SUPPLEMENTAL MATERIAL

eFIGURES

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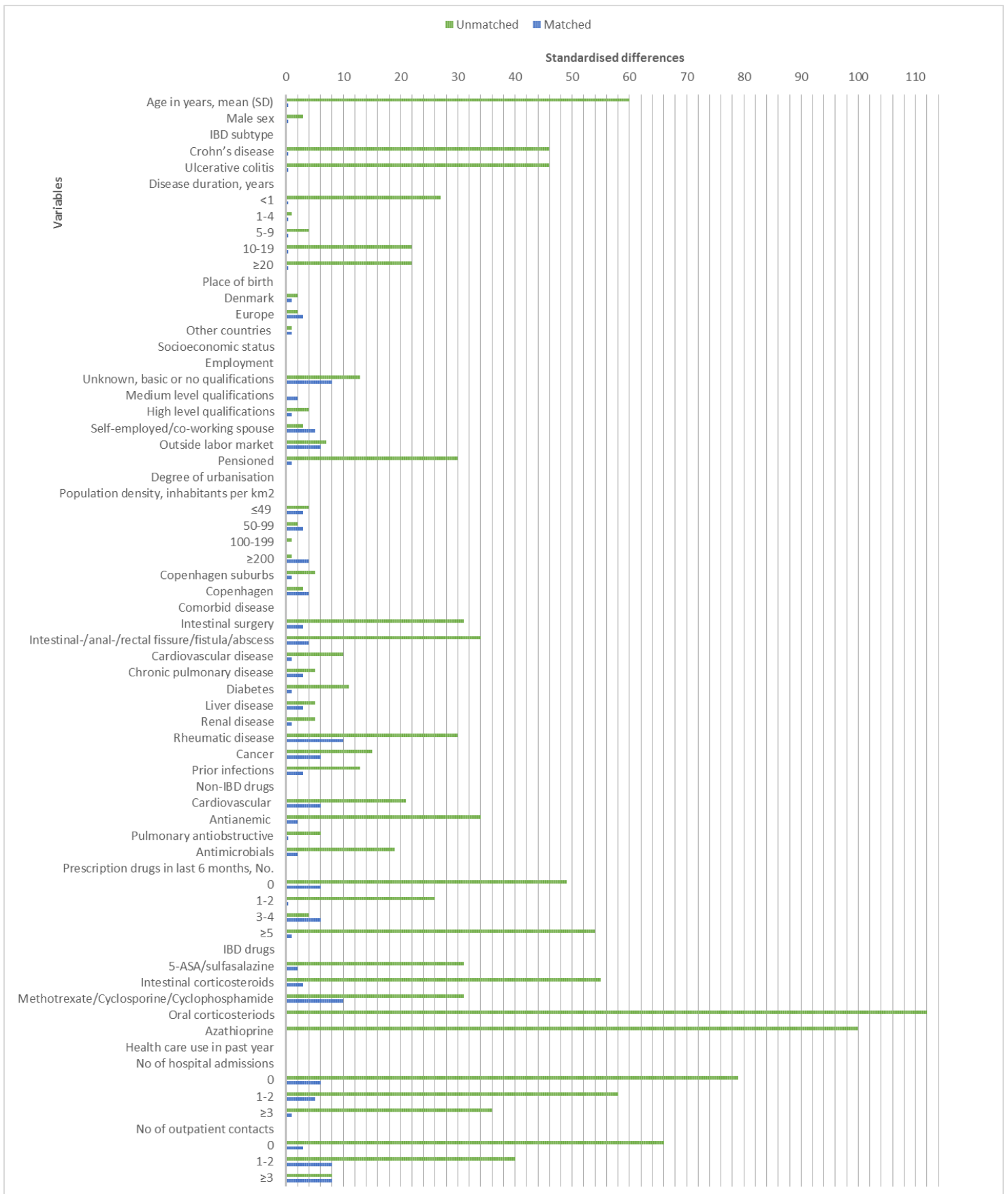
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eFigure 1. Standardised differences between TNF-α inhibitor users and non-users before and after matching on fixed factors and propensity scores.

eTable 1: All diagnoses of infections with related ICD 10-codes included as any serious infection with the subdivision into six site-specific groups.

