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Antibiotic use and the development of inflammatory bowel disease: a national case/control study in Sweden

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Abstract

Background: Early life antibiotics have been linked to childhood inflammatory bowel disease (IBD), but data on adults is mixed—particularly for ulcerative colitis (UC)—and is based on smaller investigations that have not assessed risk among siblings with shared genetic/environmental risk factors. Our objective was to determine the association of antibiotic therapy and IBD in a large, population-based investigation.

Methods: We conducted a population-based prospective case-control study of individuals aged ≥16 years in ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden), the Swedish Patient Register, and the Prescribed Drug Register to identify all consecutive cases of incident IBD (2007–2016) based on histology and ≥1 diagnosis code for IBD or its subtypes: UC and Crohn's disease (CD). Cumulative antibiotic dispensations accrued until one year prior to the time of matching for both study cases and up to five general population controls matched on the basis of age, sex, county, and calendar year. We also included unaffected full siblings as a secondary control group. Conditional logistic regression was used to estimate multivariable-adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Findings: We identified 23,982 new IBD cases (15,951 UC, 7,898 CD, 133 IBD-unclassified), 28,732 siblings, and 117,827 controls. Prior use of antibiotics (never vs. ever) was associated with a nearly two-times increased risk of IBD after adjusting for several risk factors (aOR 1·94, 95% CI: 1·85–2·03). Compared to none, one (aOR 1·11, 95% CI: 1·07–1·15), two (aOR 1·38, 95% CI: 1·32–1·44) , and ≥three antibiotic dispensations (aOR 1·55, 95% CI: 1·49–1·61) were associated with increased odds of IBD compared to controls. Increased risk was noted for UC and CD with the highest estimates corresponding to broad-spectrum antibiotics. Notably, comparable, but attenuated results were observed when siblings served as the referent (aOR 1·35, 95% CI: 1·28–1·43).

Interpretation: Higher cumulative exposure to systemic antibiotic therapy, particularly those with greater spectrum of microbial coverage, may be associated with an increase in risk for new-onset IBD and its subtypes. The association between antimicrobial treatment and IBD did not appear to differ when comparably predisposed siblings were used as the referent controls.

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Keywords

colonic microflora; IBD clinical; pharmacotherapy

INTRODUCTION

The inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gastrointestinal (GI) tract. Host genetics, environmental factors, and the gut microbiome are known to contribute to etiopathogenesis of IBD.[1] While host genetics have been studied extensively, less clearly understood are the contributions of specific environmental determinants to an alarming rise in IBD, disproportionately affecting Europe, the U.S., and parts of the world undergoing rapid economic development.[2,3] Consequently, increased sanitation and widespread use of anti-

infectious agents[4] have been proposed as reasons why this emerging disparity in disease burden is becoming more apparent—the so-called hygiene hypothesis. Prior large-scale efforts have demonstrated that individuals with IBD harbour greater numbers of facultative anaerobes (including *Escherichia coli*) and comparatively fewer obligate anaerobic producers of short-chain fatty acids (SCFAs) compared to individuals free of IBD.[5] With growing appreciation for the richness and diversity of the gut microbiome and its role in maintaining human health, so too has concern that antibiotics may perturb and permanently alter these microbial communities, increasing risk for IBD and other disorders similarly characterized by dysregulated host/microbial interactions.

Despite expanded reliance on antimicrobial therapy being a leading suspected culprit contributing to this phenomenon, current studies are limited by small sample size,[6–12] lack of histopathologic case ascertainment,[6–8,10,12–17] and mainly address risk associated with paediatric IBD.[13–18] Also, no studies have yet assessed whether risk related to antibiotics is modified within families already genetically predisposed to the development of IBD. Finally, careful assessment of pre-diagnostic antibiotic usage with an appropriate exclusionary/lead-in period (i.e. a period of time for which antibiotic dispensations just prior to an IBD diagnosis are not accrued) is necessary to limit the possibility of reverse causation, or therapy prescribed for symptoms related to undiagnosed IBD. This is particularly important for IBD, since the time to diagnosis may be delayed by four to nine months.[19] Population-scale investigations with careful case ascertainment and an appropriate lead-in period are urgently needed to help settle this controversial and unsettled question.

Thus, to our knowledge, we conducted the single largest investigation assessing cumulative exposure to antibiotic therapy and incident IBD, conservatively assessed at least one year prior to disease diagnosis. We confirmed case status by requiring both compatible histopathology and medical diagnosis coding, using the first occurrence of either criterion as the date of diagnosis, and compared antibiotic usage for those afflicted to general population controls in a large, nationally representative case-control study. To minimize the confounding effect of childhood exposures and genetic susceptibility, we also compared IBD cases to their unaffected, full siblings.

