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The corresponding author (JFL) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Abbreviations:

CI, confidence interval; CRC, colorectal cancer; ESPRESSO, Epidemiology Strengthened by histoPathology Reports in Sweden; GI, gastrointestinal; IBD, inflammatory bowel disease; OR, odds ratio; SD, standard deviation; SnoMed, Systematized Nomenclature of Medicine.

Abstract

Background & Aims: Use of antibiotics affects the composition of the microbiome and might affect development of colorectal polyps, which are precursors to colorectal cancer.

Methods: We performed a nested case–control study in Sweden of 45,744 patients with a colorectal polyp (cases) in the nationwide gastrointestinal ESPRESSO histopathology cohort, using unaffected full siblings as controls (n=93,307). Polyps were classified by morphology SnoMed codes into conventional adenomas and serrated polyps. Through linkage to the Prescribed Drug Register, we assessed use and cumulative dispensations of antibiotic until one year prior to polyp diagnosis for cases and their sibling controls.

Results: During a median study period of 6.9 years, compared with non-users, users of antibiotics (28,884 cases [63.1%] and 53,222 sibling controls [57.0%]) had a higher risk of colorectal polyps. Risk increased with higher number of dispensations (odds ratio [OR] for ≥ 6 dispensations, 1.33; 95% CI, 1.25–1.43) ($P_{\text{trend}} < .0001$). We observed a stronger association with polyps for broad-spectrum antibiotics (odds ratio [OR], 1.23; 95% CI, 1.18–1.29) than for narrow-spectrum antibiotics (OR, 1.05; 95% CI, 1.01–1.10), and for tetracyclines and quinolones (OR, 1.21) than penicillin and other classes (ORs ranged from 1.04 to 1.16). The findings remained robust with several sensitivity analyses, including use of a 2-year lead-in period for antibiotic assessment and correction for misclassification in controls. Use of broad-spectrum antibiotics was more strongly associated with risk of serrated polyps (OR, 1.29; 95% CI, 1.21–1.38) compared with risk of conventional adenomas (OR, 1.17; 95% CI, 1.11–1.24). We found no differences in risk of colon vs rectal polyps with antibiotic use ($P_{\text{heterogeneity}} > 0.10$). We found

stronger associations for younger (<50 years) vs older adults (≥50 years) for users of quinolones, sulfonamides, trimethoprim, and cephalosporins ($P_{interaction}<0.001$).

Conclusions: In a nationwide case–control study in Sweden, after accounting for hereditary and early life environmental factors, antibiotic use was associated with increased risk of colorectal polyps. Our findings indicate a role for intestinal dysbiosis in early stages of colorectal carcinogenesis.

Key words: anti-aerobic, anaerobic, bacteria, sessile serrated polyp

Need to Know

Background: Use of antibiotics affects the composition of the microbiome and might affect development of colorectal polyps, precursors to colorectal cancer

Findings: A nationwide case–control study of 45,744 adults with a colorectal polyp and 93,307 unaffected full sibling controls found an 8% increase in risk of colorectal polyps associated with users of any antibiotics and a 33% increase in risk associated with at least 6 dispensations of antibiotics. Antibiotic use was more strongly associated with higher risk of serrated polyps than conventional adenomas.

Implications for patient care: Intestinal dysbiosis might contribute to early stages of colorectal carcinogenesis. Strategies should be developed to reduce these effects of antibiotics and prevent colorectal cancer.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death worldwide.¹ The overall death rate of CRC has been decreasing at the global level (-13.5% from 1990 to 2017),² likely driven by the increasing use of CRC screening tests. However, substantial increases in CRC mortality have been seen in less developed regions, particularly south Asia and central Latin America (20.4%). Moreover, an increasing trend of early-onset CRC that occurs in adults younger than 50 years has been noted across several regions.³ Although lifestyle factors, such as smoking, Western diet, and obesity, have an established role in CRC and may contribute to 40-60% of CRC cases and deaths in many countries,^{3,4} identifying other modifiable risk factors for CRC remains a priority to improve prevention efforts.

Increasing evidence suggests a role of the gut microbiota in initiation of CRC.⁵ Compositional shifts in the gut microbiota have been observed in patients with CRC precursors, namely colorectal polyps, compared to healthy individuals.^{6,7} In support of the role of dysbiosis in CRC, exposure to antibiotics have been associated with increased risk of CRC in several studies.⁸⁻¹³ However, the findings remain inconsistent, particularly for specific classes of antibiotics and the differences by tumor subsite. Moreover, it remains largely unknown whether antibiotics play a role in the early stage of CRC development.¹⁰

Therefore, to better understand the role of antibiotics in the development of CRC precursors, we performed a nationwide nested case-control study in Sweden among patients with a colorectal polyp and their unaffected full sibling controls. We used sibling controls to reduce confounding by hereditary and shared environmental factors.

