HHS Public Access

Author manuscript

Gut. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

Gut. 2023 April ; 72(4): 663–670. doi:10.1136/gutjnl-2022-327845.

Antibiotic use as a risk factor for inflammatory bowel disease across the ages: a population-based cohort study

Adam S Faye[1], **Kristine Højgaard Allin**[2,3], **Aske T Iversen**[2], **Manasi Agrawal**[2,4], **Jeremiah Faith**[5], **Jean-Frederic Colombel**[4], **Tine Jess**[2,3]

[1]NYU Departments of Medicine & Population Health, NYU Grossman School of Medicine, New York, New York, USA

[2]Center for Molecular Prediction of Inflammatory Bowel Disease, Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark

[3]Department of Gastroenterology and Hepatology, Aalborg University, Aalborg, Denmark

[4]The Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[5]Icahn School of Medicine at Mount Sinai, New York, New York, USA

Abstract

Background—There is an increasing incidence of inflammatory bowel disease (IBD) for which environmental factors are suspected. Antibiotics have been associated with development of IBD in earlier generations, but their influence on IBD risk in adults is uncertain.

Objective—To assess the impact of antibiotic exposure, including dose–response, timing and antibiotic class, on the risk of IBD in all individuals aged ≥10 years.

Correspondence to: Dr Adam S Faye, Medicine/Population Health, NYU Langone Health, New York, NY 10016, USA; adam.faye@nyulangone.org, @AdamFayeMD.

Contributors ASF: Conception and design of the study, data analysis and interpretation, drafting and revision of article and final approval. KHA, ATI: Conception and design of the study, acquisition of data, statistical analysis and interpretation of data, revision of article and final approval. MA: Conception and design of the study, data interpretation, revision of article and final approval. JF: Conception of the study, data analysis and interpretation of data, revision of article and final approval. J-FC: Conception and design of the study, data analysis and interpretation of data, revision of article, and final approval. TJ: Conception and design of the study, statistical analysis and interpretation of data, guarantor, revision of the article and final approval.

Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2022-327845).

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Ethics approval This study involves human participants and was approved by Danish Data Protection Agency, #2015-57-0102. Existing dataset with millions of patients (some deceased)

Design—Using Denmark nationwide registries, a population-based cohort of residents aged ≥10 years was established between 2000 and 2018. Incidence rate ratios (IRRs) for IBD following antibiotic exposure were calculated using Poisson regression.

Results—There were a total of 6 104 245 individuals, resulting in 87 112 328 person-years of follow-up, and 52 898 new cases of IBD. Antibiotic exposure was associated with an increased risk of IBD as compared with no antibiotic exposure for all age groups, although was greatest among individuals aged 40–60 years and ≥60 years (age 10–40 years, IRR 1.28, 95% CI 1.25 to 1.32; age 40–60 years, IRR 1.48, 95% CI 1.43 to 1.54; age ≥60 years, IRR 1.47, 95% CI 1.42 to 1.53). For all age groups a positive dose–response was observed, with similar results seen for both ulcerative colitis and Crohn's disease. The highest risk of developing IBD was seen 1–2 years after antibiotic exposure, and after use of antibiotic classes often prescribed to treat gastrointestinal pathogens.

Conclusion—Antibiotic exposure is associated with an increased risk of IBD, and was highest among individuals aged 40 years and older. This risk increased with cumulative antibiotic exposure, with antibiotics targeting gastrointestinal pathogens and within 1–2 years after antibiotic exposure.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease of the bowel, comprising two main subtypes: Crohn's disease (CD) and ulcerative colitis (UC).[1 2] Globally, IBD affects close to seven million individuals, with this number expected to rise in the next decade.[3 4] In order to shift this trajectory, careful consideration of risk factors leading to its development need to be explored.[4–7]

IBD is thought to result from a complex interplay of genetics and environmental factors. The risk attributable to each, however, appears to vary over time, as younger adults are more likely to have a positive family history for IBD as compared with older adults who develop new-onset IBD. The lower prevalence of genetic risk factors in older adults with IBD highlights the important role that the environment plays as people age.[8 9] Despite this, there are scant data assessing the changing role of environmental factors in the development of IBD.

One risk factor that has been associated with the development of IBD in younger individuals is the exposure to antibiotics. In a Danish national cohort study, antibiotic use early in life increased the risk of developing IBD in children by almost twofold.[10] This risk was predominantly driven by those diagnosed with CD as compared with UC, and was strongest within the first few months of use. In a nationwide case–control study in Sweden, similar results were seen, with antibiotic use increasing the risk of IBD development by almost twofold.[11] On subgroup analysis, cumulative antibiotic use was also associated with the development of IBD among older adults, but only when two or more courses had been previously prescribed.