METHODS

Study design and participants

In Sweden, universal access to care is tax-funded and includes prescription medication coverage.[20] The Swedish National Board of Health and Welfare has collected patient-level data on hospital discharges nationally since 1987 using the Swedish Patient Register. Each patient record includes sex, date of birth, dates of hospital admission, as well as procedural and discharge diagnoses systematized by International Classification of Diseases (ICD) code (Fig. 1 and Appendix, p2). In 2001, this registry was expanded to outpatient specialty care, including visits to gastroenterology providers. The positive predictive value for most diagnoses in this register ranges between 85% and 95%.[21] We further integrated this national registry data with the Epidemiology Strengthened by histoPathology Reports in Sweden (ESPRESSO) study.[22] Briefly, the ESPRESSO study is an ongoing, comprehensive data harmonizing effort involving each of the 28 pathology laboratories in Sweden. This includes

all computerized GI pathology reports generated for clinical care or research purposes between 1965 and 2016, encompassing more than 2.1 million unique individuals with detailed information on topography (i.e. the anatomic location of the obtained tissue), morphology, appearance, and the pathologist's diagnostic impression. Finally, since July 2005, the Swedish Prescribed Drug Register has collected information on all medications, including antibiotics, prescribed to the entire Swedish population, as well as the date of redemption, amount dispensed, and dose allotted.[20] Patient level data from the ESPRESSO cohort and two national registries (Patient Register and the Prescribed Drug Register) were linked by a unique personal identity number assigned at birth or at the time when permanent residence was established. Thus, our study encompasses all consecutive eligible patients for the period of overlap during which the National Patient Register, the ESPRESSO study, and the Prescribed Drug Register were each actively enrolling (July 1, 2005 to December 31, 2016). This investigation was approved by the Stockholm Ethics Review Board (Protocol 2014/1287–31/4). Due to the strict registry-based nature of the study, informed consent was waived.

Ascertainment of outcomes

Using predefined anatomic and histologic criteria, as well as the attending pathologist's diagnostic impression (Appendix, p2), we identified individuals in the ESPRESSO study with GI tract histopathology compatible with the diagnosis of new-onset IBD and its subtypes, UC and CD from 2005 to 2016. If a distinction between subtypes could not be made, cases were defined as (non-infectious) indeterminate colitis or IBD-unclassified (IBD-U). We then cross-referenced potential cases and the entirety of their inpatient and outpatient records in search of at least one ICD code consistent with IBD.

We first excluded those with IBD-compatible pathology or ICD diagnostic coding prior to our study baseline (2005). The date of IBD diagnosis was defined as the earliest between the date of relevant pathology findings and the first appearance of an IBD-related diagnosis code. In a random subset of individuals with both compatible histopathology and an ICD code for IBD, we were able to validate case status using manual chart review in 95 of 100 individuals[22] yielding a positive predictive value of 95% (95% CI: 89–99%). To account for the possibility of reverse causation, or antibiotic therapy prescribed for symptoms related to undiagnosed IBD, we did not count antibiotic dispensations in the one year leading up to IBD diagnosis. Consequently, to conservatively ensure adequate at-risk exposure time (since antibiotics were not counted in the preceding 12 months), we excluded IBD cases diagnosed within the first 18 months of study baseline/initiation of the Swedish Prescribed Drug Register (Appendix, p8).

At the time of ESPRESSO inclusion, individuals were paired with up to five reference controls from the general population, matched on the basis of age, sex, calendar year, and county. Controls with undiagnosed IBD at the time of matching were allowed to later become cases if they met the prespecified diagnostic criteria, and they were then subsequently matched to five other reference controls of their own. Additionally, to further assess the association between cumulative antibiotic usage and IBD among genetically

related individuals, we also identified and enrolled unaffected full siblings of our index cases still living at the time of their siblings' IBD diagnosis.[22]

Ascertainment of primary exposure and other covariates

Our primary exposure, cumulative antibiotic usage up to one year prior to IBD diagnosis, defined as the cumulative sum of antibiotic dispensations. This was assessed using the Swedish Prescribed Drug Register and categorized using established World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes for the therapeutic subgroup of antibacterials approved for systemic usage. To achieve adequate case balance, we collected information on number of dispensations (categorized into zero, one, two, and three or greater dispensations, corresponding with median/interquartile values for dispensations across the entire study population). We also collected information on the cumulative number of prescribed days, as well as the cumulative defined daily dose (cDDD). In secondary analyses to further define the relationship between antimicrobial coverage, dysbiosis, and risk of IBD, we assessed whether different ATC classes of antibiotics (penicillins, cephalosporins, macrolides, fluoroquinolones, tetracyclines, sulphonamides, and other) and spectrum of coverage (broad vs. narrow)[23] influenced risk of disease (Appendix, p3).

When available, we obtained data on level of education (≤9 years, 10–12 years, ≥13 years, and unknown) from Statistics Sweden and the longitudinal integrated database for health insurance and labour market studies, which since 1990 has annually updated administrative information from the labour market and educational and social sectors for all individuals aged 16 years or older. This information is available in more than 98% of all individuals aged 25–64 years.[24] We also calculated the number of inpatient and outpatient encounters (continuous) for each participant during the study period up until the time of matching.

Statistical Analysis

To evaluate the association between antecedent antibiotic therapy and IBD, we performed conditional logistic regression between IBD cases and reference controls to estimate crude and multivariable-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) conditioned on matching factors (age, sex, calendar year, and county of residence) and further adjusted for potential confounding factors (education level and healthcare utilization, the latter defined as the number of inpatient and outpatient encounters during follow up). Tests for linear trend were calculated using the midpoint of each frequency category as a continuous variable. Two-sided p-values of <0.05 were considered statistically significant.

As a sensitivity analysis and to assess the robustness of our primary findings, we lengthened the lead-in period from one year in our primary analysis to a more conservative two years. We also performed subgroup analyses according to the spectrum of antibiotic coverage and class of antibiotic therapy prescribed. We conducted a joint association analysis to determine whether the number of combined broad or narrow-spectrum dispensations altered the association between antimicrobial therapy and IBD, in effect, a test of interaction between two risk factors. Finally, to minimize the influence of genetic predisposition and shared childhood exposures, we compared cases to their (unmatched) full siblings using logistic

regression with adjustment for age, sex, year of match, county, education level, and healthcare utilization. Statistical analyses were performed using SAS version 9.4 (Cary, NC, USA) and R 3.5.1 (Vienna, Austria).