Subgroup of infection	Diagnoses	ICD-10
Respiratory tract infections	Mastoiditis	H70
	Nasopharyngitis	A36.1
	Sinuitis	J01.0-J01.9
	Pharyngitis	J02.0-J02.9
	Tonsillitis	A36.0; J03.0-J03.9
	Laryngitis and tracheitis	A36.2; J04.0-J05.9; J37.0-J37.9
	Acute upper respiratory infections of multiple and unspecified sites	A36.8-A36.9; J06.0-J06.9
	Abscessus peritonsillaris	J36.0-J36.9
	Pneumonia	A48.1; B01.2; J12.0-J18.9; J10.0
	Other acute lower respiratory infections	A37.0-A37.9; A42.0; J20.0-J22.9
	Abscessus pulmonis	J85
	Empyema pleurae	J86
Infections of the gastrointestinal tract[a]	Intestinal infectious disease	A00.0-A09.9 (but not A02.1)
	Cholangitis	K830 (but not K830F and K830G)
	Acute peritonitis	K650
	Hepatitis A and C	B15, B17
	Liver abscess	K750
	Abdominal actinomycosis	A42.1
Urological and gynecological infections	Nephritis	N10.0-N10.9
	Acute prostatitis	N410
	Cystitis	N30.0
	Salpingitis and oophoritis	N70.0
	Endometritis	N71.0
	Cervicitis uteri	N72
	Syphilis	A50.0-A53.9
	Gonorrhea	A54
	Chlamydia	A55.0-A56.9
Infections of the skin and subcutaneous tissue	Erysipelas	A46.0-A46.9
	Dermatophytosis and other superficial mycoses	B35.0-B36.9
	Cellulitis and abscess	L02.0-L03.9
	Acute lymphadenitis	L04.0-L04.9
	Herpes virus	B02; B00, A60, H19.1, B01
	Pilonidal cyst	L05.0-L05.9
	Other local infections of skin and subcutaneous tissue	A36.3; L00.0-L01.0; L08.0-L08.9; L30.3
Sepsis	Streptococcal	A40
	Other, including staph. aureus	A41
	Listeria	A32.7
	Salmonella	A02.1
	Candida	B37.7
	Meningococcal	A39.2
Other infections	Infection of the eye	B30; H00.0; H03.0-H03.1; H06.1; H10.0; H10.5-H10.8
	Infections of the musculoskeletal system and connective tissue	M00.0-M01.9; M60.0; M86.0-M86.9
	Infections in the nervous system	G00-G01; A39.0; A32.1; A87; B00.3-4; B01.0; B02.1; B05.1; B06.0; A83; G04.0-G05.9; G02; G06
	Certain bacterial disease	A20.0-A29.9; A32.0-A.32.9 A.34.0-A35.9 ; A38.0; A42.2-A44.9; A48.0; A48.2-A49.9; A15-A19; A31;
	Spirochaetal disease	A65.0-A69.9
	Rickettsiosis	A75.0-A79.9
	Viral infections	A80.0-A99.9; B05.0-B06.9; B08.1-B09.9; B26-B27; B33.0-B34.9; B25;
	Mycoses	B37.0-B49.9; B59
	Protozoal diseases	B50.0-B83.9; A07.2;
	Unspecified infectious diseases	B99.9

[a]Anorectal and intestinal abscess were excluded as such a diagnosis is most probably due to IBD and not the therapy. Abbreviations: ICD, international classification of disease.

eTable 2: Variables included in the propensity score and variables for inflammatory bowel disease-related drugs with diagnostic, operation and ATC codes, categories, source of data and missing values.