Therefore, using a nationwide unselected population-based study design, we aimed to assess the risk of IBD among all individuals aged ≥10 years following treatment with antibiotics,

including evaluation of the (1) dose–response relationship between antibiotic exposure and development of IBD, (2) risk of CD and UC separately, (3) impact of antibiotic timing on the development of IBD and (4) the role of different antibiotic classes on the development of IBD.

MATERIALS AND METHODS

Study population

The Danish Civil Registration System (CRS) contains demographic information on all residents living in Denmark.[12] Each person is indexed by a unique identifier (CRS number), allowing for linkage to other population-based Danish registers. Using the CRS, we identified a unique cohort of residents aged ≥10 years between 1 January 2000 and 31 December 2018, who had not been previously diagnosed with IBD. Individuals were followed up from the earliest date at which the following criteria were satisfied: age ≥10 years and at least 5 years residence in Denmark (in order to assess antibiotic exposure). If individuals immigrated several times but satisfied the above criteria, only the first period was considered.

Antibiotic exposure

The Danish National Prescription Register is linked to the CRS and contains individual-level data for all prescribed medications redeemed at Danish community pharmacies since 1995, representing approximately 90% of all antimicrobial prescriptions in Denmark.[13] Medications are coded according to the Anatomical Therapeutic Chemical system.[14] Available data include medication identification codes and dates the prescriptions were filled. As in the study by Hviid *et al*, the antibiotic fill date was considered the date of antibiotic use.[10] Antibiotic dose–response was quantified based on number of courses, with prescriptions from the same class of antibiotics within 1 month of the previous use considered as one course.

The number of courses of antibiotics was considered a time-varying variable, with each course of antibiotics only contributing a risk time for the 1 to 5 years following exposure. The reasoning for including the 1-year lag time from antibiotic exposure was to limit the potential for reverse causality, which is in accordance with prior work.[11 15] A sensitivity analysis in which the lag time was extended to 2 years was also performed to further limit this potential. Antibiotics prescribed in Denmark were categorised by class into nitrofurantoin, narrow spectrum penicillin, extended spectrum penicillin, sulfonamides, tetracyclines, macrolides or other when there was insufficient power to assess individual antibiotics or classes, and analysed.[15] Nitroimidazoles and fluoroquinolones were also included, as these two classes are commonly prescribed to treat gastrointestinal pathogens (online supplemental table 1). In the analysis of specific types of antibiotic exposures, individuals with course of antibiotics contributed person-time according to the most recent course.[10 11]

Inflammatory bowel disease

The Danish National Patient Register, which contains data on all hospitalisations, emergency room visits and outpatient visits in Denmark since 1995 using International Classification of Diseases 8 or 10th revision (ICD-8/10) codes, was used to identify individuals with a new diagnosis of IBD.[16] IBD was defined as having one of the following ICD codes: CD: ICD-8 code 563.01–09 or ICD-10 code K50; UC: ICD-8 code 563.19, 569.04 or ICD-10 code K51. Prior work in the Danish National Patient Register has validated this methodology, demonstrating a high rate of accuracy and completeness in identifying individuals with IBD.[17 18] In the 0.46% of cases where ICD codes pertaining to both UC and CD were present during the initial IBD encounter, the primary diagnosis code associated with the encounter was used. The remaining 0.06% of cases with diagnostic codes for both CD and UC were defaulted to a diagnosis of CD.

Covariates

Demographic variables such as age and sex were captured from the Danish CRS. Urbanisation (based on number of people per square metre) and socioeconomic index were retrieved by linking address information from the Danish CRS with official summary statistics. Proton pump inhibitor (PPI), antiviral and antifungal use were also captured to account for any potential microbiome alterations as a result of these medications (online supplemental table 2).[19–25] All variables, except for sex, were included as time-varying variables in all analyses, including age, given individuals could enter the cohort at different times and ages.

Statistical analysis

In order to assess the association between antibiotic exposure and IBD, we followed up individuals aged ≥10 years longitudinally until IBD diagnosis, emigration, death or 31 December 2018, whichever occurred first. As the prescription registry was complete only from 1995 onward, our time horizon started in the year 2000 to allow for at least 5 years of antibiotic exposure data. Person-years of follow-up and number of IBD cases were categorised according to antibiotic exposure. Incidence rate ratios (IRRs) were estimated using Poisson regression (log-linear regression of the number of IBD cases with the logarithm of follow-up time as offset). All models were adjusted for sex, age (1-year periods), calendar period (1-year periods), socioeconomic status (low, mid-low, mid-high, high), degree of urbanisation (<50 people/km^2, 50–349 people/km^2, 350–999 people/km^2, 1000–1999 people/km^2, ≥2000 people/km^2), as well as PPI, antifungal and antiviral use. When analysing the risk of IBD according to specific antibiotic classes, models were additionally adjusted for the number and timing of previous antibiotic courses. All statistical analyses were completed using SAS (Cary, North Carolina. USA) version 9.4, and this study was approved by the Danish Data Protection Agency.

Patients and public involvement

No patients participated in the design of the study; however, the public is involved in dissemination of our results.