Role of Funding Sources

Sponsors had no role in study design, the collection, analysis, and interpretation of data, report writing, and the decision to submit for publication. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

We identified 32,690 unique individuals aged ≥ 16 years in the ESPRESSO study with GI tract histopathology compatible with the diagnosis of new-onset IBD and its subtypes, UC and CD from 2005 to 2016. After excluding individuals with a compatible IBD ICD diagnosis code at or prior to baseline and individuals without adequate exposure time according to our prespecified lead-in period, we enrolled 23,982 cases of biopsy and diagnosis code-confirmed IBD between January 1, 2007 and December 31, 2016 (15,951 UC, 7,898 CD, 133 IBD-U). Patients with IBD were comparable to their 117,827 matched controls by mean age (35 years), sex (52% male), education level, and region of residence, but tended to have more frequent engagement with inpatient and outpatient providers (Table 1 and Appendix, p5). Among these general population individuals, only 952 (0.8%) individuals would become cases themselves and were thus matched to their own reference individuals. We found a strong correlation between the presence of an IBD-compatible ICD code recorded in the inpatient setting with one in the outpatient setting (Spearman ρ for IBD, CD, and UC each > 0.62), which would suggest that either clinical setting (e.g. inpatient or outpatient) is suitable for valid case identification.

Prior use of antibiotics was associated with a nearly two-times increased risk of IBD after adjusting for several risk factors (multivariable OR 1·94, 95% CI: 1·85–2·03). Increased cumulative antibiotic use was associated with an increased risk for new-onset IBD and its two primary subtypes, UC and CD (Table 2). Inclusive of our matching criteria (age, sex, calendar year and county), education level, and number of prior inpatient and outpatient encounters, multivariable conditional logistic regression demonstrated a frequency-dependent relationship between increased antibiotic prescriptions and risk of IBD (*P*-trend <·0001). We found that three or more antibiotic dispensations at least one year prior to diagnosis was associated with a 55% increased risk for IBD (multivariable OR 1·55, 95% CI: 1·49–1·61) compared to no prior use. Due to significant collinearity in their measure, results were similar when cumulative antibiotic therapy was assessed by number of days prescribed or cDDD (data not shown). Risk estimates were slightly higher for CD compared to UC. Our estimates were not materially altered when a two-year, rather than one-year lead-in was employed (multivariable OR for ≥3 dispensations compared to never use 1·47, 95% CI: 1·41–1·53; *P*-trend<·0001). Results remained consistent when we removed controls who eventually became cases (data not shown).

Subgroup analyses by spectrum of antibiotic coverage demonstrated an increased risk among patients reporting more frequent use of broad-spectrum antibiotics compared to

narrow spectrum (Table 3). Heterogeneity in risk estimates appeared most pronounced for CD, though formal tests for interaction were highly significant for IBD, UC, and CD (all *P*-interaction <·0001). There was no clear synergistic effect between increasing frequency of combined broad and narrow-spectrum antimicrobial therapy (data not shown). Each class of antibiotic assessed, categorized by World Health Organization ATC subgroup, was associated with a statistically significant increase in risk per dispensation compared to never users (multivariable OR between 1·03–1·20; Fig. 2), highest for each dispensation of a cephalosporin class antibiotic (multivariable OR for IBD 1·20, 95% CI: 1·14–1·25). To further ensure our primary findings were not a consequence of infections related to undiagnosed IBD (i.e. confounding by indication), we compared the usage of a composite antibiotic, either ciprofloxacin or metronidazole—two commonly prescribed antibiotics for bacterial gastroenteritis—and found comparable results to our overall estimate (multivariable OR for IBD compared to never users of 1·15, 95% CI: 1·11–1·20). In general, we found consistent results between UC and CD. A stratified analysis by age group appeared to demonstrate a greater association among older individuals, perhaps suggesting that environmental exposures may play an outsized role in older onset IBD, while other factors may contribute to early-onset IBD, which tends to have a more dramatic disease course (Appendix, p6).

Finally, among individuals with a genetic predisposition to disease development and to partially account for shared but unspecified childhood exposures, we compared antimicrobial therapy rates among IBD cases and their full siblings, where available. Nearly 70% of cases (*n*=16,353) had at least one living sibling identified in our cohort, all of whom were captured by linkage to the National Patient Register. When comparing 28,732 full siblings free of IBD to their related cases, as expected, their mean age, region of residence, and education levels were all comparable (Appendix, p7). Notably, their number of inpatient and outpatient encounters were similarly elevated—like their case siblings—compared to unrelated reference individuals, suggesting similar childhood exposures, infections, predilection for chronic disease, and access to comparable childhood care. When siblings were used as the referent group, IBD risk estimates were only slightly attenuated compared to general population controls, with a multivariable OR of 1·35 (95%CI: 1·28–1·43; *P*-trend <·0001) when comparing three or greater antibiotic dispensations to none (Table 4). Estimates were comparable for both UC and CD.

