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

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

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Received 25 May 2022 Accepted 27 November 2022 Published Online First 9 January 2023

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To cite: Faye AS, Allin KH, Iversen AT, et al. Gut 2023;72:663-670.

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 52898 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 1-2years 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-

WHAT IS ALREADY KNOWN ON THIS TOPIC

- \Rightarrow Environmental factors are thought to play a pivotal role in the development of inflammatory bowel disease (IBD).
- \Rightarrow 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

- \Rightarrow Antibiotic exposure increased the risk of IBD in all individuals aged ≥ 10 years, but was highest among those aged 40–60 years and \geq 60 years.
- \Rightarrow 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**

 \Rightarrow 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.

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.⁸⁹ 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 timevarying 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 timevarying 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 (loglinear 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/km², 50–349 people/km², 350–999 people/ km², 1000–1999 people/km², \geq 2000 people/km²), 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 6104245 individuals aged \geq 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 87112328 person-years of follow-up, with 50.4% being female. In total, 5551441 individuals (90.9%) received at least one course of antibiotics (table 1). During follow-up, there were 36017 new cases of UC and 16881 new cases of CD.

	All /m_C 104 245)	Antibiotic users (n. E EE1 111)			
	N	Person-years of follow-up	Ν	Person-years of follow-up		
Calendar period						
2000–2005	4 5 4 2 3 8 6	22 441 131	3 078 106	13931515		
2005–2010	4631179	22 862 005	3 162 615	14447974		
2010–2015	4675949	23 101 819	3 268 277	14800199		
2015–2018	4735079	18707373	3 252 230	11 385 193		
Age group						
10–15	1 313 710	6189509	845 409	3 1 6 4 5 9 6		
15–20	1 282 683	5979831	655675	3 073 213		
20–25	1 222 016	5 599 619	825 589	3 615 661		
25–30	1 1 7 5 5 7 6	5 5 2 7 7 0 8	827878	3 561 745		
30–35	1 218 340	5 941 889	853 989	3 920 376		
35–40	1 358 868	6679422	992 429	4 496 614		
40–45	1 468 738	7 056 975	1 051 188	4 5 4 5 9 5 6		
45–50	1 498 008	7074418	1 017 555	4340187		
50–55	1 483 364	6 954 578	982 040	4232652		
55–60	1 455 285	6 728 295	975 758	4193637		
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	4317341	717 539	2 821 087		
75–80	779215	3214668	555 497	2 1 4 6 4 0 5		
80–85	576131	2 260 838	421 250	1 554 431		
85–90	372 517	1 333 483	281 263	949 545		
≥90	189304	709599				
Sex						
Female	3079011	44179769	2 868 145	30 654 268		
Male	3 0 2 5 2 3 4	42 932 559	2 683 296	23910613		
Area socioeconomic index						
Low	2123438	23 364 343	1863818	14 543 159		
Mid-low	2160007	21 401 703	1 857 488	13319462		
Mid-high	2 050 204	20 546 391	1774805	13040615		
High	2 054 089	21 799 892	1 794 665	13661644		
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 4 3 8 8 2 4	30297461		
350–999 people/km ²	1 631 068	16282927	1 405 145	10200141		
1000–1999 people/km ²	343 995	3 099 481	294011	2 001 361		
\geq 2000 people/km ²	1 371 552	13 301 222	1 181 765	8469264		

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 \geq 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

Incidence rate	e ratio for anti	biotic expos	ure								
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
s No	14085774	7076	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
s Yes	21 832 205	15974	1.28	1.25	1.32	1.40	1.33	1.47	1.21	1.17	1.26
s No	10 501 835	4023	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
s Yes	17312431	10896	1.48	1.43	1.54	1.62	1.51	1.74	1.44	1.38	1.50
No	7 959 839	3572	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	15420245	11 357	1.47	1.42	1.53	1.51	1.40	1.63	1.47	1.40	1.53
	Incidence rate Antibiotic exposure No Ves No Ves No Yes	Incidence rate ratio for antilAntibiotic exposurePerson-yearsNo14085774Yes21832205No10501835Yes17312431No7959839Yes15420245	Incidence rate ratio for antibiotic exposeAntibiotic exposurePerson-yearsNumber of IBD casesNo140857747076Yes2183220515974No105018354023Yes1731243110896No79598393572Yes1542024511357	Incidence rate atio for antibiotic exposureAntibiotic exposurePerson-yearsNumber of IBD casesIRR*, IBDNo14085 77470761.00Yes21832 205159741.28No10501 83540231.00Yes17312 431108961.48No7959 83935721.00Yes15420245113571.47	Incidence rate atio for antibiotic exposureAntibiotic exposurePerson-yearsNumber of IBD casesIRR*, IBDRR lower bound, IBDNo14085 77470761.001.00Yes21832 205159741.281.25No10501 83540231.001.00Yes17312 431108961.481.43No7959 83935721.001.00Yes15420245113571.471.42	Incidence rate atio for antibiotic exposureAntibiotic exposurePerson-yearsNumber of IBC casesIRR Nower IRR*, IBDIRR Nower bound, IBDIRR upper bound, IBDNo14085 77470761.001.001.00Yes21832 205159741.281.251.32No10501 83540231.001.001.00Yes17312 431108961.481.431.54No7959 83935721.001.001.00Yes15420245113571.471.421.53	Incidence rate atio for antibiotic exposureAntibiotic exposurePerson-yearsNumber of IBD casesIRR Iower bound, IBDIRR upper bound, IBDIRR vipper bound, IBDIRR vipper 	Incidence rate atio for antibiotic exposureAntibiotic exposurePerson-yearsNumber of IBD casesIRR+, IBDRR lower bound, IBDIRR upper bound, IBDIRR*, or bound, IBDRR lower bound, IBDIRR*, IBDIRR upper bound, IBDIRR*, IBD <td>Incidence rate variable bolic exposureAntibiotic exposurePerson-yearsNumber of IBD casesIRR inport pound, IBDIRR upper bound, IBDIRR inport bound, IBDIRR inport bound, IDDIRR upper bound, IDDIRR IDDIRR upper bound,</td> <td>Incidence rate vision biological systemAntibiotic exposurePerson-yearsNumber of IBD casesIRR lower bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR lower bound, IBDIRR*, bound, IBDIRR lower bound, IBDIRR*, bound, IBDIRR lower bound, IBDIRR*, bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR*, bound, IDDIRR*, bound, IDDIRR*, bou</td> <td>Incidence rate variable varia</td>	Incidence rate variable bolic exposureAntibiotic exposurePerson-yearsNumber of IBD casesIRR inport pound, IBDIRR upper bound, IBDIRR inport bound, IBDIRR inport bound, IDDIRR upper bound, IDDIRR	Incidence rate vision biological systemAntibiotic exposurePerson-yearsNumber of IBD casesIRR lower bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR lower bound, IBDIRR*, bound, IBDIRR lower bound, IBDIRR*, bound, IBDIRR lower bound, IBDIRR*, bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR upper bound, IBDIRR*, bound, IBDIRR*, bound, IDDIRR*, bound, IDDIRR*, bou	Incidence rate variable varia