RESULTS

A total of 6 104 245 individuals aged ≥10 years were included in the cohort, with individuals able to contribute to more than one group given advancing age and calendar time. This resulted in 87 112 328 person-years of follow-up, with 50.4% being female. In total, 5 551 441 individuals (90.9%) received at least one course of antibiotics (table 1). During follow-up, there were 36 017 new cases of UC and 16 881 new cases of CD.

Overall, any antibiotic exposure was associated with an increased risk of IBD for all age groups compared with individuals with no antibiotic exposure (age 10–40 years, IRR 1.28, 95% CI 1.25 to 1.32; age 40–60 years, IRR 1.48 95% CI 1.43 to 1.54; age ≥60 years, IRR 1.47 95% CI 1.42 to 1.53). This held true for both CD and UC, with a slightly higher risk for CD (age 10–40 years, IRR 1.40 95% CI 1.33 to 1.47; age 40–60 years, IRR 1.62 95% CI 1.51 to 1.74; age ≥60 years, IRR 1.51 95% CI 1.40 to 1.63) as compared with UC (table 2). Further, on sensitivity analysis, when including a 2-year lag time from antibiotic exposure, similar results were seen (online supplemental table 3). Additionally, there was an observed interaction between sex and number of antibiotic exposures; $p<0.01$, online supplemental table 4).

Number of antibiotic courses

When assessing the number of antibiotic courses received, each subsequent course added additional risk, leading to a positive dose–response relationship: IRRs per antibiotic course were 1.11 (95% CI 1.10 to 1.12), 1.15 (95% CI 1.14 to 1.16), and 1.14 (95% CI 1.13 to 1.15) for individuals aged 10–40 years, 40–60 years, and ≥60 years (online supplemental table 5). The highest risk was among individuals receiving five or more courses of antibiotics, and held true for all age groups (age 10–40, IRR 1.69, 95% CI 1.61 to 1.76; age 40–60, IRR 2.12, 95% CI 2.01 to 2.23; age≥60, IRR 1.95, 95% CI 1.85 to 2.04; figure 1).

Timing of antibiotic use

The highest risk for developing IBD was 1–2 years after antibiotic exposure, with each subsequent year leading to a lower risk for all age groups (table 3). Specifically, individuals aged 10–40 years had an IRR of 1.40 (95% CI 1.35 to 1.44) 1–2 years after antibiotic exposure as compared with IRR 1.13 (95% CI 1.08 to 1.20) 4–5 years after exposure. Similarly, individuals aged 40–60 years had an IRR of 1.66 (95% CI 1.59 to 1.73) 1–2 years after antibiotic exposure versus IRR 1.21 (95% CI 1.13 to 1.29) 4–5 years after exposure, whereas individuals aged ≥60 years had an IRR of 1.63 (95% CI 1.57 to 1.70) 1–2 years after antibiotic exposure versus IRR 1.22 (95% CI 1.14 to 1.31) 4–5 years after exposure. On subgroup analysis, this held true when assessing the risk for developing both UC and CD.

Antibiotic class

When evaluating by antibiotic type, nitrofurantoin was the only class of antibiotics not found to be associated with the development of IBD across all age groups (figure 2). The classes with the highest risk were the nitroimidazoles (age 10–40, IRR 1.31, 95% CI 1.19 to 1.42; age 40–60, IRR 1.43, 95% CI 1.28 to 1.58; age≥60, IRR 1.61, 95% CI 1.41 to 1.83) and

fluroquinolones (age 10–40, IRR 1.76, 95% CI 1.60 to 1.93; age 40–60, IRR 1.79, 95% CI 1.61 to 1.97; age≥60, IRR 1.54, 95% CI 1.41 to 1.69), which are commonly used to target gastrointestinal pathogens. Results remained similar when evaluating both CD and UC.

DISCUSSION

In this Danish nationwide population-based study of more than six million individuals, antibiotic use was associated with an increased risk of incident IBD, and was observed for both UC and CD. The risk of IBD was greatest among individuals aged 40 years and older, increased with each subsequent antibiotic course, and was highest following exposure to antibiotic groups commonly prescribed to treat gastrointestinal pathogens.

As individuals age, the changing microbial environment can lead to decreased diversity and an increased susceptibility to perturbations.[26–28] In one recent study comparing the microbiome of healthy older and younger adults, older adults were found to have decreased abundance of Bifidobacterium, which is a signature that has also been seen in patients with IBD.[29 30] These aging-related changes can be compounded by antibiotic use, which further deprives the gut microbiome of diversity, and has the potential to lead to longstanding microbial changes.[28] In another recent study, antibiotic perturbations led to recovery of the intestinal microbiome within 20 days in younger mice, whereas microbiome alterations were still present at 6 months among older mice, further emphasising the impact of age on microbiome shifts.[31] In our study, we see possible evidence of this, as antibiotic use was associated with a higher risk of developing IBD among older adults as compared with younger individuals. Analogous results were seen in the case–control study by Nguyen *et al*, further supporting the notion that antibiotic use, perhaps through intestinal microbial shifts, may play an increasingly important role in the development of IBD as individuals age.[11]