DISCUSSION

In this population-based study of nearly 24,000 unique IBD patients during a 10-year study period provided, we demonstrate a potential frequency-dependent relationship between the number of antibiotic dispensations and the development of UC and CD. This potential association appeared to be robust to adjustment for age, sex, level of education, and degree of healthcare utilization. Furthermore, this possible risk association appeared greater with more frequent use of broad-spectrum antibiotics, which supports the hypothesis linking greater excursions from the normal gut ecological state caused by antimicrobial therapy to elevated risk for chronic disease development.

To our knowledge, this is the largest investigation exploring the link between prior antimicrobial therapy and subsequent risk for IBD, which not only allowed for subgroup analyses that produced more confident risk estimates by WHO antibiotic class, but linked more frequent antibiotic therapy to risk of UC, a disease subtype for which prior, smaller investigations have produced mixed results. Moreover, in a secondary analysis among cases and their IBD-free siblings with whom they likely shared childhood exposures, as well as a genetic predilection for the development of IBD, we were able to show that risk associated with antibiotic use was only minimally attenuated when compared to tests against general reference individuals. This comparison among similarly predisposed persons provides further evidence to implicate cumulative antibiotic exposure as an independent risk factor in the etiopathogenesis of IBD, regardless of underlying genetic susceptibility.

Disentangling the environmental exposures that may culminate in the diagnosis of IBD is critically important, particularly as some data may suggest that risk of IBD due to antibiotics may be restricted to developed areas of the world.[3] Globally, rates of IBD are rising, particularly in areas undergoing rapid economic development. Since these trends are unlikely to be explained by drastic, population-level changes in underlying genetic architecture, the widespread adoption of increased sanitation and pervasive use of anti-infectious agents have been implicated.[25–28] Despite considerable progress in our understanding of IBD's genetic and familial underpinnings, concordance rates among monozygotic, i.e. genetically identical, twins is still just 20–50%,[29] highlighting the importance of considerable non-genetic determinants in new-onset IBD, such as antibiotic therapy.

Our primary findings are biologically plausible. While antibiotics have been widely beneficial for the maintenance of human health, they greatly impact the fragile ecology of human gut microbial communities, resulting in individualized and sometimes incomplete recovery from such insults, predisposing users to long-term chronic disease risk.[30–33] The consequences of altering the taxonomic makeup and collective activities of the gut microbiome can influence IBD risk through several, interconnected mechanisms, including a change in vital metabolic functions, vitamin and nutrient production, as well as energy extraction. Most critically, gut microbial perturbations promote the onset of intestinal barrier dysfunction[34,35], altered immune response,[36,37] defective autophagy,[38] and permissive pathogenic blooms[39–41] that are typically viewed as inciting events as early as several years prior to the development of IBD. Notably, our group has previously linked early life antibiotic exposures to a more severe, paediatric form of the disease, adding credibility to the current findings.[15]

Epidemiologic evidence on the relationship between antimicrobial therapy and risk of IBD has been mounting, though it is possible that publishing bias may have resulted in comparatively fewer negative studies. The largest and most recent meta-analysis to date, encompassing 7,208 IBD patients from 11 separate investigations—cumulatively, approximately ⅓ the size of the present study—have noted similar findings with respect to antibiotic therapy and risk of CD and also observed heterogeneous risk estimates related to class of antibiotic therapy[42] and included several studies in which no clear association was noted. However, Ungaro *et al* were unable to couple antibiotic use to an increase in risk for

UC, possibly due to sample size considerations (collective number of UC patients, *n*= 2,935). More recently, a case-control study of 455 IBD patients by Aniwan *et al* demonstrated an association between antimicrobial therapy and risk of UC, albeit with much stronger risk estimates across IBD and its subtypes (adjusted OR for IBD 2.93, 95% CI: 2·40–3·58; for UC 2·94, 95% CI: 2·23–3·88).[7] However, compared to our nationally representative, population-based study, they enrolled individuals from an ethnically and socioeconomically homogenous region of the U.S. Given our *a priori* hypothesis linking hygiene, economic development, and increased utilization of antibiotics to IBD, it is unclear how generalizable their findings may be. Additionally, Aniwan *et al* only excluded prescriptions in the three months prior to diagnosis, increasing the possibility of reverse causation, or therapy initiated for symptoms due to undiagnosed IBD, a disease for which the time to diagnosis may be delayed by months.[19] Our study did not allow dispensations to accrue in the one year prior to IBD diagnosis/time of match, making it much less likely that antibiotics were masking symptoms of IBD that had already developed, and our estimates were not significantly attenuated when we employed an even stricter two-year lead-in period. Finally, comparable observational studies have helped elucidate the role of antibiotics in other GI conditions, such as colorectal cancer and its precursor lesions and celiac disease.

Strengths of this investigation include the enrolment of all consecutive, eligible patients with new-onset IBD from a population-based register over a ten-year study period, limiting selection bias. In Sweden, there is universal medication coverage with virtually complete information on all drug dispensations, including antibiotics, minimizing ascertainment bias (<0.3% of all prescriptions lack identifying information).[43] To complement the use of a large, nationally representative sample, we employed stringent outcome ascertainment, requiring both compatible histopathologic findings and confirmatory ICD coding for adjudicating cases. With a positive predictive value of 95%, this validated method of case identification allowed us to confidently leverage and retain the power to detect even relatively modest risk increases among certain antibiotic classes, such as cephalosporins (multivariable OR 1.20 for IBD per dispensation) and penicillins (multivariable OR 1·05). Thus, we were able to demonstrate that all antimicrobial classes tested conferred additive—at times, modest—disease risk, strongly arguing for universal antibiotic stewardship and prescriber restraint.