Materials and methods

Study population

Sweden has a public health care system with universal coverage. Individual-level data from various national registries were linked based on the unique personal identity number assigned at birth to all Swedish residents.¹⁴ Participants with polyps were drawn from the ESPRESSO study (Epidemiology Strengthened by histoPathology Reports in Sweden) that included gastrointestinal (GI) biopsies from all 28 pathology departments in Sweden between 1965 and 2017.¹⁵ In ESPRESSO, histopathologic findings were defined by codes of topography and morphology (a Swedish modification of the Systematized Nomenclature of Medicine [SnoMed] coding system). We used topography codes of T67 (for colon) and T68 (for rectum) in combination with SnoMed codes to identify colorectal polyps.¹⁶ For conventional adenomas, we used the SnoMed codes of M82100 (tubular adenoma), M82630 (tubulovillous adenoma), and M82611 (villous adenoma). Serrated polyps included hyperplastic polyps and sessile serrated polyps (SSPs). We used the SnoMed code of M72040 for hyperplastic polyps, and used a combination of SnoMed codes (M82160, M82130, and M72041) and free text search for SSPs. The accuracy of polyp identification has been described in our previous studies.¹⁶⁻¹⁸

Information on antibiotic use was derived from the Swedish Prescribed Drug Register, which has collected information on all medications prescribed to the entire Swedish population since July 1, 2005.¹⁹ To ensure that we had at least one-year information on antibiotic use, we identified

participants with the first diagnosis of colorectal polyps aged at least 18 years in ESPRESSO since July 1, 2006. To minimize the influence of hereditary predisposition and shared early life exposures, we selected unaffected full siblings of participants with polyps as the control group. We excluded individuals who had a history of CRC. To reduce the influence of missed cancers at the time of endoscopy, we also excluded individuals who had a diagnosis of CRC within the first 6 months after the diagnosis of polyps for cases and their sibling controls. After further excluding individuals with inflammatory bowel disease (IBD), unspecified histology of polyps, and erroneous records on the date of diagnosis, and those without sibling controls, a total of 45,744 polyp cases and 93,307 matched sibling controls were included in the study (see flowchart in **Figure 1**). The mean number of sibling controls per case was 2.0 (standard deviation [SD], 1.4). The study was approved by the Stockholm Ethics Review Board. Informed consent was waived by the board since the study was strictly register-based.²⁰

Exposure and covariate assessment

We identified antibiotic use from the register using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes for the therapeutic subgroup of antibacterials approved for systemic usage. To minimize reverse causality, we assessed the total number of antibiotic dispensations up to one year prior to the diagnosis of polyps for cases and their sibling controls. We examined antibiotics according to class (penicillin, cephalosporins, macrolides, fluoroquinolones, tetracyclines, sulfonamides, and others) and categorization (anti-anaerobic and anti-aerobic; narrow and broad-spectrum; **Supplementary Table 1**). Details of covariate assessment are described in the **Supplementary Methods**.

Statistical analysis

We calculated means (SD) for continuous variables and percentages for categorical variables among cases and controls. We used conditional logistic regression to calculate the odds ratio (OR) and 95% confidence interval (CI) of colorectal polyps according to use of antibiotics (yes, no) and cumulative dispensations (0, 1, 2, 3-5, and ≥ 6). We considered two models: model 1 was adjusted for age (continuous), sex (binary), and year of birth (continuous); and model 2 was further adjusted for income levels (quintiles), education (9 years or less, 10-12 years, >12 years, missing), total number of prior clinic visits (quintiles), Charlson comorbidity score (continuous), and major comorbidities with a prevalence of at least 1% (all binary, including diabetes, cardiovascular disease, non-colorectal cancer, liver disease, chronic pulmonary disease, connective tissue disease, and peptic ulcer disease). P_{trend} was calculated using the number of dispensations as a continuous variable. We also conducted several sensitivity analyses. First, to minimize confounding by utilization of endoscopic exams, we assessed use of endoscopic exams at the time of polyp diagnosis for cases and their matched sibling controls using the established procedure codes in the patient registries²¹ and included this variable in the multivariable model. Second, given the potential confounding effect by smoking and that patients with chronic pulmonary disease are frequently prescribed with broad-spectrum antibiotics, particularly tetracyclines, we performed a sensitivity analysis by excluding individuals with a history of chronic pulmonary disease. Third, because diverticulitis relates to antibiotic prescription, inflammation in the colorectum and possibly polyp diagnostics, we excluded individuals with diverticular disease in another sensitivity analysis. Fourth, to minimize reverse causality, we excluded antibiotic dispensations within 2 years of polyp diagnosis. Finally, because polyps are

common and sibling controls may have undetected polyps due to lack of national screening programs in Sweden, we performed two additional analyses to account for outcome misclassification in sibling controls using the method proposed by Fox et al²² and to assess the relationship between antibiotic use and polyp risk according to the likelihood of outcome misclassification in sibling controls (details are described in the Supplementary Materials). All these sensitivity analyses were adjusted for the same set of covariates as in the primary analysis.

Furthermore, we examined the risk of polyps according to type of antibiotics and major individual classes of antibiotics. We performed subgroup analyses according to histology (conventional adenomas and serrated polyps) and sublocation (colon and rectum) of polyps, and calculate the *P* for heterogeneity using the contrast test method.²³ For conventional adenomas, we further examined the associations according to the most advanced histology a patient had (the precedence order being villous adenoma [n=397], tubulovillous adenoma [n=7,784], and tubular adenoma [n=15,716]). Given the speculated role of the gut microbiota in early-onset CRC, we conducted a secondary analysis by stratifying according to age. We calculated *P* for interaction using Wald test for the product term between age and antibiotic use.

We used SAS 9.4 for the analyses. All statistical tests were two-sided with the significance level of 0.05.

