

# Supplementary Appendix

## Supplement to “Antibiotic use and the development of inflammatory bowel disease: a national case/control study in Sweden”

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## Supplementary Tables

**Supplementary Table 1: Histopathology and International Classification of Disease (ICD) codes used to define the study population**

		Ulcerative colitis (UC)	Crohn's disease (CD)	IBD-unclassified (IBD-U)
<b>Histopathology</b>	<b>Anatomic location</b>	T65, T66, T67, T68	T62, T63, T64, T65, T66, T67, T68	T65, T66, T67, T68
	<b>Histologic features (morphology codes)</b>		M41, M42, M43, M44, M46300, M47	
<b>Diagnostic codes from the Swedish Patient Register</b>	<b>Diagnostic code</b>	D6255	D6216	D6214
	<b>ICD-7</b>	572.20, 572.21	572.00, 572.09	NA
	<b>ICD-8</b>	563.10, 563.99, 569.02	563	NA
	<b>ICD-9</b>	556	555	NA
	<b>ICD-10</b>	K51	K50	K52.3

Abbreviations: ICD - international classification of disease

**Supplementary Table 2: Antibiotic classification by class and coverage**

Antibiotics class	Spectrum
tetracyclines	
doxycycline	broad
lymecycline	broad
oxytetracycline	broad
tetracycline	broad
minocycline	broad
tigecycline	broad
beta-lactam antibacterials and penicillins	
ampicillin	broad
pivampicillin	broad
amoxicillin	broad
pivmecillinam	narrow
piperacillin	broad
benzylpenicillin	narrow
phenoxymethylpenicillin	narrow
benzathine benzylpenicillin	narrow
dicloxacillin	narrow
cloxacillin	narrow
flucloxacillin	narrow
amoxicillin and beta-lactamase inhibitor	broad
piperacillin and beta-lactamase inhibitor	broad
other beta-lactam antibacterials	
cefalexin	narrow
cefadroxil	narrow
cefoxitin	broad
cefuroxime	broad
loracarbef	broad
cefotaxime	broad
ceftazidime	broad
ceftriaxone	broad
cefepodoxime	broad
ceftibuten	broad
ceftriaxone, combinations	broad
aztreonam	broad
meropenem	broad
ertapenem	broad
imipenem and cilastatin	broad
Sulfonamides and trimethoprim	
trimethoprim	broad
sulfadiazine	broad
sulfamethoxazole and trimethoprim	broad
Macrolides, lincosamides, and streptogramins	

erythromycin	narrow
roxithromycin	narrow
clarithromycin	narrow
azithromycin	narrow
telithromycin	broad
clindamycin	narrow
pristinamycin	broad

#### Aminoglycoside antibacterials

tobramycin	broad
gentamicin	broad
amikacin	broad
netilmicin	broad

#### Quinolone antibacterials

ofloxacin	broad
ciprofloxacin	broad
norfloxacin	broad
levofloxacin	broad
moxifloxacin	broad

#### Other Antibacterials

vancomycin	narrow
teicoplanin	narrow
colistin	broad
fusidic acid	narrow
metronidazole	broad
nitrofurantoin	narrow
fosfomycin	broad
methenamine	narrow
linezolid	broad

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**Supplementary Table 3: Patient characteristics at the time of inflammatory bowel disease diagnosis and their matched general population controls, (IBD vs. control), 2007-2016**

	Cases <i>n</i> =23,982 <sup>#</sup>	Controls <i>n</i> =117,827
<b>Age, years</b>	35 [22-54]	35 [22-54]
<18	3,461 (15)	17,699 (15)
18-24	3,997 (17)	20,421 (17)
25-34	4,558 (19)	22,785 (19)
35-44	3,198 (13)	15,843 (13)
45-54	2,719 (11)	13,451 (12)
55-64	2,957 (12)	13,487 (12)
≥65	3,092 (13)	14,141 (12)
<b>Male sex, <i>n</i> (%)</b>	12,616 (52)	62,010 (52)
<b>County of residence, <i>n</i> (%)</b>		
Northern Sweden	2,017 (8)	9,926 (8)
Southeastern Sweden	2,758 (12)	13,572 (12)
Southern Sweden	4,554 (19)	22,390 (19)
Stockholm-Gotland	5,134 (21)	25,229 (21)
Uppsala-Örebro	5,124 (21)	25,216 (21)
Western Sweden	4,250 (18)	20,922 (18)
Unknown	155 (1)	572 (1)
<b>Education, <i>n</i> (%)</b>		
≤9 years	4,395 (18)	21,030 (18)
10-12 years	10,653 (44)	50,542 (43)
≥13 years	8,035 (35)	41,092 (35)
Unknown	899 (4)	5,163 (4)
<b>Number of encounters*, <i>n</i></b>		
Inpatient	2 [0-4]	1 [0-3]
Outpatient	5 [2-12]	3 [1-9]
<b>Calendar year</b>		
2007-2009	7,013 (29)	34,449 (29)
2010-2013	10,671 (44)	52,373 (44)
2014-2016	6,298 (26)	31,005 (26)