Variables	Diagnostic ICD-10 codes, operation codes, ATC codes	Categories	Source of data	% missing
Demographics				
Age		Five year interval	Danish Civil Registration System	0
Country of birth		Denmark, Europe or other	Danish Civil Registration System	0
Socioeconomic status		1/ Employment with unknown, basic or no qualifications 2/ Employment with medium level qualifications 3/ Employment with high level qualifications 4/ Self-employed/co-working spouse 5/ Outside labor market 6/ Pensioned	Statistics Denmark	0.08
Degree of urbanisation		1/ ≤ 49 inhabitants 2/ 50-99 inhabitants 3/ 100-199 inhabitants 4/ ≥ 200 inhabitants 5/ Residence in Copenhagen suburbs 6/ Residence in Copenhagen	Statistics Denmark	0
Others				
Subtype of IBD	ICD-8 codes: 56300-02, 56308-09, 56319 and 56309 ICD-10 code: K50, K51	Ulcerative colitis or Crohn's disease	National Patient Registry	0
Comorbid disease[a]	**ICD-10 codes**			
Cardiovascular disease	I200, I21-22, I11, I20, I24, I25, I110, I130, I132, I42, I43, I50, J81, I34-37, Q20-26, I65, I70-I77, K550-551, I44-49, I26, I801-809, I81	Yes/no	National Patient Registry	0
Chronic pulmonary disease	I27, J40-47, J60-70, J84, J92, J96, J982, J983	Yes/no	National Patient Registry	0
Renal disease	I12-13, N00-08, N17-19, N25, Z49, Z940, Z992	Yes/no	National Patient Registry	0
Liver disease	B18, I850, I859, I982, K70-K77	Yes/no	National Patient Registry	0
Cancer (non-melanoma skin cancer excluded)	C00-C43, C45-C97	Yes/no	National Patient Registry	0
Diabetes mellitus	E10-E14 (or at least two prescriptions fills for antidiabetics, ATC code A10)	Yes/no	National Patient Registry, Danish Drug Prescription Registry	0
Rheumatic disease	M05-09, M30-34, M351, M353, M45	Yes/no	National Patient Registry	0
Prior infections	See eTable 1 for ICD-10 codes	Yes/no	National Patient Registry	0
Intestinal, rectal or anal fistula, abscess or fissure	K60-K61, K63.0, K63.2	Yes/no	National Patient Registry	0

Surgery[a]	Operation codes			
Intestinal surgery	KJH, KJE, KJF, KJG	Yes/no	National Patient Registry	0
Non-IBD drugs[a]	**ATC-codes**			
Antianemic	B03	Yes/no	Danish Drug Prescription Registry	0
Cardiovascular	C01-C10	Yes/no	Danish Drug Prescription Registry	0
Pulmonary antiobstructive	R03	Yes/no	Danish Drug Prescription Registry	0
Antimicrobials	J01, J02, J04, J05, J06	Yes/no	Danish Drug Prescription Registry	0
IBD drugs[a]	**ATC-codes**			
Oral corticosteroids[b]	H02AB		Danish Drug Prescription Registry	0
Azathioprine[b]	L04AX01		Danish Drug Prescription Registry	0
5-ASA/sulfasalazine	A07EC01		Danish Drug Prescription Registry	0
Intestinal corticosteroids	A07EA		Danish Drug Prescription Registry	0
Methotrexate/Cyclosporine/Cyclophosphamide	L04AX03/ L04AD01/ L04AA01		Danish Drug Prescription Registry	0
Prescription drugs used in last 6 months		0,1-2,3-4, ≥5	Danish Drug Prescription Registry	0
Health status				
Hospital admissions in last year		0, 1-2, ≥3	National Patient Registry	0
Outpatient hospital contacts in last year		0, 1-2, ≥3	National Patient Registry	0

ATC, anatomic therapeutic chemical; ICD, nternational classification of diseases;

[a]Registered within 1 years prior to cohort entry

[b]Not included in the propensity score

eTable 3. Characteristics of TNF-α inhibitor users and non-users before* matching on propensity scores.