Results

Table 1 shows the basic characteristics of participants. The mean age was 60.6 (SD, 11.8) years for cases and 60.8 (11.8) years for sibling controls. During a median follow-up of 6.9 years, 28,884 cases (63.1%) and 53,222 sibling controls (57.0%) had at least one dispensation of antibiotics. Among antibiotic users in cases, the interval between the first recorded dispensation and polyp diagnosis ranged from 1.0 to 12.8 years (median, 5.0 years; interquartile range, 3.0-7.2 years). There were more users for narrow- than broad-spectrum antibiotics (47% vs. 34% in controls) and for anti-aerobic than anti-anaerobic antibiotics (56% vs. 8% in controls). Common classes of antibiotics included penicillin, tetracyclines, and quinolones. Cases had a higher number of clinic visits and comorbidities than sibling controls.

Table 2 shows the association of antibiotic use with risk of colorectal polyps. Compared with non-users, users of antibiotics had a higher risk of colorectal polyps. The OR (95% CI) was 1.31 (1.26-1.36) in the model adjusted for age, sex and birth year only; and attenuated to 1.08 (1.04-1.13) after further adjustment for other covariates. The change appeared to be due to a cumulative effect of multiple covariates rather than driven by individual covariates. A stronger association was found for broad-spectrum (multivariable OR=1.23, 95% CI=1.18-1.29) compared with narrow-spectrum antibiotics (1.05, 1.01-1.10), and for tetracyclines (1.21, 1.16-1.27) and quinolones (1.21, 1.14-1.28) compared with penicillin (1.04, 1.00-1.09) and other classes.

We conducted a sensitivity analysis by accounting for potential misclassification of polyp status in controls (**Supplementary Table 3**). The associations of total and different classes of antibiotics with polyp risk were all strengthened, with the OR ranged from 1.72 to 2.14. The OR was 1.84 (95% CI, 1.17-2.95) for any antibiotics and 2.13 (95% CI, 1.33-3.56) for broad-spectrum antibiotics. In the sensitivity analysis further adjusted for use of prior endoscopic

exams (8.9% in cases and 0.9% in controls), similar results were observed (OR for any antibiotics=1.07, 95% CI=1.02-1.12; OR for broad-spectrum antibiotics=1.21, 95% CI=1.16-1.27). Moreover, the results did not essentially change, after excluding individuals with a history of chronic pulmonary disease who were more likely to use tetracyclines and other broad-spectrum antibiotics (OR for broad-spectrum antibiotics=1.18, 95% CI=1.13-1.24; OR for tetracyclines=1.16, 95% CI=1.10-1.22), excluding individuals with diverticular disease (OR for broad-spectrum antibiotics=1.18, 95% CI=1.13-1.23), and excluding antibiotic dispensations within 2 years of polyp diagnosis (OR for broad-spectrum antibiotics=1.15, 95% CI=1.08-1.22).

When polyps were classified into conventional adenomas and serrated polyps, antibiotic use showed a generally stronger association with serrated polyps than conventional adenomas (**Figure 2A**). The difference was particularly prominent for broad-spectrum antibiotics (OR for serrated polyps=1.29, 95% CI=1.21-1.38; OR for conventional adenomas=1.17, 95% CI=1.11-1.24; $P_{\text{heterogeneity}}=0.04$) and anti-anaerobic antibiotics (OR for serrated polyps=1.20, 95% CI=1.08-1.34; OR for conventional adenomas=1.02, 95% CI=0.93-1.12; $P_{\text{heterogeneity}}=0.03$). No differences were observed for the association of antibiotics with colon or rectal polyps (**Figure 2B**). When conventional adenomas were further classified by histology (**Supplementary Figure 1**), we found that most of the antibiotic groups tended to be more strongly associated with higher risk of villous adenomas than tubulovillous or tubular adenomas, although the confidence interval for villous adenomas were wide due to the limited case number (n=397).

A dose-response relationship was observed when antibiotic use was assessed by cumulative dispensations ($P_{\text{trend}}<0.0001$, **Table 3**). The increased risk of polyps did not emerge until 3-5 dispensations of antibiotics (OR=1.19, 95% CI=1.12-1.26) and became higher with at least 6 dispensations (OR=1.33, 95% CI=1.25-1.43). Again, the associations appeared stronger for

broad-spectrum than narrow-spectrum antibiotics. A statistically significant trend was found for anti-anaerobic but not anti-aerobic antibiotics, although the number of cases with more than two dispensations of anti-anaerobic antibiotics was small (n=572). The risk of polyps also increased with more dispensations of penicillin, tetracyclines, and quinolones ($P_{\text{trend}} < 0.0001$), but not with other classes.

In the stratified analysis by age, although the P for interaction was less than 0.05 for overall antibiotic use and several individual categories of antibiotics, most of the differences in ORs were fairly modest, except for a particularly stronger association with increased risk of polyps in younger than older adults for quinolones, sulfonamides and trimethoprim, and cephalosporins ($P_{\text{interaction}} < 0.001$, **Supplementary Figure 2**). For example, the OR (95% CI) for quinolones was 1.33 (1.08-1.62) in adults aged <50 years and 1.16 (1.01-1.33) in ≥ 70 years; the OR for sulfonamides and trimethoprim was 1.37 (1.08-1.75) in <50 years and 1.10 (0.94-1.29) in ≥ 70 years.