*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.

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4 course 19D 1,724,214 1,543 1++ 1,714,158 to 1.58 UC 1,724,214 923 1++ 1,37 (1,27 to 1.47 5* courses 137 (1,27 to 1.47 5* 200 2,672,321 1,232 1++ 1,69 (1,61 to 1.76 2.01 (1,87 to 2.16 CD 2,672,321 1,232 1++ 1,69 (1,61 to 1.76 2.01 (1,87 to 2.16 2.01 (1,17 to 1.16 2.01 (1,16 to 1.27	UC	2,979,771	1,446		1.29 (1.22 to 1.37)
IBD1,724,2141,543Image of the second secon	4 courses				
CD1,724,214620Imm1,71 (1,56 to 1,87UC1,724,214923Imm1,37 (1,27 to 1,475r courses1,68 (1,51 to 1,751,68 (1,51 to 1,751,68 (1,51 to 1,75CD2,672,3211,232Imm1,69 (1,61 to 1,75CD2,672,3211,232Imm1,69 (1,61 to 1,75Age 40-6011,27 (1,21 to 1,331,27 (1,21 to 1,33CD7,099,4423,580Imm1,27 (1,21 to 1,33CD7,099,4423,580Imm1,28 (1,21 to 1,33CD7,099,4422,670Imm1,28 (1,21 to 1,33CD7,099,4422,670Imm1,28 (1,21 to 1,33CD7,099,4422,670Imm1,28 (1,21 to 1,33CD4,118,1912,425Imm1,38 (1,31 to 1,51CD4,118,1911,734Imm1,58 (1,42 to 1,57CD2,354,3811,594Imm1,57 (1,48 to 1,57CD2,354,3811,155Imm1,58 (1,43 to 1,61 to 1,57CD2,363,4591,011Imm1,69 (1,57 to 1,81 to 2,39CD2,363,4591,011Imm1,69 (1,57 to 1,81 to 2,39CD2,363,4597,66Imm2,12 (2,01 to 2,23CD2,363,4597,66Imm1,20 (1,02 to 2,39CD2,363,4597,66Imm1,20 (1,02 to 2,39CD2,363,4597,66Imm1,20 (1,01 to 1,39CD2,363,4597,66Imm1,20 (1,01 to 1,39 <t< td=""><td>IBD</td><td>1,724,214</td><td>1,543</td><td>HeH</td><td>1.49 (1.41 to 1.58)</td></t<>	IBD	1,724,214	1,543	HeH	1.49 (1.41 to 1.58)
UC 1,724,214 923 I++ 1,37 (1,27 to 1,47 5 ⁺ courses 180 2,672,321 2,913 I++ 1,89 (1,61 to 1,76 UC 2,672,321 1,282 I++ 2,01 (1,87 to 2,16 1,89 (1,61 to 1,76 UC 2,672,321 1,282 I++ 2,01 (1,87 to 2,16 1,89 (1,61 to 1,76 UC 2,672,321 1,681 I++ 1,49 (1,41 to 1,58 Age 40-60 127 (1,21 to 1,34 1,27 (1,21 to 1,34 IBD 7,099,442 2,670 I++ 1,26 (1,14 to 1,37 UC 7,099,442 2,670 I++ 1,28 (1,21 to 1,34 2 courses 128 (1,21 to 1,34 1,28 (1,21 to 1,34 1,39 (1,31 to 1,45 CD 4,118,191 6,42 I++ 1,56 (1,42 to 1,72 UC 4,118,191 1,754 I++ 1,56 (1,42 to 1,72 UC 2,364,381 1,564 I++ 1,57 (1,48 to 1,67 UC 2,364,381 1,564 I++ 1,70 (1,52 to 1,90 UC 1,376,959 340 I++ 1,89 (1,57 to 1,81 CD 1,376,959 340 I++ 1,89 (1,57 to 1,81 CD 2,363,459 2,316 I++ 1,21 (1,15 to 1,27 C	CD	1,724,214	620	H H H	1.71 (1.56 to 1.87)
5+ course5+ course5+ course1IBD2,672,3211,2321,4321,441,69 (1,61 to 1,76CD2,672,3211,2321,441,20 (1,16 1,76Age 40-311,27 (2,10 1,331,27 (2,10 1,33CD7,099,4423,5801,471,27 (1,21 0,133CD7,099,4429,001,471,26 (1,11 0,137CD7,099,4429,001,471,26 (1,11 0,137CD7,099,4429,001,471,26 (1,11 0,137CD7,099,4429,001,471,26 (1,11 0,137CD7,099,4429,001,471,26 (1,11 0,137CD4,118,1912,4251,441,36 (1,21 0,137CD4,118,1911,741,471,56 (1,42 0,172CD2,364,3811,5641,441,57 (1,48 0,157CD2,364,3811,5641,441,57 (1,48 0,157CD2,364,3811,5641,441,57 (1,48 0,157CD2,364,3811,5641,441,56 (1,57 0,18 0,12 0,18	UC	1,724,214	923	i H e H	1.37 (1.27 to 1.47)
IBD2.672.3212.913Image: method of the sector of the sect	5+ courses				
CD $2,872,321$ $1,322$ i i $2,01(187 to 2.16)$ UC $2,872,321$ $1,681$ i $1,49(1,411 to 1.58)$ Age 40-60 1 $2,09,442$ $3,580$ i $1,27(1,21 to 1.33)$ CD $7,099,442$ 910 i $1,27(1,21 to 1.33)$ CD $7,099,442$ $2,670$ i $1,27(1,21 to 1.33)$ CD $7,099,442$ $2,670$ i $1,27(1,21 to 1.33)$ CD $7,099,442$ $2,670$ i $1,27(1,21 to 1.33)$ CD $4,118,191$ $6,91$ i $1,26(1,21 to 1.37)$ CD $4,118,191$ $6,91$ i $1,97(1,62 to 1.61)$ CD $2,354,381$ $1,564$ i i $1,57(1,48 to 1.61)$ CD $2,354,381$ $1,564$ i i $1,57(1,48 to 1.61)$ CD $2,354,381$ $1,564$ i i $1,69(1,57 to 1.81)$ CD $1,376,959$ 340 i i i i i i i i	IBD	2,672,321	2,913	Hei	1.69 (1.61 to 1.76)
