oxford University Press, 1993:227–36.
15. **Fonager K,** Sorensen HT, Rasmussen SN, *et al*. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. *Scand J Gastroenterol* 1996;**31**:154–9.
16. **Frisch M,** Pedersen BV, Andersson RE. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. *BMJ* 2009;**338**:b716.
17. **Muscat M,** Monnet DL, Klemmensen T, *et al*. Patterns of antibiotic use in the community in Denmark. *Scand J Infect Dis* 2006;**38**:597–603.
18. **Loftus EV Jr.** Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004;**126**:1504–17.
19. **Garcia Rodriguez LA,** Ruigomez A, Panes J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology* 2006;**130**:1588–94.
20. **Gradel KO,** Nielsen HL, Schonheyder HC, *et al*. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. *Gastroenterology* 2009;**137**:495–501.
21. **Jakobsen C,** Paerregaard A, Munkholm P, *et al*. Paediatric inflammatory bowel disease during a 44-year period in Copenhagen County: occurrence, course and prognosis—a population-based study from the Danish Crohn Colitis Database. *Eur J Gastroenterol Hepatol* 2009;**21**:1291–301.

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