Discussion

In this nationwide case-control study, even after accounting for hereditary and early life environmental factors, we found that patients with a colorectal polyp were more likely to have been exposed to antibiotics than their unaffected siblings. The risk elevation of colorectal polyps associated with antibiotic use was higher for broad-spectrum compared to narrow-spectrum antibiotics, and for tetracyclines and quinolones compared to penicillin and other classes. The

associations became stronger after accounting for potential misclassification in the control group due to the unknown polyp status. Our findings complement earlier reports of an association between antibiotics and increase risk of CRC and provide novel evidence for the role of the gut dysbiosis in early development of colorectal neoplasia.

Exposure to antibiotics induces pervasive changes in the gut microbial community. Although the overall community can be largely restored within 4 weeks after antibiotic treatment, the recovery varies between individuals and classes of antibiotics and is often incomplete.^{24,25} Particularly, repeated exposures to antibiotics can lead to a persistent regime shift.²⁴ A recent study in the UK reported that use of antibiotics, primarily anti-aerobic antibiotics, was associated with an increased risk of colon cancer, but a lower risk of rectal cancer.¹³ In contrast, anti-anaerobic, but not anti-aerobic, antibiotics were associated with a higher risk of both colon and rectal cancer in a case-control study in patients with type 2 diabetes in Taiwan.¹² Increasing data suggest that the pro-CRC effect of gut dysbiosis starts early in carcinogenesis. Patients with colorectal polyps have already demonstrated substantial shifts in the composition of the gut microbiota.^{6,7} However, existing epidemiologic evidence is largely cross-sectional and unable to address whether microbial alterations are a cause or consequence of colorectal carcinogenesis.⁵ Moreover, given the long latency period of CRC and that infection can be associated with the clinical presentation of CRC, short-term studies using CRC as the endpoint are prone to reverse causality. Therefore, to shed light on the role of gut microbiota in initiation of colorectal carcinogenesis, we focused on generally asymptomatic CRC precursors and examined antibiotic exposures at a median of 5 years prior to diagnosis of colorectal polyps. By further excluding polyp cases diagnosed within one year after exposure assessment, we minimized any influence of reverse causality. In line with our findings, prior evidence in CRC also suggest an early-acting effect of

antibiotics. Two studies found that use of antibiotics more than 10 years before the cancer diagnosis were more strongly associated with increased CRC risk, compared to antibiotic use within 10 years before CRC diagnosis.^{8, 13} For conventional adenomas, we found that antibiotics tended to be more strongly associated with villous adenomas than tubular and tubulovillous adenomas, indicating potential role of antibiotics in the malignant transformation of precancers.

Furthermore, we found a stronger association for broad-spectrum than narrow-spectrum antibiotics. This is not unexpected, since antibiotics with broad-spectrum activity can influence a wide variety of microbial populations and produce long-lasting effects on the microbiota.²⁶

Among the broad-spectrum antibiotics, we found a particularly strong association for tetracycline and quinolone family of antibiotics with increased risk of both colon and rectal polyps. These findings contrast with a recent study that observed a beneficial association of tetracyclines with rectal cancer.¹³ While there is some evidence for the anti-inflammatory effects of tetracyclines, doxycycline, the most commonly used agent within the tetracycline family in our study population, increased colonic tumor multiplicity and promoted metastasis in an *in vivo* study.²⁷ Moreover, exposure to tetracyclines has been associated with increased risk of other GI disorders, such as IBD and irritable bowel syndrome.^{28, 29} As for quinolones, these drugs are commonly prescribed for GI infections and have been associated with higher CRC risk in several prior studies.^{8, 9, 11}

CRC is a heterogeneous disease. Conventional adenomas and serrated polyps represent two distinct groups of precursors for the adenoma-carcinoma pathway and the serrated pathway, respectively.³ Compared to other CRCs, serrated CRCs are more likely to have *BRAF* mutation and microsatellite instability. Some risk factors, such as smoking and obesity, have been more strongly associated with serrated polyps than conventional adenomas.³⁰ Positivity of *F*.

nucleatum, one of the most studied pro-CRC microbes, has been associated with clinicopathological and molecular features of serrated neoplasia.⁵ Despite these data, no study has yet examined whether antibiotic use was differentially associated with adenomatous versus serrated colorectal neoplasia. In the current study, we found that antibiotic use was more strongly associated with increased risk of serrated polyps than conventional adenomas (for 11 out of the 12 studied antibiotic categories, **Figure 2A**), suggesting a particularly important role of gut dysbiosis in the serrated pathway of colorectal neoplasia. Further studies assessing CRC by molecular features will be important to better understand the mechanisms through which gut microbiota influences CRC.

Strengths of our study include the use of a large, nationally representative sample, a validated approach for polyp ascertainment, and linkage of the national drug registry that has virtually complete information on all drug dispensations, including antibiotics. Moreover, our use of full sibling controls eliminated any confounding effect of ethnicity and hereditary predisposition and minimized the confounding by shared environmental factors.

Our study also has several limitations. First, residual confounding cannot be excluded, particularly because we lacked data on indications for antibiotic use and major CRC risk factors, such as smoking and adiposity status. However, our observations for the dose-response relationship and differences in the associations across classes of antibiotics that have common indications suggest that confounding by indication is unlikely to fully explain our findings. Furthermore, we adjusted for the Charlson comorbidity score and several major individual comorbidities that are strongly associated with smoking and obesity. Second, the Prescribed Drug Register does not contain antibiotics data from inpatient care or use of parenteral antibiotics. However, more than 75% of parenteral antibiotics in Sweden consisted of

benzylpenicillin³¹ that has a limited impact on the microbiota.³² Third, because the Drug Register did not start until 2005, we were unable to assess use of antibiotics in the remote past. However, this is less of a concern for studies of colorectal polyps, which represent the very early alterations in the continuum of colorectal carcinogenesis. Fourth, the polyp status of sibling controls is largely unknown due to the lack of endoscopic screening programs. However, any misclassification in the control group could only have attenuated our effect estimates, as demonstrated in our sensitivity analysis. Finally, the prescription patterns may differ between countries and thus the generalizability of our findings needs to be confirmed.