UC $2,672,321$ $1,681$ $1+49$ $1.49(1.41 to 1.58)$ Age 40-60 1 $7.099,442$ $3,580$ $1+40$ $1.27(1.21 to 1.33)$ CD $7.099,442$ 910 $1+27(1.21 to 1.33)$ $1.28(1.21 to 1.34)$ CD $7.099,442$ $2,670$ $1e^{-1}$ $1.28(1.21 to 1.34)$ 2 courses $1418,191$ $2,245$ $1e^{-1}$ $1.28(1.21 to 1.34)$ CD $4,118,191$ 691 $1e^{-1}$ $1.28(1.21 to 1.34)$ CD $4,118,191$ 691 $1e^{-1}$ $1.39(1.31 to 1.48)$ Gourses 100 $2,354,381$ 1.564 $1e^{-1}$ $1.57(1.48 to 1.57)$ IBD $2,354,381$ 1.115 $1e^{-1}$ $1.57(1.48 to 1.67)$ $1.57(1.48 to 1.67)$ CD $2,363,459$ $2,316$ $1e^{-1}$ $1.57(1.48 to 1.67)$ $1.57(1.48 to 1.67)$ CD $2,363,459$ $2,316$ $1e^{-1}$ $1.57(1.48 to 1.67)$ $1.57(1.48 to 1.67)$ CD $2,363,459$ $2,316$ $1e^{-1}$ $1.21(1.67 to 2.39)$ $1.22(2.01 to 2.39)$ UC $2,363,459$	CD	2,672,321	1,232	H H H	2.01 (1.87 to 2.16)
Age 40-60 1 course I IBD 7.099,442 910 Het 1.27 (1.21 to 1.33 CD 7.099,442 910 Het 1.28 (1.14 to 1.37 UC 7.099,442 910 Het 1.28 (1.21 to 1.33 CD 7.099,442 910 Het 1.28 (1.21 to 1.34 Courses U 1.43 (1.36 to 1.51 1.56 (1.42 to 1.72 UC 4,118,191 6.91 Het 1.39 (1.31 to 1.48 3 courses U 1.57 (1.48 to 1.57 1.57 (1.48 to 1.57 UC 2,354,381 1.155 Het 1.57 (1.48 to 1.67 CD 2,354,381 1.151 Het 1.69 (1.57 to 1.81 CD 1,376,959 340 Het 1.69 (1.57 to 1.81 CD 1,376,959 340 Het 1.69 (1.57 to 1.81 CD 2,363,459 7.66 1.21 (1.41 to 1.57 CD 2,363,459 7.66 1.22 (1.50 to 2.23 CD 2,363,459 7.66 1.21 (1.50 to 1.23 UC 2,565,766 3.144 Het <td>UC</td> <td>2,672,321</td> <td>1,681</td> <td>HOH</td> <td>1.49 (1.41 to 1.58)</td>	UC	2,672,321	1,681	HOH	1.49 (1.41 to 1.58)
1 course 1 IBD 7,099,442 3,580 ● 1.27 (1.21 to 1.33 CD 7,099,442 910 ● 1.28 (1.21 to 1.34 LC 7,099,442 2,670 ● 1.28 (1.21 to 1.34 2 courses 1 1.38 (1.36 to 1.51 1.43 (1.36 to 1.51 CD 4,118,191 691 ● 1.56 (1.42 to 1.72 1.60 UC 4,118,191 1.734 ● 1.56 (1.42 to 1.72 1.60 UC 4,118,191 1.734 ● 1.57 (1.48 to 1.67 1.56 (1.42 to 1.72 UC 2,354,381 1.564 ● 1.57 (1.48 to 1.67 1.57 (1.48 to 1.67 CD 2,354,381 1.564 ● 1.76 (1.52 to 1.80 1.69 (1.57 to 1.81 UC 1,376,959 3.40 ● ● 1.54 (1.41 to 1.67 CD 1,376,959 3.40 ● ● 1.54 (1.41 to 1.67 CD 2,363,459 2.516 ● 1.21 (1.67 to 2.39 CD 2,363,459	Age 40-60)		1	
IBD 7,099,442 3,580 ●●● 1,27 (1,21 to 1,33 CD 7,099,442 910 ●●● 1,26 (1,14 to 1,37 UC 7,099,442 2,670 ●● 1,28 (1,21 to 1,33 2 courses ●●● 1,28 (1,21 to 1,34 1,28 (1,21 to 1,34 2 courses ●●● 1,43 (1,36 to 1,57 1,56 (1,42 to 1,72 UC 4,118,191 6,91 ●●● 1,57 (1,48 to 1,67 CD 2,354,381 1,156 ●● 1,57 (1,48 to 1,67 CD 2,354,381 1,115 ●● 1,57 (1,48 to 1,67 CD 2,354,381 1,115 ●● 1,57 (1,48 to 1,67 CD 1,376,959 1,011 ●● 1,57 (1,48 to 1,67 CD 1,376,959 3,04 ●● 1,21 (1,47 to 2,39 UC 1,376,959 3,04 ●● 1,21 (2,01 to 2,39 CD 2,363,459 7,66 ● 1,21 (1,47 to 2,39 UC 2,363,459 7,66 ● 1,22 (1,16 to 2,39 CD 2,363,459 7,66 ● 1,22 (1,16 to 2,39 UC </td <td>1 course</td> <td></td> <td></td> <td>1</td> <td></td>	1 course			1	