Furthermore, with repeated courses of antibiotics, these shifts can become more pronounced, ultimately limiting recovery of the intestinal microbiota.[32] This, in part, further supports our finding that an increasing number of antibiotic courses was associated with a higher risk for developing IBD. On subgroup analysis, we also observed an increased risk of both UC and CD after antibiotic use. Prior studies, however, have found less consistent results, with some finding antibiotic use to be associated with the development of CD but not UC.[33] This is probably influenced by the younger age of inclusion in these prior studies, as the association between UC and antibiotic use was lowest in the 10–40-year-old age group in our study. The higher risk for developing both UC and CD observed among older adults, further emphasises the strong role of environmental factors in the development of IBD later in life, and implicates microbiome alterations as a risk factor for both the development of UC and CD.[8 34]

When evaluating the timing of antibiotic use, including a 1-year lag time to minimise the risk for reverse causality, we found that the highest risk for all individuals was 1–2 years after antibiotic exposure.[11 15] This held true for both UC and CD and suggests the importance of antibiotic use as a potential trigger for the development of IBD. Additionally, on sensitivity analysis, when including a 2-year lag time for our exposure, analogous results were seen. This further supports our findings, particularly as the diagnostic delay in UC

is assumed to be limited since the presence of haematochezia often prompts immediate evaluation.[35 36] Although attenuated, we also observed an increased risk for developing IBD 4–5 years after exposure. In conjunction with prior data, this may be the result of persisting changes in the microbial environment as a result of antibiotic use, which ultimately contribute to the development of IBD.[28 32]

When evaluating specific antibiotic classes, we found that those affecting the gut microbiota increased the risk of developing IBD. As such, this risk was highest when using nitroimidazole or fluoroquinolones, which particularly target bacterial pathogens in the gastrointestinal tract, and persisted when evaluating UC and CD separately. This has been shown in children and younger adults, but has not been previously assessed among older individuals.[11 33 37] Moreover, although the risk was attenuated among antibiotics less commonly used to target gastrointestinal pathogens (ie, narrow-spectrum penicillins), their use was still associated with the development of IBD. This further supports the notion that alterations in the gut microbial environment may play a significant role in the development of IBD, and highlights the important point that many antibiotics, including those not used to treat gastrointestinal pathogens, can affect the intestinal microflora.[38]

We also observed that nitrofurantoin, a drug that has less of an impact on the gastrointestinal flora, was not associated with the risk of developing IBD across all age groups.[38] This finding is in accordance with prior data from Nguyen *et al*, showing that antibiotic classes targeting gastrointestinal specific pathogens carry the highest risk for developing IBD.[11] In this prior study, however, it should be noted that all antibiotic classes assessed were found to be associated with the development of IBD. This specific difference probably stems from the fact that the prior study did not assess nitrofurantoin as its own class, did not assess antibiotic classes by age, did not adjust for PPIs, antifungal or antiviral use, or an individual's use of multiple antibiotic classes over time, as was performed in this analysis.

Strengths of this study include the design and size, prospectively following up an unselected population of over six million adults across Denmark for 19 years, with almost no loss to follow-up. This ensures adequate power and a high generalis-ability of our findings. Additionally, the national register data available in Denmark allow for all individuals and prescriptions to be tracked carefully and prospectively over time, hence eliminating the risk of recall or selection bias. Furthermore, our study is unique in that it adjusts for PPI use, as well as the use of antifungal and antiviral agents, which can all affect the intestinal microbiome.[19–24] Lastly, adjusting for prior antibiotic courses allows for a more accurate assessment of risk estimates for individual classes.

Despite these strengths, there are still several limitations which warrant discussion. Although we included both a 1- and 2-year lag time from antibiotic exposure, the possibility of reverse causality still exists. As noted above, however, we feel this is less likely due to the persistence of findings among individuals who have (1) shorter diagnostic delays (new-onset UC), (2) disease onset 4–5 years after antibiotic exposure and (3) used antibiotics not traditionally prescribed to treat gastrointestinal infections (ie, narrow-spectrum penicillin). Second, although antibiotic classes were obtained, specific indications relating to antibiotic use, as well as the potential pathogen, are not publicly available within the data registries.

Thus, although we see an association between antibiotic use and the development of IBD, it is plausible that the underlying infection itself might be the main driver for these results. This, however, may be less likely, as antimicrobial therapy in the setting of an infection has been shown to contribute additional risk for developing IBD.[39] Third, although complete data regarding outpatient antibiotic prescriptions can be obtained, inpatient antibiotic use and medication adherence cannot be confirmed. Last, although we adjusted for age, sex, time period, degree of urbanisation, socioeconomic index, PPI use, antiviral and antifungal use, as well as prior antibiotic courses, the possibility of additional confounders still exist.