In conclusion, antibiotic use was associated with increased risk of colorectal polyps. The association was stronger for broad-spectrum antibiotics and tetracyclines and quinolones. A greater risk elevation associated with antibiotics was also noted for serrated polyps compared to conventional adenomas. Our findings support a role of the gut dysbiosis in early colorectal carcinogenesis.

Figure Legends

Figure 1. Flowchart of participant selection

Abbreviations: ESPRESSO, Epidemiology Strengthened by histoPathology Reports in Sweden;
IBD, inflammatory bowel disease.

Figure 2. Multivariable association between antibiotic use and risk of conventional adenomas and serrated polyps (A), and colon and rectal polyps (B).

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Table 1. Basic characteristics of study participants

	Cases (n=45,744)	Sibling Controls (n=93,307)
Age, year, mean (SD)	60.6 (11.8)	60.8 (11.8)
<50 years	7,884 (17.2)	15,837 (17.0)
≥50, <60 years	9,047 (19.8)	22,007 (23.6)
≥60, <70 years	18,330 (40.1)	34,300 (36.8)
≥70 years	10,483 (22.9)	21,163 (22.7)
Women, n (%)	23,564 (51.5)	45,851 (49.1)
Birth year, mean (SD)	1951 (12)	1951 (12)
Year of diagnosis, n (%)		
2006-2007	4,481 (9.8)	-
2008-2010	12,316 (26.9)	-
2011-2013	14,050 (30.7)	-
≥2014	14,897 (32.6)	-
Total number of prior clinic visit, mean (SD)	15.5 (16.3)	8.8 (12.9)
Antibiotics dispensations, n (%)		
No	16,860 (36.9)	40,085 (43.0)
1	8,094 (17.7)	17,583 (18.8)
2	5,629 (12.3)	10,970 (11.8)
3-5	8,563 (18.7)	14,719 (15.8)
≥6	6,598 (14.4)	9,950 (10.7)
Use of narrow-spectrum antibiotics, n (%)	23,465 (51.3)	43,453 (46.6)
Use of broad-spectrum antibiotics, n (%)	19,094 (41.7)	31,788 (34.1)
Use of anti-aerobic antibiotics, n (%)	28,437 (62.2)	52,267 (56.0)
Use of anti-anaerobic antibiotics, n (%)	4,330 (9.5)	7,382 (7.9)
Use of antibiotics by class, n (%)		
Penicillin	22,414 (49.0)	41,419 (44.4)
Tetracyclines	11,670 (25.5)	18,578 (19.9)
Quinolones	6,701 (14.7)	10,672 (11.4)
Macrolides	5,262 (11.5)	8,700 (9.3)
Sulfonamides and trimethoprim	3,854 (8.4)	6,278 (6.7)
Cephalosporins and other non-penicillin beta-lactams	2,680 (5.9)	4,586 (4.9)
Other classes	2,959 (6.5)	5,124 (5.5)
Charlson comorbidity score, mean (SD)*	0.8 (1.1)	0.5 (1.0)
Individual comorbidity, n (%)*		

Myocardial Infarction	1,967 (4.3)	3,883 (4.2)
Congestive Heart Failure	1,347 (2.9)	2,114 (2.3)
Peripheral Vascular Disease	1,198 (2.6)	1,275 (1.4)
Cerebrovascular Disease	2,655 (5.8)	4,791 (5.1)
Dementia	137 (0.3)	402 (0.4)
Chronic Pulmonary Disease	4,246 (9.3)	5,208 (5.6)
Connective Tissue Disease-Rheumatic Disease	1,355 (3.0)	1,205 (1.3)
Peptic Ulcer Disease	1,352 (3.0)	1,224 (1.3)
Mild Liver Disease	852 (1.9)	1,012 (1.1)
Diabetes without complications	3,092 (6.8)	3,608 (3.9)
Diabetes with complications	1,099 (2.4)	724 (0.8)
Paraplegia and Hemiplegia	264 (0.6)	467 (0.5)
Renal Disease	714 (1.6)	782 (0.8)
Cancer	14,006 (30.6)	18,690 (20.0)
Moderate or Severe Liver Disease	259 (0.6)	339 (0.4)
Metastatic Carcinoma	428 (0.9)	1,870 (2.0)
AIDS/HIV	34 (0.1)	51 (0.1)

* The complete list of ICD codes for comorbidities is presented in Supplementary Table 2.