CD 7,099,442 910 ▶ 1,25 (1,14 to 1,37 UC 7,099,442 2,670 ▶ 1,28 (1,21 to 1,34 2 courses 1 1,36 (1,36 to 1,57) 1,56 (1,42 to 1,72) UC 4,118,191 2,425 ▶ 1,36 (1,42 to 1,72) UC 4,118,191 1,734 ▶ 1,39 (1,31 to 1,48) 3 courses IBD 2,354,381 4,49 ▶ 1,57 (1,48 to 1,67) UC 2,354,381 1,115 ▶ 1,53 (1,43 to 1,64) 4 courses IBD 1,376,959 1,011 ▶ 1,54 (1,41 to 1,67) CD 2,363,459 7,66 2,42 (2,11 to 2,39) 1,24 (1,41 to 1,67) CD 1,376,959 671 ▶ 1,54 (1,41 to 1,67) CD 2,363,459 7,66 2,42 (2,11 to 2,39) 1,24 (2,21 to 2,39) UC 2,363,459 7,66 2,54 (2,31 to 2,40) 1,22 (1,15 to 2,40) UC 2,363,459 7,66 2,54 (2,31 to 2,40) 1,22 (1,15 to 1,29) UC 2,556,766 7,89 ▶ 1,22 (1,15 to 1,29) CD <t< td=""><td>IBD</td><td>7,099,442</td><td>3,580</td><td>I III</td><td>1.27 (1.21 to 1.33)</td></t<>	IBD	7,099,442	3,580	I III	1.27 (1.21 to 1.33)
UC 7,099,442 2,67 Image: Contract of the second of	CD	7.099.442	910	H B H	1.25 (1.14 to 1.37)
2 courses	UC	7 099 442	2 670		1 28 (1 21 to 1 34)
IBD 4,118,191 2,425 Image: Constraint of the second of	2 courses	1,000,112	2,070	1	1.20 (1.21 to 1.01)
InD 4,116,191 2,423 Image: Margine		4 119 101	2 425		1 42 (1 26 to 1 51)
CCD 4,118,191 1,591 Fm 1,39 (1,31 to 1,32 UC 4,118,191 1,564 Fm 1,39 (1,31 to 1,48 3 courses 1 1,564 Fm 1,57 (1,48 to 1,67 IBD 2,354,381 449 Fm 1,53 (1,43 to 1,64 4 courses 1 1,53 (1,43 to 1,64 Fm 1,53 (1,43 to 1,64 4 courses 1,376,959 1,011 Fm 1,69 (1,57 to 1,81 CD 1,376,959 671 Fm 1,54 (1,41 to 1,67 CD 1,376,959 671 Fm 2,12 (2,01 to 2,23 UC 1,376,959 671 Fm 2,12 (2,01 to 2,23 UC 2,363,459 766 2,54 (2,31 to 2,40 UC 2,363,459 766 1,97 (1,45 to 1,20 UC 2,363,459 1,550 Fm 1,97 (1,45 to 1,20 UC 2,363,459 7,66 1,97 (1,45 to 1,20 1,00 (1,01 to 1,30 UC 2,363,459 7,66 7,99 1,20 (1,09 to 1,32 UC 5,556,766 7,89 1,20 (1,09 to 1,32 1,20 (1,09 to 1,32 <t< td=""><td>CD</td><td>4,110,191</td><td>2,423</td><td></td><td>1.45 (1.30 to 1.31)</td></t<>	CD	4,110,191	2,423		1.45 (1.30 to 1.31)
0.0 4,116,191 1,74 1.39 1.3116 1.48 3 courses 1.57 1.48 to 1.67 1.57 (1.48 to 1.67 CD 2,354,381 449 1.70 (1.52 to 1.90 UC 2,354,381 449 1.70 (1.52 to 1.90 UC 2,354,381 1.15 1.69 (1.57 to 1.81 CD 1,376,959 1.011 1.69 (1.57 to 1.81 CD 1,376,959 671 1.54 (1.41 to 1.67 54 courses 2.12 (2.01 to 2.23 2.12 (2.01 to 2.23 CD 2,363,459 7.66 1.97 (1.85 to 2.10 Age 60+ 1.20 (1.09 to 1.32 1.20 (1.09 to 1.32 1.20 (1.09 to 1.32 UC 5,556,766 7.89 1.20 (1.09 to 1.32 1.22 (1.15 to 1.29 UC 5,556,766 7.89 1.20 (1.09 to 1.32 1.22 (1.15 to 1.29 UC 3,444,961 6.21 1.43 (1.36 to 1.50 1.22 (1.15 to 1.29 CD	00	4,110,191	4 704		1.36 (1.42 (0 1.72)
3 courses 1.50 2,354,381 1,564 Immediate interval inter	UC	4,118,191	1,734		1.39 (1.31 to 1.48)
IBD 2,354,381 1,564 Impair (1,48 to 1,67 CD 2,354,381 449 Impair (1,48 to 1,67 UC 2,354,381 1,115 Impair (1,48 to 1,67 IBD 1,376,959 1,011 Impair (1,48 to 1,67 CD 1,376,959 340 Impair (1,69 (1,57 to 1,81 CD 1,376,959 340 Impair (1,69 (1,57 to 1,81 CD 1,376,959 671 Impair (1,69 (1,57 to 1,81 CD 2,363,459 766 2,12 (1,67 to 1,23 UC 2,363,459 766 1,97 (1,85 to 2,10 Agg 60+ 2,363,459 1,550 Impair (1,85 to 2,10 IBD 5,556,766 2,354 Impair (1,85 to 1,20 CD 3,444,961 2,374 Impair (1,43 (1,36 to 1,50 CD 3,444,961 1,57 Impair (1,63 to	3 courses				
CD 2,354,381 449 Immediate of the second sec	IBD	2,354,381	1,564	HOH	1.57 (1.48 to 1.67)
UC 2,354,381 1,115 Image: Marrier	CD	2,354,381	449		1.70 (1.52 to 1.90)
4 courses 1,376,959 1,011 Image: Marrier	UC	2,354,381	1,115	I H€H	1.53 (1.43 to 1.64)
IBD 1,376,959 1,011 Image: Marrier Marrie	4 courses			1	
CD 1,376,959 340 Image: State S	IBD	1,376,959	1,011	I H●H	1.69 (1.57 to 1.81)
UC 1,376,959 671 Image: Marrie Marri Marrie Marrie Marri Marrie Marrie Marri Marrie Marrie Marrie Ma	CD	1,376,959	340	———	2.12 (1.87 to 2.39)
5+ courses 2,363,459 2,316 Image: Contract of the	UC	1,376,959	671	H H H	1.54 (1.41 to 1.67)