In conclusion, this is the first national cohort study providing critical insights into the role that antibiotics play in the development of IBD across the ages. Our results demonstrate a positive dose–response, highlighting the strong association between antibiotic exposure and the development IBD, particularly among adults aged 40 years and older. Furthermore, this risk was highest in the years immediately following antibiotic use, persisted across antibiotic classes affecting the gastrointestinal microbiome and was associated with the development of both UC and CD. Thus, as a public health measure, antibiotic stewardship may be important to limit the development of multidrug-resistant organisms, and also to reduce the risk of IBD. In order to further our understanding of the underlying pathophysiology, future research should build on this work, investigating changes in the intestinal microbiome as a result of antibiotic use that are associated with the development of IBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Jill Gregory for contribution to the visual abstract design.

Funding

ASF: National Institute of Aging (R03AG078927-01). MA: National Institute of Diabetes and Digestive and Kidney Diseases (K23DK129762-01). TJ: Danish National Research Foundation (grant no. DNRF148).

Competing interests

ASF: Research support from Crohn’s and Colitis Foundation; consultant for GLG, M3, Janssen, Guidepoint. JF: consultant Vedanta Biosciences and Innovation Pharmaceuticals; Scientific Advisory Board Vedanta Biosciences. JC: research grants from AbbVie, Janssen Pharmaceuticals and Takeda; payment for lectures from AbbVie, Amgen, Allergan, Inc. Ferring Pharmaceuticals, Shire and Takeda; consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, BMS, Celgene Corporation, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Genentech, Glaxo Smith Kline, Janssen Pharmaceuticals, Kaleido Biosciences, Imedex, Immunic, Iterative Scopes, Merck, Microba, Novartis, PBM Capital, Pfizer, Sanofi, Takeda, TiGenix, Vifor; holds stock options in Intestinal Biotech Development.

Data availability statement

Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Further data are available upon reasonable request.

REFERENCES

1. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. Lancet 2017;389:1756–70. [PubMed: 27914657]
2. Torres J, Mehandru S, Colombel J-F, et al. Crohn's disease. The Lancet 2017;389:1741–55.
3. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet Gastroenterol Hepatol 2020;5:17–30. [PubMed: 31648971]
4. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2021;18:56–66. [PubMed: 33033392]
5. Ananthakrishnan AN, Donaldson T, Lasch K, et al. Management of inflammatory bowel disease in the elderly patient: challenges and opportunities. Inflamm Bowel Dis 2017;23:882–93. [PubMed: 28375885]
6. Everhov Åsa H, Halfvarson J, Myrelid P, et al. Incidence and treatment of patients diagnosed withinflammatory bowel diseases at 60 years or older in Sweden. Gastroenterology 2018;154:518–28. [PubMed: 29102619]
7. European Crohn's and Colitis Organisation. ECCO - P653 The changing epidemiology of IBD in the western world: a population-based study from Denmark. Available: https://www.ecco-ibd.eu/publications/congress-abstracts/item/p653-the-changing-epidemiology-of-ibd-in-the-western-world-a-population-based-study-from-denmark.html
8. Ruel J, Ruane D, Mehandru S, et al. IBD across the age spectrum: is it the same disease? Nat Rev Gastroenterol Hepatol 2014;11:88–98. [PubMed: 24345891]
9. Nimmons D, Limdi JK. Elderly patients and inflammatory bowel disease. World J Gastrointest Pharmacol Ther 2016;7:51–65. [PubMed: 26855812]
10. Hviid A, Svanström H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. Gut 2011;60:49–54. [PubMed: 20966024]
11. Nguyen LH, Örtqvist AK, Cao Y, et al. Antibiotic use and the development of inflammatory bowel disease: a national case-control study in Sweden. Lancet Gastroenterol Hepatol 2020;5:986–95. [PubMed: 32818437]
12. Pedersen CB, Gøtzsche H, Møller JO, et al. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006;53:441–9. [PubMed: 17150149]
13. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:38–41. [PubMed: 21775349]
14. Veimer Jensen ML, Aabenhus RM, Holzknecht BJ, et al. Antibiotic prescribing in Danish general practice in the elderly population from 2010 to 2017. Scand J Prim Health Care 2021;39:498–505. [PubMed: 34818137]
15. Zhang J, Haines C, Watson AJM, et al. Oral antibiotic use and risk of colorectal cancer in the United Kingdom, 1989–2012: a matched case-control study. Gut 2019;68:1971–8. [PubMed: 31427405]
16. Andersen TF, Madsen M, Jørgensen J. A valuable source of data for modern health sciences. Dan Med Bull 1999;46:263–8. [PubMed: 10421985]
17. Fonager K, Sørensen 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. [PubMed: 8658038]
18. Albaek Jacobsen H, Jess T, Larsen L. Validity of inflammatory bowel disease diagnoses in the Danish National Patient Registry: a population-based study from the North Denmark region. Clin Epidemiol 2022;14:1099–109. [PubMed: 36226162]
19. Jackson MA, Goodrich JK, Maxan M-E, et al. Proton pump inhibitors alter the composition of the gut microbiota. Gut 2016;65:749–56. [PubMed: 26719299]
20. Stamatiades GA, Ioannou P, Petrikkos G, et al. Fungal infections in patients with inflammatory bowel disease: a systematic review. Mycoses 2018;61:366–76. [PubMed: 29453860]