Table 2. Association between use of antibiotics and risk of colorectal polyps

	Nonusers		Users		OR (95% CI)		<i>P</i> value†
	No. of cases	No. of sibling controls	No. of cases	No. of sibling controls	Model 1*	Model 2†	
All antibiotics	16,860	40,085	28,884	53,222	1.31 (1.26-1.36)	1.08 (1.04-1.13)	0.0003
Narrow-spectrum antibiotics	22,279	49,854	23,465	43,453	1.23 (1.18-1.27)	1.05 (1.01-1.10)	0.01
Broad-spectrum antibiotics	26,650	61,519	19,094	31,788	1.40 (1.35-1.46)	1.23 (1.18-1.29)	<0.0001
Anti-aerobic antibiotics	17,307	41,040	28,437	52,267	1.30 (1.25-1.35)	1.08 (1.04-1.13)	0.0003
Anti-anaerobic antibiotics	41,414	85,925	4,330	7,382	1.23 (1.16-1.31)	1.10 (1.03-1.18)	0.006
Penicillin	23,330	51,888	22,414	41,419	1.21 (1.17-1.26)	1.04 (1.00-1.09)	0.04
Tetracyclines	34,074	74,729	11,670	18,578	1.36 (1.30-1.42)	1.21 (1.16-1.27)	<0.0001
Quinolones	39,043	82,635	6,701	10,672	1.36 (1.29-1.44)	1.21 (1.14-1.28)	<0.0001
Macrolides	40,482	84,607	5,262	8,700	1.28 (1.21-1.36)	1.14 (1.08-1.22)	<0.0001
Sulfonamides and trimethoprim	41,890	87,029	3,854	6,278	1.26 (1.18-1.35)	1.16 (1.08-1.24)	<0.0001
Cephalosporins and other non-penicillin beta-lactams	43,064	88,721	2,680	4,586	1.24 (1.15-1.34)	1.13 (1.04-1.23)	0.005
Other classes	42,785	88,183	2,959	5,124	1.15 (1.06-1.24)	1.07 (0.99-1.16)	0.10

*Conditional logistic regression was used with adjustment for age (continuous), sex (binary), and year of birth (continuous).

†Multivariable model was further adjusted for income levels (quintiles), education (9 years or less, 10-12 years, >12 years, missing), total number of prior clinic visits (quintiles), Charlson comorbidity score (continuous), and major comorbidities (all binary, including diabetes, cardiovascular disease, non-colorectal cancer, liver disease, chronic pulmonary disease, connective tissue disease, and peptic ulcer disease).

Table 3. Association between cumulative dispensations of antibiotics and risk of colorectal polyps

	No prior use	1 prior dispensation	2 prior dispensations	3-5 prior dispensations	≥6 prior dispensations	<i>P</i> _{trend}
All antibiotics						
No. of cases	16,860	8,094	5,629	8,563	6,598	
No. of sibling controls	40,085	17,583	10,970	14,719	9,950	
OR (95% CI)*	1 (ref)	0.95 (0.90-1.01)	1.05 (0.98-1.12)	1.19 (1.12-1.26)	1.33 (1.25-1.43)	<0.0001
Narrow-spectrum antibiotics						
No. of cases	22,279	9,482	5,267	5,982	2,734	
No. of sibling controls	49,854	19,115	9,906	10,152	4,280	
OR (95% CI)*	1 (ref)	1.00 (0.95-1.05)	1.02 (0.96-1.09)	1.17 (1.10-1.25)	1.19 (1.09-1.30)	0.03
Broad-spectrum antibiotics						
No. of cases	26,650	8,184	4,196	4,424	2,290	
No. of sibling controls	61,519	15,269	6,714	6,543	3,262	
OR (95% CI)*	1 (ref)	1.12 (1.06-1.18)	1.32 (1.23-1.42)	1.37 (1.28-1.47)	1.38 (1.25-1.52)	<0.0001
Anti-aerobic antibiotics						
No. of cases	17,307	8,271	5,679	8,386	6,101	
No. of sibling controls	41,040	17,904	10,938	14,289	9,136	
OR (95% CI)*	1 (ref)	0.95 (0.90-1.01)	1.05 (0.98-1.11)	1.19 (1.13-1.26)	1.33 (1.24-1.43)	<0.0001
Anti-anaerobic antibiotics						
No. of cases	41,414	2,965	793	439	133	
No. of sibling controls	85,925	5,189	1,229	728	236	
OR (95% CI)*	1 (ref)	1.08 (1.00-1.17)	1.20 (1.03-1.39)	1.18 (0.97-1.44)	0.76 (0.53-1.10)	0.36
Penicillin						
No. of cases	23,330	9,487	5,186	5,633	2,108	
No. of sibling controls	51,888	19,149	9,660	9,383	3,227	
OR (95% CI)*	1 (ref)	0.98 (0.93-1.03)	1.06 (0.99-1.13)	1.14 (1.07-1.22)	1.23 (1.11-1.36)	<0.0001
Tetracyclines						
No. of cases	34,074	6,685	2,423	1,899	663	
No. of sibling controls	74,729	11,554	3,509	2,589	926	
OR (95% CI)*	1 (ref)	1.13 (1.07-1.19)	1.33 (1.22-1.46)	1.37 (1.24-1.52)	1.43 (1.20-1.69)	<0.0001
Quinolones						
No. of cases	39,043	3,902	1,443	1,049	307	