IBD 2,363,459 2,316 Image: Algorithm of the state of the s	5+ courses			1	
CD 2,363,459 766 Image of the second	IBD	2,363,459	2,316	HeH	2.12 (2.01 to 2.23)
UC 2,363,459 1,550 1.97 (1.85 to 2.10) Age 60+ 1 1.97 (1.85 to 2.10) 1.97 (1.85 to 2.10) 1 course 1 1.21 (1.15 to 1.27) 1.20 (1.09 to 1.32) IBD 5,556,766 789 1.20 (1.09 to 1.32) UC 5,556,766 2,355 1.12 (1.15 to 1.27) 2 courses 1.22 (1.15 to 1.29) 1.22 (1.15 to 1.29) 2 courses 1.22 (1.15 to 1.29) 1.22 (1.15 to 1.29) 2 courses 1.43 (1.36 to 1.50) 1.43 (1.36 to 1.50) CD 3,444,961 621 1.45 (1.31 to 1.61) UC 3,444,961 621 1.45 (1.31 to 1.61) UC 3,444,961 1.753 1.44 1.45 (1.31 to 1.61) UC 3,444,961 1.753 1.44 1.50 (1.41 to 1.59) GD 2,121,202 1.1576 1.50 (1.41 to 1.59) 1.50 (1.40 to 1.61) GD 2,31,472 1.158 1.50 (1.40 to 1.61) 1.50 (1.40 to 1.61) GD 1,331,472 1.164 1.72 (1.61 to 1.84) 1.61 (1.68 to 2.16) UC 1,331,472 3.40 1.91 (1.68 to 2.16)	CD	2,363,459	766	⊢ ●−−1	2.54 (2.31 to 2.80)
Age 60+ 1 1 course 1 1BD 5,556,766 3,144 ● 1.21 (1.15 to 1.27 CD 5,556,766 789 ● 1.20 (1.09 to 1.32 UC 5,556,766 2,355 ● 1.22 (1.15 to 1.27 CD 5,556,766 2,355 ● 1.22 (1.15 to 1.27 2 courses 1.22 (1.15 to 1.29 1.22 (1.15 to 1.29 2 courses 1 1.43 (1.36 to 1.50 CD 3,444,961 6.21 ● UC 3,444,961 6.21 ● JC 3,444,961 6.21 ● UC 3,444,961 1.753 ●● 1.43 (1.34 to 1.50 JC 3,444,961 1.753 ●● 1.50 (1.41 to 1.59 JC 2,12,02 1.1576 ●● 1.50 (1.41 to 1.59 JC 2,12,02 1.1576 ●● 1.50 (1.41 to 1.59 JC 1,331,472 1.1576 ●● 1.50 (1.40 to 1.61 JC 1,331,472 1.158 ● 1.50 (1.41 to 1.59 JC 1,331,472 3.40<	UC	2,363,459	1,550	HHH I	1.97 (1.85 to 2.10)
1 course IBD 5,556,766 3,144 IM 1.21 (1.15 to 1.27 CD 5,556,766 789 IM 1.20 (1.09 to 1.32 UC 5,556,766 2,355 IM 1.22 (1.15 to 1.29 UC 5,556,766 2,355 IM 1.22 (1.15 to 1.29 2 courses 1.22 (1.15 to 1.29 1.22 (1.15 to 1.29 2 courses IIBD 3,444,961 2,374 IM 1.43 (1.36 to 1.50 CD 3,444,961 621 IM 1.45 (1.31 to 1.61 UC 3,444,961 1,753 IM 1.43 (1.34 to 1.51 3 courses IIBD 2,121,202 1,576 IM 1.50 (1.41 to 1.59 GD 2,121,202 1,159 IM 1.50 (1.40 to 1.61 1.50 (1.40 to 1.61 4 courses IIBD 1,331,472 1,164 IM 1.72 (1.61 to 1.84 GD 1,331,472 1,164 IM 1.91 (1.68 to 2.16 1.91 (1.68 to 2.16 UC 1,331,472 3,00 IM 1.91 (1.68 to 2.16 1.95 (1.85 to 2.04 GD 1,331,472 3,009 IM <	Age 60+			1	
IBD 5,556,766 3,144 IM 1.21 (1.15 to 1.27 CD 5,556,766 789 Im 1.20 (1.09 to 1.32) UC 5,556,766 2,355 Im 1.22 (1.15 to 1.29) 2 courses Im 1.22 (1.15 to 1.29) 1.22 (1.15 to 1.29) 2 courses Im 1.22 (1.15 to 1.29) 1.22 (1.15 to 1.29) 2 courses Im 1.22 (1.15 to 1.29) 1.43 (1.36 to 1.50) CD 3,444,961 621 Imm 1.43 (1.36 to 1.50) CD 3,444,961 1.753 Imm 1.43 (1.31 to 1.61) UC 3,444,961 1.753 Imm 1.43 (1.31 to 1.61) UC 3,444,961 1.753 Imm 1.45 (1.31 to 1.61) UC 2,121,202 1.159 Imm 1.50 (1.41 to 1.59) GD 2,121,202 1.159 Imm 1.50 (1.41 to 1.61) 4 courses IBD 1,331,472 1.164 Imm 1.72 (1.61 to 1.64) UC 1,331,472 1,164 Imm 1.91 (1.68 to 2.16) 1.91 (1.68 to 2.16) IBD 1,331,472 3.09	1 course			1	
CD 5,556,766 789 Image: constant of the state	IBD	5,556,766	3,144	I	1.21 (1.15 to 1.27)
UC 5,556,766 2,355 Image: Contrast of the state of the sta	CD	5,556,766	789		1.20 (1.09 to 1.32)
2 courses 1.42 1.43 1.43 1.43 1.45 1.45 1.45 IBD 3,444,961 621 Image: Courses 1.45 1.52 1.45 1.52 1.45 1.52 1.45 1.52 1.55 1.40 1.52 1.55 1.70 1.52 1.52 1.55 1.70 1.64 1.52 1.52 1.61 1.61 1.45 1.52 1.61 1.61 1.51 1.51 1.51 1.51 1.51 1.51 1.51 <t< td=""><td>UC</td><td>5.556.766</td><td>2.355</td><td>101</td><td>1.22 (1.15 to 1.29)</td></t<>	UC	5.556.766	2.355	101	1.22 (1.15 to 1.29)