21. Risum M, Astvad K, Johansen HK, et al. Update 2016–2018 of the nationwide Danish fungaemia surveillance study: epidemiologic changes in a 15-year perspective. J Fungi 2021;7. doi:10.3390/jof7060491. [Epub ahead of print: 19 Jun 2021].
22. Le Cleach L, Trinquart L, Do G, et al. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. Cochrane Database Syst Rev 2014:CD009036. [PubMed: 25086573]
23. Liu J-W, Lin S-H, Wang L-C, et al. Comparison of antiviral agents for seasonal influenza outcomes in healthy adults and children: a systematic review and network meta-analysis. JAMA Netw Open 2021;4:e2119151. [PubMed: 34387680]
24. Leach SA, Connell R. Reversal of fissure caries in the albino rat by stimulating salivary flow with pilocarpine. Caries Res 1990;24:127–9. [PubMed: 2340543]
25. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;65:740–8. [PubMed: 26657899]
26. Ragonnaud E, Biragyn A. Gut microbiota as the key controllers of "healthy" aging of elderly people. Immun Ageing 2021;18:2. [PubMed: 33397404]
27. Schwartz DJ, Langdon AE, Dantas G. Understanding the impact of antibiotic perturbation on the human microbiome. Genome Med 2020;12:82. [PubMed: 32988391]
28. Jeffery IB, Lynch DB, O'Toole PW. Composition and temporal stability of the gut microbiota in older persons. ISME J 2016;10:170–82. [PubMed: 26090993]
29. Glassner KL, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. J Allergy Clin Immunol 2020;145:16–27. [PubMed: 31910984]
30. Li J, Si H, Du H, et al. Comparison of gut microbiota structure and actinobacteria abundances in healthy young adults and elderly subjects: a pilot study. BMC Microbiol 2021;21:13. [PubMed: 33407122]
31. Laubitz D, Typpo K, Midura-Kiela M, et al. Dynamics of gut microbiota recovery after antibiotic exposure in young and old mice (a pilot study). Microorganisms 2021;9. doi:10.3390/microorganisms9030647. [Epub ahead of print: 20 03 2021].
32. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci U S A 2011;108 Suppl 1:4554–61. [PubMed: 20847294]
33. Ungaro R, Bernstein CN, Gearry R, et al. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. Am J Gastroenterol 2014;109:1728–38. [PubMed: 25223575]
34. Fenneman AC, Weidner M, Chen LA, et al. Antibiotics in the pathogenesis of diabetes and inflammatory diseases of the gastrointestinal tract. Nat Rev Gastroenterol Hepatol 2022. doi:10.1038/s41575-022-00685-9. [Epub ahead of print: 18 Oct 2022].
35. Taleban S, Colombel J-F, Mohler MJ, et al. Inflammatory bowel disease and the elderly: a review. J Crohns Colitis 2015;9:507–15. [PubMed: 25870198]
36. Kang HS, Koo JS, Lee KM, et al. Two-year delay in ulcerative colitis diagnosis is associated with anti-tumor necrosis factor alpha use. World J Gastroenterol 2019;25:989–1001. [PubMed: 30833804]
37. Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. Gut 2016;65:1906–15. [PubMed: 27531828]
38. Elvers KT, Wilson VJ, Hammond A, et al. Antibiotic-induced changes in the human gut microbiota for the most commonly prescribed antibiotics in primary care in the UK: a systematic review. BMJ Open 2020;10:e035677.
39. Axelrad JE, Olén O, Askling J, et al. Gastrointestinal infection increases odds of inflammatory bowel disease in a nationwide case-control study. Clin Gastroenterol Hepatol 2019;17:1311–22. [PubMed: 30389589]

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Environmental factors are thought to play a pivotal role in the development of inflammatory bowel disease (IBD).
- Antibiotics have been implicated in the development of IBD among younger individuals; however, limited data are available assessing this among adults.

WHAT THIS STUDY ADDS

- Antibiotic exposure increased the risk of IBD in all individuals aged ≥10 years, but was highest among those aged 40–60 years and ≥60 years.
- A positive dose–response was observed, with highest risk seen in the 1–2 years following exposure, and with antibiotics targeting gastrointestinal pathogens.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- The association between antibiotic exposure and the development of IBD underscores the importance of antibiotic stewardship as a public health measure, and suggests the gastrointestinal microbiome as an important factor in the development of IBD, particularly among older adults.