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

<sup>#</sup> includes ulcerative colitis, Crohn's disease, and IBD-unclassified

\* calculated the number of inpatient and outpatient encounters (continuous) for each participant during the study period up until the time of matching

**Supplementary Table 4.** Overall antibiotic use and inflammatory bowel disease comparing cases and their matched general population controls by age group, 2007-2016

	Cumulative antibiotic use				<i>P</i> -trend
	No use	1 dispensation	2 dispensations	≥3 dispensations	
<b>&lt;18 years</b>					
Cases, <i>n</i> (%)	1,593 (35)	1,711 (38)	457 (10)	795 (17)	
Controls, <i>n</i> (%)	8,734 (49)	3,680 (21)	1,939 (11)	3,346 (19)	
Multivariable OR (95% CI)‡	1.0 (ref)	1.04 (0.94, 1.15)	1.26 (1.12, 1.42)	1.25 (1.12, 1.40)	<0-0001
<b>18-39 years</b>					
Cases, <i>n</i> (%)	4,380 (42)	2,160 (20)	1,345 (13)	2,566 (25)	
Controls, <i>n</i> (%)	25,349 (49)	10,872 (21)	5,655 (11)	9,893 (19)	
Multivariable OR (95% CI)‡	1.0 (ref)	1.15 (1.08, 1.21)	1.38 (1.29, 1.48)	1.46 (1.37, 1.55)	<0-0001
<b>40-59 years</b>					
Cases, <i>n</i> (%)	2,119 (40)	1,108 (51)	668 (13)	1,402 (26)	
Controls, <i>n</i> (%)	12,662 (49)	5,600 (21)	2,896 (11)	4,971 (19)	
Multivariable OR (95% CI)‡	1.0 (ref)	1.19 (1.10, 1.29)	1.40 (1.27, 1.55)	1.61 (1.48, 1.76)	<0-0001
<b>≥60 years</b>					
Cases, <i>n</i> (%) <sup>4678</sup>	1,585 (34)	834 (18)	617 (13)	1,642 (35)	
Controls, <i>n</i> (%)	9,495 (43)	4,712 (21)	2,662 (12)	5,361 (24)	
Multivariable OR (95% CI)‡	1.0 (ref)	1.09 (0.99, 1.19)	1.43 (1.28, 1.69)	1.81 (1.66, 1.98)	<0-0001

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

Abbreviations: OR - odds ratio, CI - confidence interval

<sup>#</sup>Includes ulcerative colitis, Crohn's disease, and IBD-unspecified

<sup>†</sup>Conditional logistic regression matched for age, sex, calendar year, and county

<sup>‡</sup>Further adjusted for number of inpatient and outpatient encounters and education level

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

**Supplementary Table 5: Sibling characteristics at the time of their case sibling's inflammatory bowel disease diagnosis, 2007-2016**

	<b>IBD</b> <i>n</i> =16,353	<b>Non-IBD siblings</b> <i>n</i> =28,732
<b>Age, years</b>	31 [20-49]	33 [21-53]
<18	2,898 (18)	4,827 (17)
18-24	3,289 (20)	5,028 (18)
25-34	3,182 (19)	5,222 (18)
35-44	2,083 (13)	3,726 (13)
45-54	1,787 (11)	3,615 (13)
55-64	1,827 (11)	3,620 (12)
≥65	1,287 (8)	2,694 (9)
<b>Male sex, n (%)</b>	8,714 (53)	14,570 (51)
<b>County of residence, n (%)</b>		
Northern Sweden	1,446 (9)	2,741 (10)
Southeastern Sweden	1,984 (12)	3,484 (12)
Southern Sweden	3,092 (19)	5,454 (19)
Stockholm-Gotland	3,210 (20)	5,315 (18)
Uppsala-Örebro	3,597 (22)	6,396 (22)
Western Sweden	2,925 (18)	5,154 (18)
Unknown	99 (1)	188 (1)
<b>Education, n (%)</b>		
<9 years	2,632 (16)	5,023 (18)
10-12 years	7,536 (46)	13,047 (45)
≥13 years	5,568 (34)	9,143 (32)
Unknown	617 (4)	1,519 (5)
<b>Number of encounters, n</b>		
Inpatient	1 [0-4]	1 [0-3]
Outpatient	5 [2-11]	4 [1-10]
<b>Calendar year</b>		
2007-2009	4,709 (29)	8,319 (29)
2010-2013	7,293 (44)	12,789 (44)
2014-2016	4,351 (26)	7,624 (27)

Values are median [IQR] or absolute figures (percentages). Polytomous variables may not sum to 100% due to rounding. Distributions may differ between (unmatched) groups. IBD cases without siblings not shown.

## Supplementary Figures

Supplementary Figure 1: Description of study period with lead-in