No. of sibling controls	82,635	6,354	2,211	1,607	500	
OR (95% CI)*	1 (ref)	1.20 (1.11-1.29)	1.32 (1.18-1.49)	1.16 (1.01-1.32)	1.12 (0.88-1.42)	<0.0001
Macrolides						
No. of cases	40,482	3,453	961	630	218	
No. of sibling controls	84,607	5,903	1,506	949	342	
OR (95% CI)*	1 (ref)	1.12 (1.04-1.21)	1.15 (1.00-1.32)	1.33 (1.12-1.57)	1.01 (0.76-1.36)	0.08
Sulfonamides and trimethoprim						
No. of cases	41,890	2,617	657	434	146	
No. of sibling controls	87,029	4,159	1,109	751	259	
OR (95% CI)*	1 (ref)	1.19 (1.10-1.30)	1.09 (0.92-1.28)	1.09 (0.89-1.34)	1.06 (0.76-1.48)	0.31
Cephalosporins and other non-penicillin beta-lactams						
No. of cases	43,064	2,045	408	176	51	
No. of sibling controls	88,721	3,541	663	317	65	
OR (95% CI)*	1 (ref)	1.17 (1.07-1.29)	1.01 (0.82-1.25)	0.89 (0.64-1.22)	1.11 (0.57-2.18)	0.09
Other classes						
No. of cases	42,785	1,786	502	415	256	
No. of sibling controls	88,183	3,098	862	725	439	
OR (95% CI)*	1 (ref)	1.11 (1.00-1.23)	1.10 (0.91-1.33)	1.04 (0.84-1.27)	0.83 (0.64-1.08)	0.20

*Multivariable conditional logistic regression model was adjusted for age (continuous), sex (binary), year of birth (continuous), income levels (quintiles), education (9 years or less, 10-12 years, >12 years, missing), total number of prior clinic visits (quintiles), Charlson comorbidity score (continuous), and major comorbidities (all binary, including diabetes, cardiovascular disease, non-colorectal cancer, liver disease, chronic pulmonary disease, connective tissue disease, and peptic ulcer disease).