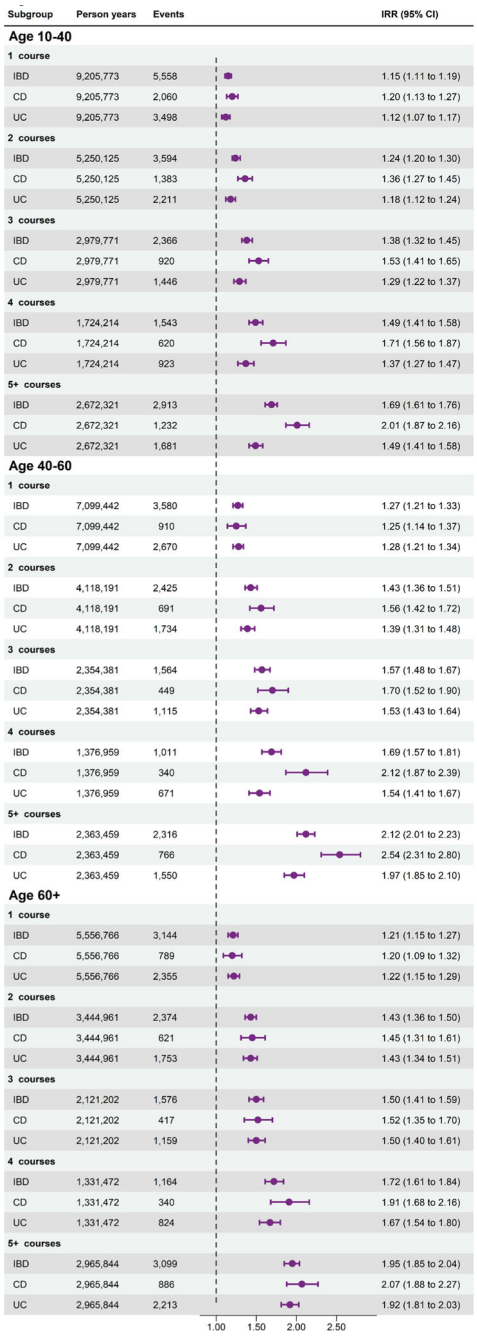

Figure 1.

Incidence rate ratios (IRRs) for the development of inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD) based on the number of antibiotic courses.

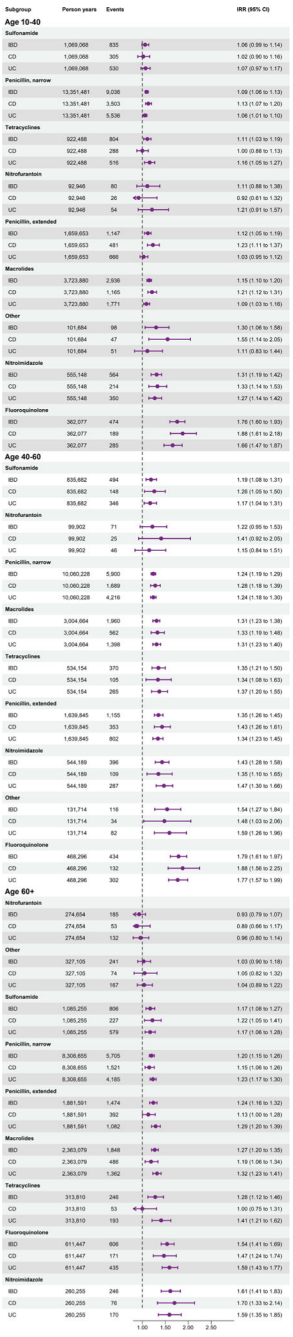

Figure 2.

Incidence rate ratios (IRRs) for the development of inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD) based on antibiotic class.

Table 1

Demographic information of study cohort

	All (n=6 104 245)		Antibiotic users (n=5 551 441)	
	N	**Person-years of follow-up**	**N**	**Person-years of follow-up**
Calendar period				
2000–2005	4 542 386	22 441 131	3 078 106	13 931 515
2005–2010	4 631 179	22 862 005	3 162 615	14 447 974
2010–2015	4 675 949	23 101 819	3 268 277	14 800 199
2015–2018	4 735 079	18 707 373	3 252 230	11 385 193
Age group				
10–15	1 313 710	6 189 509	845 409	3 164 596
15–20	1 282 683	5 979 831	655 675	3 073 213
20–25	1 222 016	5 599 619	825 589	3 615 661
25–30	1 175 576	5 527 708	827 878	3 561 745
30–35	1 218 340	5 941 889	853 989	3 920 376
35–40	1 358 868	6 679 422	992 429	4 496 614
40–45	1 468 738	7 056 975	1 051 188	4 545 956
45–50	1 498 008	7 074 418	1 017 555	4 340 187
50–55	1 483 364	6 954 578	982 040	4 232 652
55–60	1 455 285	6 728 295	975 758	4 193 637
60–65	1 356 575	6 172 838	935 054	3 953 960
65–70	1 208 921	5 371 316	842 749	3 464 737
70–75	1 021 265	4 317 341	717 539	2 821 087
75–80	779 215	3 214 668	555 497	2 146 405
80–85	576 131	2 260 838	421 250	1 554 431
85–90	372 517	1 333 483	281 263	949 545
≥90	189 304	709 599		
Sex				
Female	3 079 011	44 179 769	2 868 145	30 654 268
Male	3 025 234	42 932 559	2 683 296	23 910 613