IBD 3,444,961 2,374 Imit 1.43 (1.36 to 1.50 CD 3,444,961 621 Imit 1.45 (1.31 to 1.61 UC 3,444,961 1.753 Imit 1.43 (1.34 to 1.51 JUC 3,444,961 1.753 Imit 1.43 (1.34 to 1.51 JUC 3,444,961 1.753 Imit 1.43 (1.34 to 1.51 JUC 3,444,961 1.756 Imit 1.50 (1.41 to 1.59 JBD 2,121,202 1.576 Imit 1.50 (1.41 to 1.59 CD 2,121,202 1.159 Imit 1.50 (1.40 to 1.61 4 courses IBD 1,331,472 1.164 Imit 1.72 (1.61 to 1.84 CD 1,331,472 34.0 Imit 1.67 (1.68 to 2.16 1.91 (1.68 to 2.16 UC 1,331,472 34.0 Imit 1.95 (1.85 to 2.04 1.67 (1.54 to 1.80 St courses IBD 2,965,844 3,099 Imit 1.95 (1.85 to 2.04 UC 2,965,844 3,099 Imit 1.95 (1.85 to 2.04 1.92 (1.81 to 2.03 UC 2,965,844 2,070 Imit	2 courses	0,000,100	2,000		1.22 (1.10 to 1.20)
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CD 3,444,901 521 1.43 (1.3116 1.01 UC 3,444,901 1,753 1.43 (1.3116 1.01 3 courses 1.43 (1.34 to 1.51 BD 2,121,202 1,576 1.50 (1.41 to 1.59 CD 2,121,202 1,576 1.51 (1.40 to 1.61 4 courses 1.52 (1.35 to 1.70 1.52 (1.35 to 1.70 BD 1,331,472 1,164 1.52 (1.61 to 1.84 CD 1,331,472 340 1.91 (1.68 to 2.16 UC 1,331,472 824 1.67 (1.54 to 1.80 5+ courses 1.67 (1.54 to 1.80 2.16 (1.63 to 2.04 CD 2,965,844 3,099 1.95 (1.85 to 2.04 CD 2,965,844 886 2.07 (1.88 to 2.27 UC 2,965,844 2,213 1.92 (1.81 to 2.03		3,444,901	2,374		1.43 (1.36 to 1.50)
UC 3,444,961 1,753 Image: Mark 1,753 1,43 (1.34 to 1.51 3 courses IBD 2,121,202 1,576 Image: Mark 1,50 (1.41 to 1.59 CD 2,121,202 417 Image: Mark 1,50 (1.41 to 1.59 1,52 (1.35 to 1.70 UC 2,121,202 1,159 Image: Mark 1,50 (1.40 to 1.61 1,50 (1.40 to 1.61 4 courses IBD 1,331,472 1,164 Image: Mark 1,272 (1.61 to 1.84 UC 1,331,472 340 Image: Mark 1,272 (1.61 to 1.84 1.91 (1.68 to 2.16 UC 1,331,472 340 Image: Mark 1,272 (1.61 to 1.84 1.91 (1.68 to 2.16 UC 1,331,472 824 Image: Mark 1,272 (1.61 to 1.84 1.91 (1.68 to 2.16 UC 2,965,844 3,099 Image: Mark 1,272 (1.61 to 1.80 2.07 (1.88 to 2.27 UC 2,965,844 2,213 Image: Mark 1,272 (1.81 to 2.03 1.92 (1.81 to 2.03	CD	3,444,961	021		1.45 (1.31 to 1.61)
3 courses 1.50 (1.41 to 1.59) IBD 2,121,202 1,576 Image: Marcel State St	UC	3,444,961	1,753	l Hen	1.43 (1.34 to 1.51)
IBD 2,121,202 1,576 Image: model of the second seco	3 courses			1	
CD 2,121,202 417 Image: March and a constraint of the second and constraint of the constraint of the second a	IBD	2,121,202	1,576	l H ● H	1.50 (1.41 to 1.59)
UC 2,121,202 1,159 Image: March and the second and the	CD	2,121,202	417	H H H	1.52 (1.35 to 1.70)
4 courses IBD 1,331,472 1,164 Image: mail of the second s	UC	2,121,202	1,159	HOH	1.50 (1.40 to 1.61)
IBD 1,331,472 1,164 Image: model with the sector withe sector with the sector with the sector wit	4 courses			1	
CD 1,331,472 340 Image: Constraint of the second sec	IBD	1,331,472	1,164	H H H	1.72 (1.61 to 1.84)
UC 1,331,472 824 Image: Marcological system in the sy	CD	1,331,472	340	⊢ ●−−1	1.91 (1.68 to 2.16)
5+ courses IBD 2,965,844 3,099 Image: Fee the state	UC	1,331,472	824	H H H	1.67 (1.54 to 1.80)
IBD 2,965,844 3,099 Image: here 1.95 (1.85 to 2.04 CD 2,965,844 886 Image: here 2.07 (1.88 to 2.27) UC 2,965,844 2,213 Image: here 1.92 (1.81 to 2.03)	5+ courses			1	
CD 2,965,844 886 Image: Head State Stat	IBD	2,965,844	3,099	H e H	1.95 (1.85 to 2.04)
UC 2,965,844 2,213	CD	2,965,844	886		2.07 (1.88 to 2.27)
	UC	2,965.844	2,213	HeH	1.92 (1.81 to 2.03)
		.,,		00 150 200 250	