Figure 1

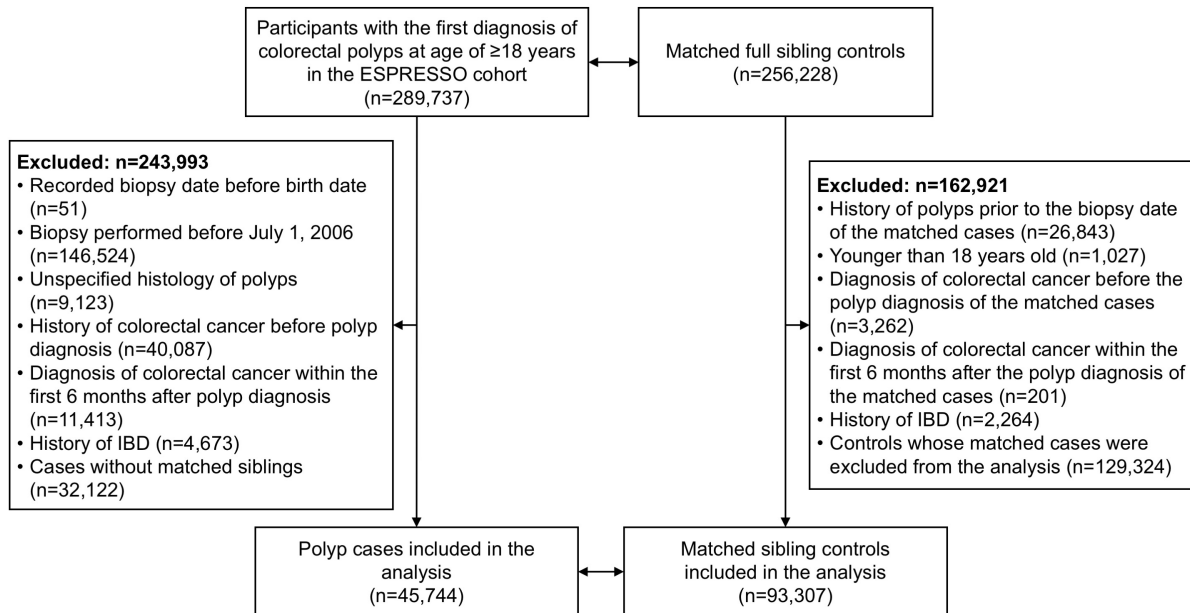


Figure 2A

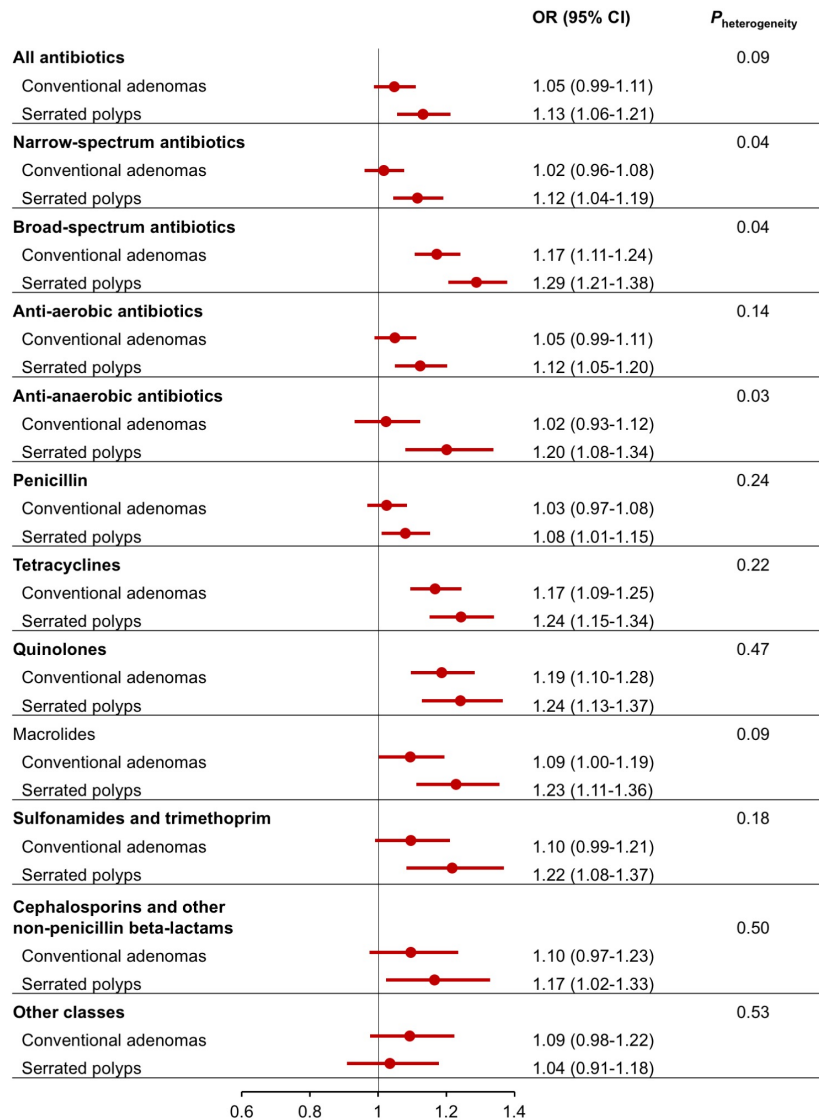
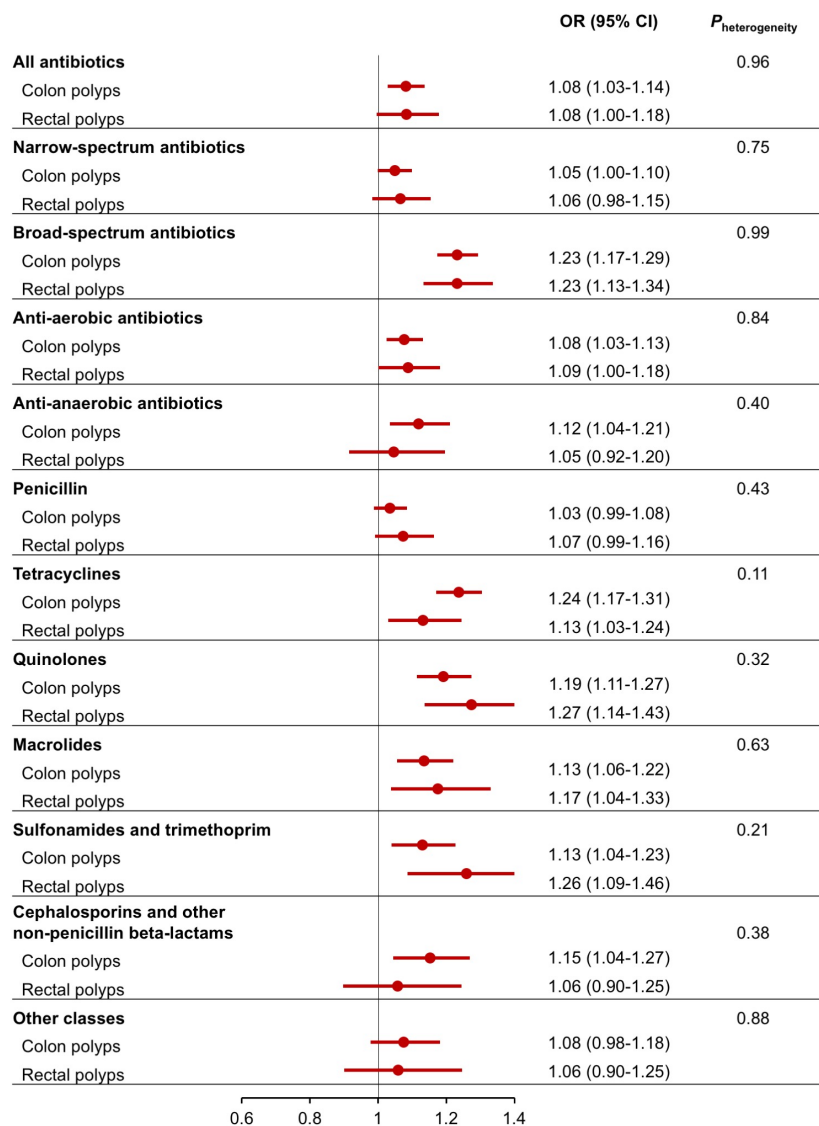


Figure 2B



What You Need to Know

Background: Use of antibiotics affects the composition of the microbiome and might affect development of colorectal polyps, precursors to colorectal cancer

Findings: A nationwide case–control study of 45,744 adults with a colorectal polyp and 93,307 unaffected full sibling controls found an 8% increase in risk of colorectal polyps associated with users of any antibiotics and a 33% increase in risk associated with at least 6 dispensations of antibiotics. Antibiotic use was more strongly associated with higher risk of serrated polyps than conventional adenomas.

Implications for patient care: Intestinal dysbiosis might contribute to early stages of colorectal carcinogenesis. Strategies should be developed to reduce these effects of antibiotics and prevent colorectal cancer.