We acknowledge several limitations. As with all large-scale pharmacoepidemiologic studies, medication dispensation ascertained through the Swedish Prescribed Drug Register may not capture any given patient's actual usage. However, due to the short-term nature of most antibiotic courses and the presumption that most dispensations were attributable to positive symptoms suggestive of an infection, adherence was not likely a major issue. Furthermore, such bias would have resulted in attenuation towards the null from non-differential misclassification. The Prescribed Drug Register does not contain information on hospital administered drugs, though this could be partially accounted for in our multivariable models adjusting for number of hospitalizations over the follow-up period. Given the observational nature and epidemiologic scale of this investigation, the possibility of unmeasured confounding remains, and our case-control design did not allow estimates of incidence rates and absolute risks. Our results will need to be validated in other populations given Sweden's

elevated rates of IBD[2,44,45] and lower antibiotic dispensation patterns compared to other nations.[46,47] We did not have information on the type of infection/indication for antibiotics dispensed. We found a low rate of IBD-U during the study period, which may be a function of improved histopathologic criteria,[48,49] our focus on adult-onset IBD,[50,51] and a prolonged lead-in period which may not have allowed IBD-U to develop from presumed UC or CD cases.[48,51] Finally, we cannot fully eliminate the possibility of reverse causation (therapy initiated for undiagnosed IBD) or confounding by indication (therapy initiated for GI infections related to IBD), though we attempted to minimize this in several ways. First, by only accounting for prescriptions at least one year prior to diagnosis, we can be more confident that antibiotic dispensations were not likely to be prescribed for undiagnosed IBD, a disease with a typical time to diagnosis between four and nine months.[19] An even more stringent sensitivity analysis extended the lead-in period to two years, which demonstrated similar findings. We also demonstrated a consistent frequency-response relationship in our primary analysis and a secondary analysis for an elevated risk for broad-spectrum antibiotics that are more likely to adversely impact gut microbial communities. Lastly, we used an early, conservative date of diagnosis (at the time of either the earliest IBD-compatible histopathology or ICD coding) which minimizes the time period for which antibiotic dispensations could be attributable to symptoms of IBD.

In closing, we found that higher cumulative exposure to systemic antibiotic therapy in the past 10 years, particularly those with greater spectrum of microbial coverage, was associated with an increase in risk for new-onset IBD and its two main subtypes, UC and CD. The relationship between antimicrobial treatment and IBD was not materially altered when comparably predisposed siblings were used as the referent controls. Further studies are needed to investigate how antibiotics may permanently alter gut microbial communities, potentially culminating in disease development, and whether that risk may be reduced by probiotics to prevent expansive blooms of pathogenic bacteria in place of beneficial microbes affected by antibiotic treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Interests:

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RESEARCH IN CONTEXT

Evidence before this study

Rates of inflammatory bowel disease (IBD) are increasing, particularly in Europe, the U.S., and other parts of the world undergoing rapid economic development, increased sanitation, and more frequent use of antibiotics. With growing appreciation for the gut microbiome's role in maintaining human health, so too has concern that antibiotics may perturb and permanently alter these fragile microbial communities. We searched PubMed for articles published between January 1, 1990 and April 30, 2020, using the terms "inflammatory bowel disease" and "antibiotics". Despite this compelling rationale, prior efforts to address this question have been conflicting—particularly in ulcerative colitis—and have been characterized by smaller-scale investigations with the most recent meta-analysis on the topic (with 11 prior studies and 7,208 IBD cases) disclosing a pooled odds ratio (OR) of 1.57 for risk of IBD, 1.74 for risk of Crohn's disease, and was not significantly different for ulcerative colitis (OR 1.08; Ungaro *et al*, Am J Gastroenterol 2014). Thus, it remains controversial and unsettled as to whether or not antibiotic therapy is linked to new-onset IBD.

Added value of this study

Among 23,982 individuals with IBD matched to 117,827 controls, number of antibiotic dispensations was significantly associated with risk for both ulcerative colitis and Crohn's disease in a frequency-dependent fashion. Risk appeared greater with more frequent use of broad-spectrum antibiotics. The positive association between antibiotic therapy and IBD remained observable even when cases were compared to their unaffected siblings with whom they likely shared genetic susceptibilities and childhood exposures, offering further support for the potential, independent role of antibiotics in IBD development.

Implications of all the available evidence

Our findings, if confirmed in longer-term prospective studies in humans or mechanistic pre-clinical investigations, suggest the need to further emphasize antibiotic stewardship to prevent the rise in dysbiosis-related chronic diseases, including IBD.