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 \geq 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 \geq 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 \geq 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 \geq 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 Incid	ence rate ratio by t	timing of an	tibiotic course	2						
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.

0	Person years	Events		IRR (95% CI)
Sulfonamide				
IBD	1,069,068	835		1.06 (0.99 to 1.1
CD	1,069,068	305		1.02 (0.90 to 1.1)
Penicillin, narrow	1,000,000	000		1.07 (0.07 10 1.1
IBD	13,351,481	9,036	•	1.09 (1.06 to 1.1
CD	13,351,481	3,503	iei	1.13 (1.07 to 1.2
UC	13,351,481	5,536		1.06 (1.01 to 1.1
IBD	922 488	804		1.11 (1.03 to 1.1
CD	922,488	288	- H	1.00 (0.88 to 1.1
UC	922,488	516	Here:	1.16 (1.05 to 1.2
Nitrofurantoin				
IBD	92,946	80		1.11 (0.88 to 1.3
CD	92,946	26		0.92 (0.61 to 1.3
OC Penicillin extended	92,940	04		1.21 (0.91 to 1.5
IBD	1,659,653	1,147	i i i i i i i i i i i i i i i i i i i	1.12 (1.05 to 1.1
CD	1,659,653	481	144	1.23 (1.11 to 1.3
UC	1,659,653	666	- Her	1.03 (0.95 to 1.1)
Macrolides				
IBD	3,723,880	2,936		1.15 (1.10 to 1.2
UC	3,723,880	1,165		1.21 (1.12 to 1.3
Other	0,120,000	1,771		1.00 (1.00 10 1.1
IBD	101,684	98		1.30 (1.06 to 1.5
CD	101,684	47		1.55 (1.14 to 2.0
UC	101,684	51		1.11 (0.83 to 1.4
Nitroimidazole				4.00
CD IRD	555,148	564		1.31 (1.19 to 1.4
UC	555.148	214	Here	1.27 (1.14 to 1.5
Fluoroquinolone		,		
IBD	362,077	474		1.76 (1.60 to 1.9
CD	362,077	189		1.88 (1.61 to 2.1
UC	362,077	285		1.66 (1.47 to 1.8
Age 40-60				
IBD	835.682	494		1,19 (1.08 to 1.2
CD	835,682	148		1.26 (1.05 to 1.5
UC	835,682	346		1.17 (1.04 to 1.3
Nitrofurantoin				
IBD	99,902	71		1.22 (0.95 to 1.5
CD	99,902	25		1.41 (0.92 to 2.0
Penicillin, narrow	99,902	46		1.15 (0.84 to 1.5
IBD	10.060.228	5 900		1.24 (1.19 to 1.2
CD	10,060,228	1,689	HH	1.28 (1.18 to 1.3
UC	10,060,228	4,216		1.24 (1.18 to 1.3
Macrolides				
IBD	3,004,664	1,960	Hel	1.31 (1.23 to 1.3
CD	3,004,664	562	Here	1.33 (1.19 to 1.4
Tetracyclines	3,004,004	1,390		1.31 (1.23 (0 1.4
IBD	534,154	370		1.35 (1.21 to 1.5
CD	534,154	105		1.34 (1.08 to 1.6
UC	534,154	265	H#H	1.37 (1.20 to 1.5
Penicillin, extended				
IBD	1,639,845	1,155	HeH	1.35 (1.26 to 1.4
UC	1,639,845	802		1.34 (1.23 to 1.4
Nitroimidazole				
IBD	544,189	396	H#H	1.43 (1.28 to 1.5
CD	544,189	109		1.35 (1.10 to 1.6
UC	544,189	287		1.47 (1.30 to 1.6
Other	131 714	116	_	154/127 to 18
CD	131,714	34		1.48 (1.03 to 2.0
uc	131,714	82		1.59 (1.26 to 1.9
Fluoroquinolone				
IBD	468,296	434		1.79 (1.61 to 1.9
CD	468,296	132		1.88 (1.56 to 2.2
UC	468,296	302		1.77 (1.57 to 1.9
nye ou+				
Nitrofurantoin				
Nitrofurantoin IBD	274,654	185	**	0.93 (0.79 to 1.0
Nitrofurantoin IBD CD	274,654 274,654	185 53		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1
Nitrofurantoin IBD CD UC	274,654 274,654 274,654	185 53 132		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1 0.96 (0.80 to 1.1
Nitrofurantoin IBD CD UC Other	274,654 274,654 274,654	185 53 132		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1 0.96 (0.80 to 1.1
Nitrofurantoin IBD CD UC Other IBD	274,854 274,854 274,854 327,105	185 53 132 241		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1 0.96 (0.80 to 1.1 1.03 (0.90 to 1.1
Nitrofurantoin IBD CD UC Other IBD CD UC	274,854 274,854 274,854 327,105 327,105 327,105	185 53 132 241 74		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1 0.96 (0.80 to 1.1 1.03 (0.90 to 1.1 1.05 (0.82 to 1.3 1.05 (0.82 to 1.3
Nitrofurantoin IBD CD UC Other IBD CD UC UC Sulfonamide	274,854 274,854 274,854 327,105 327,105 327,105	185 53 132 241 74 167		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1 0.96 (0.80 to 1.1 1.03 (0.90 to 1.1 1.05 (0.82 to 1.3 1.04 (0.89 to 1.2
Nitrofurantoin IBD CD UC Other IBD CD UC Sulfonamide IBD	274,654 274,654 274,654 327,105 327,105 327,105 1,085,255	185 53 132 241 74 167 806		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1 0.96 (0.80 to 1.1 1.03 (0.90 to 1.1 1.05 (0.82 to 1.3 1.04 (0.89 to 1.2 1.17 (1.08 to 1.2
Nitroturantoin IBD CD UC Other IBD CD Sulfonamide IBD CD	274,654 274,654 274,654 327,105 327,105 327,105 1,085,255 1,085,255	185 53 132 241 74 167 806 227		0.93 (0.79 to 1.0 0.88 (0.88 to 1.1 0.96 (0.80 to 1.1 1.03 (0.90 to 1.1 1.05 (0.82 to 1.3 1.04 (0.89 to 1.2 1.17 (1.08 to 1.2 1.22 (1.05 to 1.4