	TNF-α inhibitor users (n=4 216) n (%)	TNF-α inhibitor non-users (n=46 091) n (%)
Age in years, mean (SD)	39.2 (13.8)	47.9 (14.8)
Male sex	1820 (43)	20 609 (45)
IBD subtype		
Crohn's disease	2224 (53)	14 200 (31)
Ulcerative colitis	1992 (47)	31 891 (69)
Disease duration, years		
<1	1083 (26)	6856 (15)
1-4	1433 (34)	15 961 (35)
5-9	1100(26)	11 156 (24)
10-19	561 (13)	10 054 (22)
≥20	39 (1)	2064 (5)
Place of birth		
Denmark	4016 (95)	43 689 (95)
Europe	82 (2)	1030 (2)
Other countries	118 (3)	1372 (3)
Socioeconomic status		
Employment		
Unknown, basic or no qualifications	1738 (41)	15 967 (35)
Medium level qualifications	555 (13)	6059 (13)
High level qualifications	403 (10)	4923(11)
Self-employed/co-working spouse	152 (4)	1932 (4)
Outside labor market	1190 (28)	11 528 (25)
Pensioned	178 (4)	5682 (12)
Degree of urbanisation		
Population density, inhabitants per km2		
≤49	318 (8)	3059 (7)
50-99	1273 (30)	13 399 (29)
100-199	946 (22)	10 112 (22)
≥200	468 (11)	4921 (11)
Copenhagen suburbs	833 (20)	10 115 (22)
Copenhagen	378 (9)	4485 (10)
Comorbid disease[a]		
Gastrointestinal		
Intestinal surgery	519 (12)	1865 (4)
Intestinal-/anal-/rectal fissure/fistula/abscess	339 (8)	515 (1)
Cardiovascular disease	257 (6)	4541 (10)
Chronic pulmonary disease	179 (4)	2452 (5)
Diabetes	208 (5)	3484 (8)

Liver disease	44 (1)	726 (2)
Renal disease	27 (1)	512 (1)
Rheumatic disease	439 (10)	1316 (3)
Cancer	63 (2)	1848 (4)
Prior infections[b]	329 (8)	2172 (5)
Non-IBD drugs[a]		
Cardiovascular	703 (17)	11 558 (25)
Antianemic	900 (21)	4178 (9)
Antiobstructive pulmonary	377 (9)	4911 (11)
Antimicrobials	2101 (50)	18 719 (41)
No of prescription drugs used in last 6 months		
0	150 (4)	8443 (18)
1-2	475 (11)	9481 (21)
3-4	608 (14)	7354 (16)
≥5	2983 (71)	20 813 (45)
IBD drugs[a]		
5-ASA/sulfasalazine	2021 (48)	15 079 (33)
Intestinal corticosteroids	1323 (31)	4520 (10)
Methotrexate/Cyclosporine/Cyclophosphamide	299 (7)	482 (1)
Oral corticosteroids	2545 (60)	6166 (13)
Azathioprine	2064 (49)	3979 (9)
Health care use in past year		
No of hospital admissions		
0	1606 (38)	34 427 (75)
1-2	1966 (47)	9461 (21)
≥3	644 (15)	2203 (5)
No of outpatient contacts		
0	610 (15)	19 741 (43)
1-2	2826 (67)	22 059 (48)
≥3	780 (19)	4291 (9)

Abbreviations: 5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease; SD, standard deviation; TNF, tumour necrosis factor.

All characteristics are as current at cohort entry unless stated otherwise.

*Not matched on propensity scores but matched on fixed factors including sex, age, disease duration and IBD subtype.

[a]As registered within 1 year prior cohort entry.