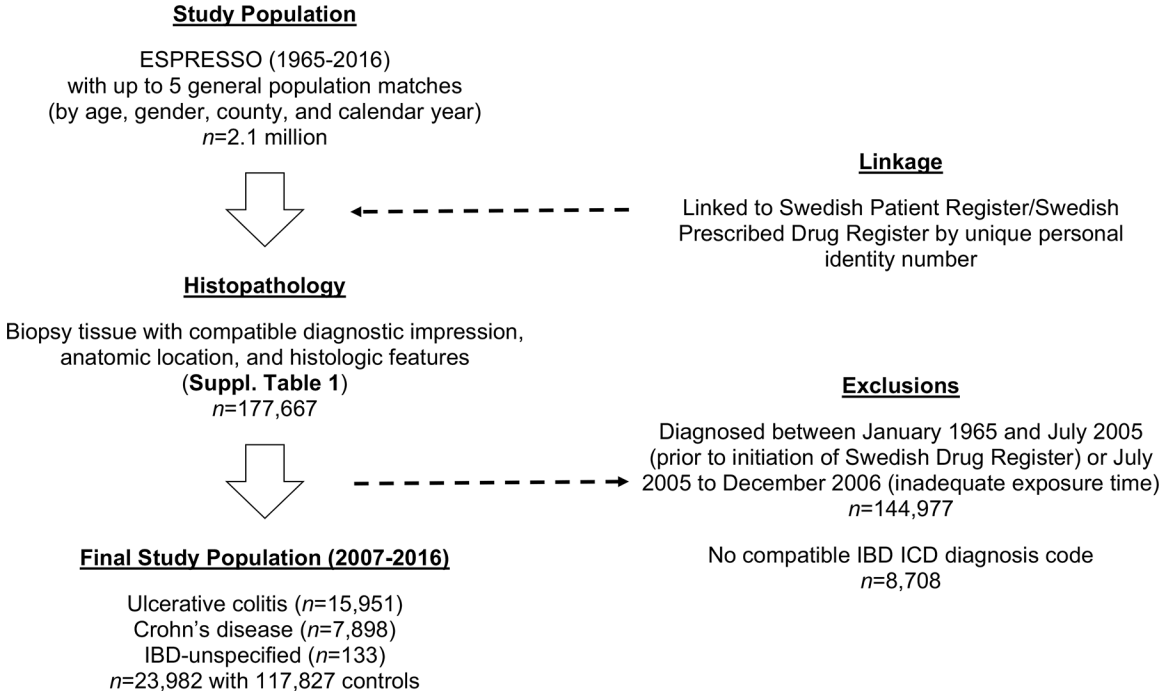

Figure 1:
Study overview

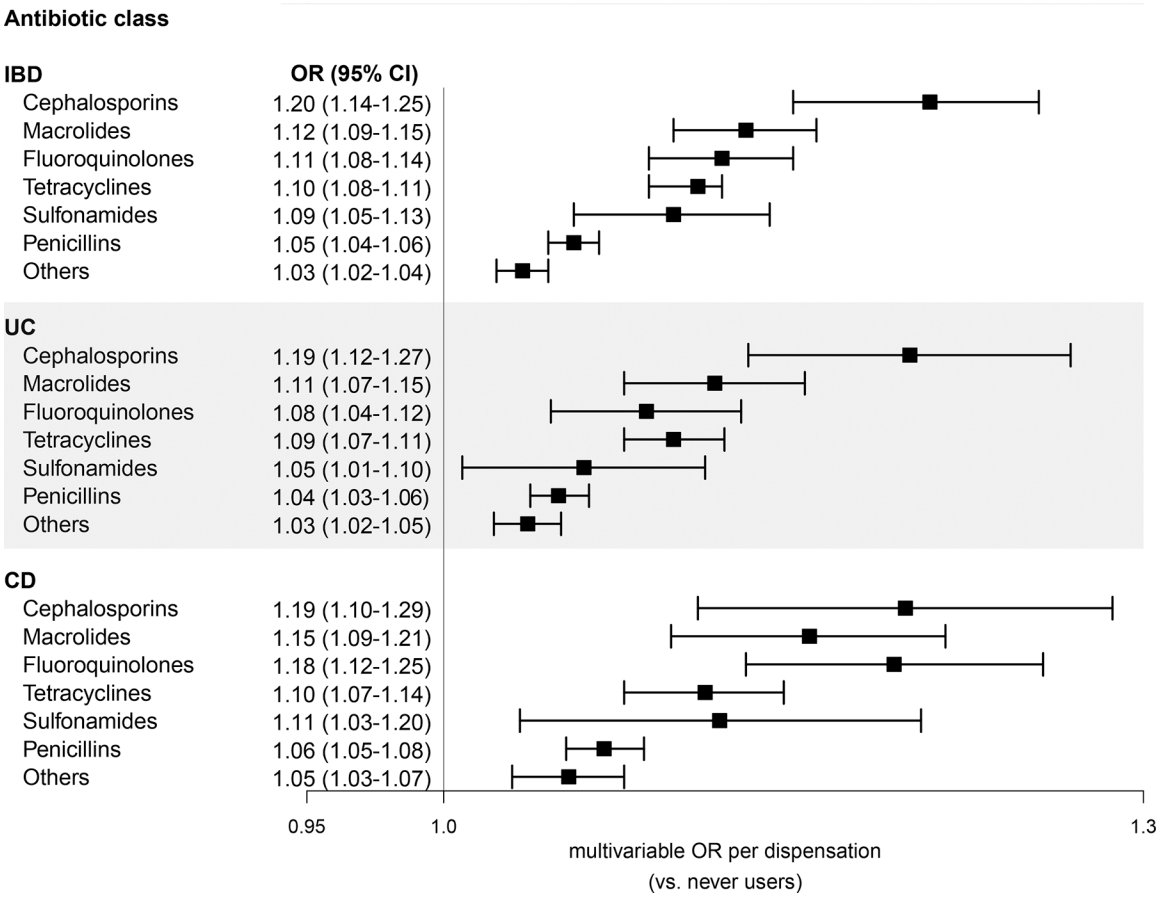

Figure 2:

Antibiotic use by antibiotic class and inflammatory bowel disease comparing cases and their matched general population controls, 2007–2016. Conditional logistic regression matched for age, sex, and county and further adjusted for number of inpatient and outpatient encounters and education level. Referent group had no prior exposure to antibiotics of any kind at the time of matching. Cumulative dispensations accrued from study baseline up until one year prior to diagnosis/match. IBD includes ulcerative colitis, Crohn's disease, and IBD-unclassified. Abbreviations: OR - odds ratio, CI - confidence interval, IBD - inflammatory bowel disease, UC - ulcerative colitis, CD - Crohn's disease.