	All (n=6 104 245)		Antibiotic users (n=5 551 441)	
	N	Person-years of follow-up	N	Person-years of follow-up
Area socioeconomic index				
Low	2 123 438	23 364 343	1 863 818	14 543 159
Mid-low	2 160 007	21 401 703	1 857 488	13 319 462
Mid-high	2 050 204	20 546 391	1 774 805	13 040 615
High	2 054 089	21 799 892	1 794 665	13 661 644
Degree of urbanisation				
<50 people/km^2	532 034	5 680 746	465 536	3 596 654
50–349 people/km^2	3 845 987	48 747 951	3 438 824	30 297 461
350–999 people/km^2	1 631 068	16 282 927	1 405 145	10 200 141
1000–1999 people/km^2	343 995	3 099 481	294 011	2 001 361
≥2000 people/km^2	1 371 552	13 301 222	1 181 765	8 469 264

Table 2

Incidence rate ratio for antibiotic exposure

Age group	Antibiotic exposure	Person-years	Number of IBD cases	IRR*, IBD	IRR lower bound, IBD	IRR upper bound, IBD	IRR*, CD	IRR lower bound, CD	IRR upper bound, CD	IRR*, UC	IRR lower bound, UC	IRR upper bound, UC
10–40 years	No	14 085 774	7076	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
10–40 years	Yes	21 832 205	15 974	1.28	1.25	1.32	1.40	1.33	1.47	1.21	1.17	1.26
40–60 years	No	10 501 835	4023	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
40–60 years	Yes	17 312 431	10 896	1.48	1.43	1.54	1.62	1.51	1.74	1.44	1.38	1.50
>60 years	No	7 959 839	3572	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
>60 years	Yes	15 420 245	11 357	1.47	1.42	1.53	1.51	1.40	1.63	1.47	1.40	1.53

*Adjusted for sex, calendar time, antiviral and antifungal exposure, proton pump inhibitor exposure, socioeconomic index and population density.

CD, Crohn’s disease; IBD, inflammatory bowel disease; IRR, incidence rate ratio; UC, ulcerative colitis.

Table 3

Incidence rate ratio by timing of antibiotic course

Age group	Most recent antibiotic use	IRR*, IBD	IRR lower bound, IBD	IRR upper bound, IBD	IRR*, CD	IRR lower bound, CD	IRR upper bound, CD	IRR*, UC	IRR lower bound, UC	IRR upper bound, UC
10–40 years	No use in the last 5 years	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
10–40 years	4 to 5 years	1.13	1.08	1.20	1.12	1.03	1.23	1.14	1.06	1.21
10–40 years	3 to 4 years	1.18	1.13	1.24	1.23	1.14	1.33	1.15	1.09	1.22
10–40 years	2 to 3 years	1.24	1.19	1.29	1.34	1.26	1.43	1.18	1.12	1.24
10–40 years	1 to 2 years	1.40	1.35	1.44	1.59	1.51	1.68	1.28	1.23	1.34
40–60 years	No use in the last 5 years	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
40–60 years	4 to 5 years	1.21	1.13	1.29	1.22	1.07	1.39	1.21	1.12	1.31
40–60 years	3 to 4 years	1.36	1.29	1.44	1.36	1.22	1.52	1.37	1.28	1.46
40–60 years	2 to 3 years	1.41	1.34	1.48	1.53	1.39	1.68	1.37	1.29	1.45
40–60 years	1 to 2 years	1.66	1.59	1.73	1.89	1.75	2.04	1.58	1.51	1.66
60+years	No use in the last 5 years	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
60+years	4 to 5 years	1.22	1.14	1.31	1.23	1.06	1.41	1.22	1.12	1.33
60+years	3 to 4 years	1.26	1.18	1.33	1.29	1.15	1.46	1.25	1.16	1.34
60+years	2 to 3 years	1.39	1.32	1.46	1.37	1.24	1.52	1.41	1.32	1.49
60+years	1 to 2 years	1.63	1.57	1.70	1.72	1.58	1.86	1.62	1.54	1.70

*Adjusted for sex, calendar time, antiviral and antifungal exposure, proton pump inhibitor exposure, socioeconomic index and population density.

CD, Crohn's disease; IBD, inflammatory bowel disease; IRR, incidence rate ratio; UC, ulcerative colitis.