Original research

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

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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.

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.

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.

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.

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
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

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

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.

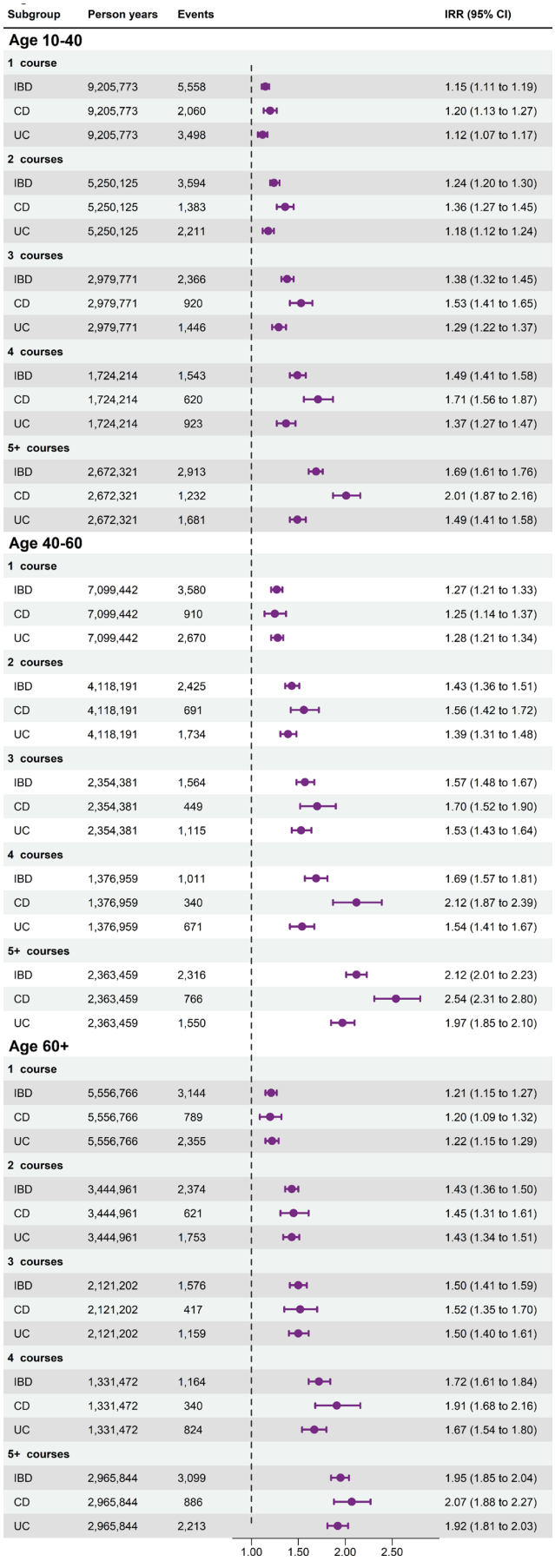

Figure 1 Incidence rate ratios (IRRs) for the development of inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD) based on the number of antibiotic courses.

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]

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.

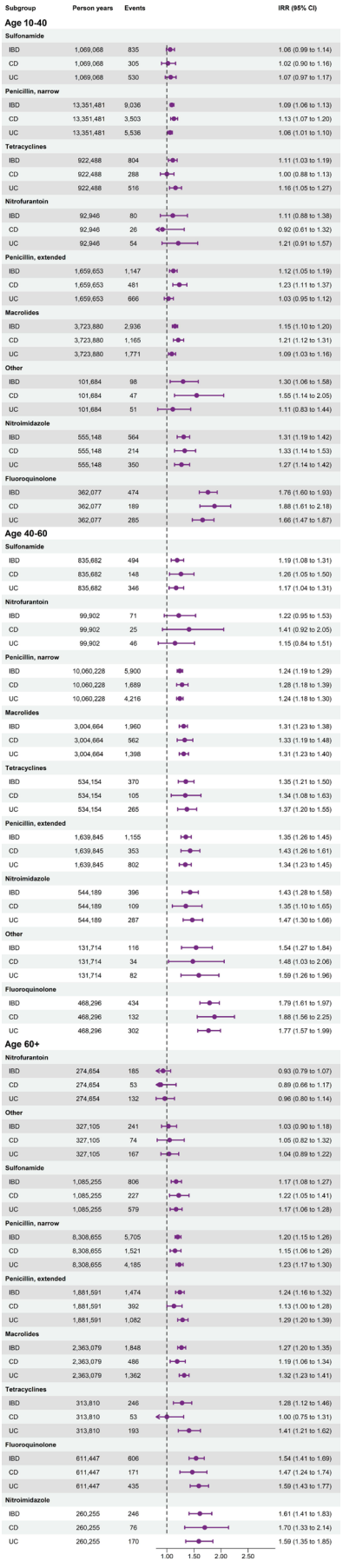

Figure 2 Incidence rate ratios (IRRs) for the development of inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD) based on antibiotic class.

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 generalisability 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.

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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)

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