Table 1:

Patient characteristics at the time of inflammatory bowel disease diagnosis and their matched general population controls, 2007–2016

	Cases n=23,982[#]		Controls *n*=117,827
	Ulcerative colitis *n*=15,951	**Crohn's disease *n*=7,898**	
Age, years	36 [24–56]	31 [19–51]	35 [22–54]
<18	1,755 (11)	1,686 (21)	17,699 (15)
18–24	2,552 (16)	1,422 (18)	20,421 (17)
25–34	3,190 (20)	1,343 (17)	22,785 (19)
35–44	2,233 (14)	948 (12)	15,843 (13)
45–54	1,914 (12)	790 (10)	13,451 (12)
55–64	2,072 (13)	869 (11)	13,487 (12)
≥65	2,235 (14)	840 (11)	14,141 (12)
Male sex, *n* (%)	8,543 (54)	3,997 (51)	62,010 (52)
Region of residence, *n* (%)			
Northern Sweden	1,417 (9)	590 (7)	9,926 (8)
Southeastern Sweden	1,816 (11)	923 (12)	13,572 (12)
Southern Sweden	3,030 (19)	1,518 (19)	22,390 (19)
Stockholm-Gotland	3,071 (19)	2,047 (26)	25,229 (21)
Uppsala-Örebro	3,489 (22)	1,592 (20)	25,216 (21)
Western Sweden	3,026 (19)	1,178 (15)	20,922 (18)
Unknown	102 (1)	50 (1)	572 (1)
Education, *n* (%)			
≤9 years	2,829 (18)	1,540 (20)	21,030 (18)
10–12 years	7,121 (45)	3,473 (44)	50,542 (43)
≥13 years	5,563 (35)	2,430 (31)	41,092 (35)
Unknown	438 (3)	455 (6)	5,163 (4)
Number of encounters [*], *n*			
Inpatient	2 [0–4]	2 [0–4]	1 [0–3]
Outpatient	5 [2–11]	6 [2–13]	3 [1–9]
Calendar year			
2007–2009	4,786 (30)	2,186 (28)	34,449 (29)
2010–2013	7,031 (44)	3,570 (45)	52,373 (44)
2014–2016	4,134 (26)	2,142 (27)	31,005 (26)

Values are median [IQR] or absolute figures (percentages). Polytomous variables may not sum to 100% due to rounding.

[#] includes ulcerative colitis, Crohn's disease, and IBD-unclassified

[*] calculated the number of inpatient and outpatient encounters (continuous) for each participant during the study period up until the time of matching/case diagnosis.

Table 2.

Overall antibiotic use and inflammatory bowel disease comparing cases and their matched general population controls, 2007–2016

	Cumulative antibiotic use				
	No use	**1 dispensation**	**2 dispensations**	**≥3 dispensations**	***P*-trend***
Inflammatory bowel disease (IBD)[#]					
Cases, *n* (%)	9,677 (40)	4,813 (20)	3,087 (13)	6,405 (27)	
Controls, *n* (%)	56,240 (48)	24,864 (21)	13,152 (11)	23,571 (20)	
Unadjusted OR (95% CI)[†]	1·0 (ref)	1·14 (1·10, 1·19)	1·46 (1·40, 1·53)	1·78 (1·71,1·84)	<·0001
Multivariable OR (95% CI)[‡]	1·0 (ref)	1·11 (1·07, 1·15)	1·38 (1·32, 1·44)	1·55 (1·49, 1·61)	<·0001
Ulcerative colitis (UC)					
Cases, *n* (%)	6,587 (41)	3,274 (21)	2,004 (12)	4,086 (26)	
Controls, *n* (%)	37,642 (48)	16,570 (21)	8,656 (11)	15,481 (20)	
Unadjusted OR (95% CI)	1·0 (ref)	1·16 (1·11, 1·22)	1·39 (1·32, 1·47)	1·63 (1·55, 1·71)	<·0001
Multivariable OR (95% CI)	1·0 (ref)	1·13 (1·08, 1·19)	1·33 (1·25, 1·41)	1·47 (1·40, 1·54)	<·0001
Crohn's disease (CD)					
Cases, *n* (%)	3,030 (38)	1,521 (19)	1,061 (14)	2,286 (29)	
Controls, *n* (%)	18,255 (47)	8,152 (21)	4,425 (11)	7,986 (21)	
Unadjusted OR (95% CI)	1·0 (ref)	1·18 (1·10, 1·26)	1·56 (1·44, 1·69)	1·94 (1·81, 2·07)	<·0001
Multivariable OR (95% CI)	1·0 (ref)	1·14 (1·06, 1·22)	1·46 (1·35, 1·58)	1·64 (1·53, 1·76)	<·0001

Cumulative dispensations accrued from study baseline up until one year prior to diagnosis/match

Abbreviations: OR - odds ratio, CI - confidence interval

[#] Includes ulcerative colitis, Crohn's disease, and IBD-unclassified

[†] Conditional logistic regression matched for age, sex, calendar year, and county

[‡] Further adjusted for number of inpatient and outpatient encounters and education level

[*] Calculated using the median of each category as a continuous variable.