Nitrofurantoin IBD CD UC Other IBD UC Sulfonamide IBD CD UC	274,854 274,854 274,854 327,105 327,105 327,105 1,085,255 1,085,255 1,085,255	185 53 132 241 74 167 806 227 579		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1 0.96 (0.80 to 1.4 1.03 (0.90 to 1.4 1.05 (0.82 to 1.3 1.04 (0.89 to 1.2 1.17 (1.08 to 1.2 1.22 (1.05 to 1.4 1.17 (1.06 to 1.2
Nitrofurantoin IBD CD UC UC UC UC UC UC Sulfonamide IBD CD UC UC UC	274,854 274,854 274,854 327,105 327,105 327,105 1,085,255 1,085,255 1,085,255	185 53 132 241 74 167 806 227 579		0.93 (0.79 to 1.0 0.89 (0.66 to 1.1 0.96 (0.80 to 1.1 1.03 (0.90 to 1.1 1.05 (0.82 to 1.3 1.04 (0.89 to 1.2 1.17 (1.08 to 1.2 1.22 (1.05 to 1.4 1.17 (1.06 to 1.2
Nitrofurantoin IBD CD UC Other IBD CD Sulfonamide IBD CD VC VC Penicillin, narrow IBD	274,854 274,854 274,854 327,105 327,105 1,085,255 1,085,255 1,085,255 8,308,855 8,308,855	185 53 132 241 74 167 806 227 579 5,705		0.93 (0.79 to 10 0.89 (0.66 to 1.1 0.96 (0.80 to 1.4 1.03 (0.90 to 1.4 1.05 (0.82 to 1.3 1.04 (0.89 to 1.2 1.17 (1.06 to 1.2 1.22 (1.05 to 1.4 1.17 (1.06 to 1.2 1.20 (1.15 to 1.2)
Nitrofurantoin IBD CD UC Other IBD CD Sulfonamide IBD CD UC Penicillin, narrow IBD CD UC	274,854 274,854 274,854 327,105 327,105 1,085,255 1,085,255 1,085,255 8,308,855 8,308,855	185 53 132 241 74 167 806 227 579 5,705 1,521 4,185		0.93 (0.79 to 10 0.89 (0.66 to 1.1 0.96 (0.80 to 1.4 1.03 (0.90 to 1.4 1.03 (0.90 to 1.4 1.06 (0.82 to 1.3 1.04 (0.89 to 1.2 1.17 (1.08 to 1.2 1.22 (1.05 to 1.4 1.17 (1.08 to 1.2 1.20 (1.15 to 1.4 1.23 (1.17 to 1.3
Nitrofurantoin IBD CD CD CD CD CD CD CD CD CD CD CD CD Panicillin, narrow IBD CD CD CD CD CD CD CD CD CD CD CD CD CD	274,854 274,854 274,854 327,105 327,105 327,105 327,105 327,105 1,085,255 1,085,255 1,085,255 8,308,855 8,308,855	185 53 132 241 74 167 806 227 579 5,705 1,521 4,185	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	0.93 (0.79 to 1.0 0.88 (0.66 to 1.1 0.96 (0.80 to 1.1 0.96 (0.80 to 1.1 1.03 (0.90 to 1.1 1.06 (0.82 to 1.3 1.04 (0.89 to 1.2 1.22 (1.05 to 1.4 1.17 (1.06 to 1.2 1.22 (1.05 to 1.4 1.17 (1.06 to 1.2 1.20 (1.15 to 1.2 1.23 (1.17 to 1.3
Nitrofurantoin IBD CD UC Other IBD CD Sulfonamide IBD Penicillin, earrow IBD CD UC IBD	274,854 274,854 274,854 327,105 327,105 327,105 327,105 327,105 1,085,255 1,085,255 1,085,255 1,085,255 1,085,255 8,308,855 8,308,855 8,308,855	185 53 132 241 74 167 806 227 579 5,705 1,521 4,185 1,474		0.93 (0.79 to 10 0.88 (0.86 to 1.1 0.96 (0.80 to 1.1 105 (0.80 to 1.1 105 (0.80 to 1.1 105 (0.82 to 13, 1.17 (1.08 to 12 1.22 (1.05 to 14 1.17 (1.06 to 12 1.20 (1.15 to 12 1.23 (1.17 to 1.3 1.24 (1.16 to 13,
Nitofurantia IBD CO CO CO CO CO CO CO CO CO CO CO Penicilin, narrow IBO CO CO CO CO CO CO CO CO CO CO CO CO CO	274,854 274,854 274,854 327,105 327,10	185 53 132 241 74 167 806 227 579 5,705 1,521 4,185 1,474 392		0.93 (0.79 to 1.0 0.88 (0.66 to 1.1 0.96 (0.66 to 1.1 0.96 (0.86 to 1.1 1.03 (0.90 to 1.1 1.15 (0.82 to 1.3 1.16 (0.88 to 1.2 1.17 (1.08 to 1.2 1.17 (1.08 to 1.2 1.12 (1.17 to 1.3 1.23 (1.17 to 1.3 1.23 (1.17 to 1.3 1.23 (1.17 to 1.3 1.13 (1.00 to 1.2
Nitofurantia CD CD CD VC VC VC VC VC VC VC VC VC VC VC VC VC	274,854 274,854 274,854 327,105 327,10	185 53 132 241 74 167 806 227 579 5,705 1,521 4,185 1,474 392 1,082		0 93 (0.79 to 10 0 86 (0.69 to 11 0 86 (0.69 to 11 0 96 (0.69 to 11 10 96 (0.89 to 11 10 96 (0.89 to 11 10 96 (0.89 to 12 10 46 (0.89 to 12 11 77 (1.08 to 12 12 71 76 to 13 12 71 7
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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.³

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 1and 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 multidrugresistant 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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Acknowledgements Jill Gregory for contribution to the visual abstract design.

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Inflammatory bowel disease

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, Novartis, PBM Capital, Pfizer, Sanofi, Takeda, TiGenix, Vifor; holds stock options in Intestinal Biotech Development.

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.

Patient consent for publication Not applicable.

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)

Provenance and peer review Not commissioned; externally peer reviewed.

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.

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