Table 3.

Spectrum of antibiotic coverage and inflammatory bowel disease comparing cases and their matched general population controls, 2007–2016

	Cumulative antibiotic use				
	No prior use	**1 prior dispensation**	**2 prior dispensations**	**≥3 prior dispensations**	***P*-interaction**
Inflammatory bowel disease (IBD)[#]					
Broad-spectrum antibiotics					<0·0001
Cases, *n* (%)	9,677 (57)	3,690 (22)	1,592 (9)	2,040 (12)	
Controls, *n* (%)	56,240 (66)	16,302 (19)	5,803 (7)	6,620 (8)	
Multivariable OR (95% CI)[‡]	1·0 (ref)	1·31 (1·25, 1·37)	1·58 (1·48, 1·68)	1·69 (1·59, 1·79)	
Narrow-spectrum antibiotics					
Cases *n* (%)	9,677 (44)	5,212 (24)	2,797 (13)	4,109 (19)	
Controls *n* (%)	56,240 (52)	25,023 (23)	11,768 (11)	15,134 (14)	
Multivariable OR (95% CI)	1·0 (ref)	1·18 (1·13, 1·22)	1·37 (1·30, 1·43)	1·49 (1·43, 1·56)	
Ulcerative colitis (UC)					
Broad-spectrum antibiotics					<0·0001
Cases *n* (%)	6,587 (60)	2,440 (21)	1,015 (9)	1,299 (11)	
Controls *n* (%)	37,642 (66)	10,934 (19)	3,873 (7)	4,465 (8)	
Multivariable OR (95% CI)	1·0 (ref)	1·29 (1·22, 1·36)	1·50 (1·38, 1·63)	1·57 (1·45, 1·70)	
Narrow-spectrum antibiotics					
Cases *n* (%)	6,587 (45)	3,524 (24)	1,779 (11)	2,590 (18)	
Controls *n* (%)	37,642 (52)	16,571 (23)	7,775 (11)	9,750 (14)	
Multivariable OR (95% CI)	1·0 (ref)	1·20 (1·15, 1·26)	1·28 (1·21, 1·36)	1·43 (1·35, 1·52)	
Crohn's disease (CD)					
Broad-spectrum antibiotics					<0·0001
Cases *n* (%)	3,030 (54)	1,236 (22)	587 (11)	729 (13)	
Controls *n* (%)	18,255 (66)	5,277 (19)	1,909 (7)	2,130 (8)	
Multivariable OR (95% CI)	1·0 (ref)	1·40 (1·29, 1·52)	1·79 (1·60, 2·00)	1·78 (1·59, 1·99)	
Narrow-spectrum antibiotics					
Cases *n* (%)	3,030 (42)	1,667 (23)	1,003 (14)	1,497 (21)	
Controls *n* (%)	18,255 (51)	8,310 (23)	3,933 (11)	5,317 (15)	
Multivariable OR (95% CI)	1·0 (ref)	1·21 (1·13, 1·30)	1·50 (1·37, 1·63)	1·57 (1·44, 1·70)	

Cumulative dispensations accrued from study baseline up until one year prior to diagnosis/match.

Abbreviations: OR - odds ratio, CI - confidence interval

[#]Includes ulcerative colitis, Crohn's disease, and IBD-unclassified

[†]Conditional logistic regression matched for age, sex, and county. Referent group is no antibiotic use of any kind.

[‡]Further adjusted for number of inpatient and outpatient encounters and education level

Table 4:

Overall antibiotic use and inflammatory bowel disease comparing cases and their unaffected siblings, 2007–2016

	Cumulative antibiotic use				
	No prior use	**1 prior dispensation**	**2 prior dispensations**	**≥3 prior dispensations**	***P*-trend**
Inflammatory bowel disease (IBD)[#]					
Cases, *n* (%)	6,502 (40)	3,407 (21)	2,170 (13)	4,274 (26)	
Siblings, *n* (%)	12,688 (44)	6,278 (22)	3,341 (12)	6,425 (22)	
Multivariable OR (95% CI)[≠]	1·0 (ref)	1·06 (1·01, 1·12)	1·32 (1·24, 1·41)	1·35 (1·28, 1·43)	<0·0001
Ulcerative colitis (UC)					
Cases, *n* (%)	4,428 (41)	2,279 (21)	1,392 (13)	2,739 (25)	
Siblings, *n* (%)	8,459 (45)	4,209 (22)	2,204 (11)	4,160 (22)	
Multivariable OR (95% CI)	1·0 (ref)	1·06 (0·99, 1·14)	1·23 (1·13, 1·34)	1·29 (1·20, 1·39)	<0·0001
Crohn's disease (CD)					
Cases, *n* (%)	2,036 (38)	1,117 (20)	762 (14)	1,514 (28)	
Siblings, *n* (%)	4,073 (43)	2,030 (21)	1,111 (12)	2,221 (24)	
Multivariable OR (95% CI)	1·0 (ref)	1·13 (1·02, 1·25)	1·41 (1·26, 1·58)	1·46 (1·23, 1·62)	<0·0001

Cumulative dispensations accrued from study baseline up until one year prior to case diagnosis.

Abbreviations: OR - odds ratio, CI - confidence interval

[#]Includes ulcerative colitis, Crohn's disease, and IBD-unclassified

[≠]Further adjusted for age, sex, county, number of inpatient and outpatient encounters, and education level