[b]Defined as prior infections associated with hospital admission within 1 year prior to cohort entry.

eTable 4. Characterisation of the distribution of the serious infection cases observed in TNF-α inhibitor users and non-users within 365 days of treatment initiation.

	Number of infections in TNF-α inhibitor users	Number of infections in TNF-α inhibitor non-users
Skin and soft tissue infections		
Abscess, furuncles, carbuncles	9	7
Erysipelas	5	3
Herpes, including zoster	3	0
Pilonidal cysts	1	1
Acute lymphadenitis	1	1
Impetigo	2	0
Pyoderma	1	0
Pityrosporum folliculitis	1	0
Skin infection, unspecified	3	1
Total	26	13
Respiratory tract infections		
Pneumonia	26	24
Acute sinusitis	1	0
Acute laryngitis	1	0
Pharyngitis/tonsillitis	0	1
Upper/lower respiratory tract infections	1	2
Peritonsillar abscess	1	1
Total	30	28
Gastrointestinal infections		
Clostridium difficile	4	2
Gastroenteritis, unspecified	18	13
Peritonitis	3	1
Salmonella enteritis	1	2
Cholangitis	2	3
Abdominal abscess	0	1
Viral enteritis	0	1
Alimentary infection	0	1
Total	28	24
Sepsis		
Sepsis caused by staphylococcus	3	0
Sepsis, unspecified	3	4
Total	6	4
Urological and gynecological infections		
Acute cystitis	6	3
Endometritis	0	1
Salpingo-oophoritis	2	0
Acute prostatitis	1	0
Total	9	4
Other infections		
Infection, unspecified	0	1
Cytomegalovirus	1	0
Candida infection	3	2
Purulent arthritis	1	0
Eye infections	2	1
Viral infections, unspecified	0	1
Listeria meningitis	1	0
Total	8	5
Total	**107**	**78**

Abbreviations: TNF, tumour necrosis factor

eTable 5. Characteristics of cohort patients with inflammatory bowel disease treated with TNF-α inhibitors and azathioprine as monotherapy, before* and after matching on propensity scores.

	Before propensity score matching		After propensity score matching	
	TNF-α inhibitor users (n=1211) *n* (%)	Azathioprine users (n=5545) *n* (%)	TNF-α inhibitor users (n=268) *n* (%)	Azathioprine users (n=268) *n* (%)
Age in years, mean (SD)	40.0 (14.1)	38.6 (14.7)	33.5 (12.1)	33.6 (12.2)
Male sex	520 (43)	2441 (44)	116 (43)	116 (43)
IBD subtype				
Crohn's disease	508 (42)	2566 (46)	144 (54)	144 (54)
Ulcerative colitis	703 (58)	2979 (54)	124 (46)	124 (46)
Disease duration, years				
<1	499 (41)	2709 (49)	154 (58)	153 (57)
1-4	285 (24)	1528 (28)	69 (26)	71 (27)
5-9	197 (16)	763 (14)	20 (8)	19 (7)
10-19	213 (18)	515 (9)	25 (9)	25 (9)
≥20	17 (1)	30 (1)	0	0
Place of birth				
Denmark	1155 (95)	5274 (95)	263 (98)	257 (96)
Europe	23 (2)	107 (2)	2 (1)	3 (1)
Other countries	33 (3)	164 (3)	3 (1)	8 (3)
Socioeconomic status				
Employment				
Unknown, basic or no qualifications	457 (38)	2409 (43)	119 (44)	122 (46)
Medium level qualifications	160 (13)	692 (13)	40 (15)	34 (13)
High level qualifications	130 (11)	505 (9)	21 (8)	23 (9)
Self-employed/co-working spouse	38 (3)	192 (4)	8 (3)	8 (3)
Outside labor market	364 (30)	1503 (27)	78 (29)	77 (29)
Pensioned	62 (5)	244 (4)	2 (1)	4 (2)
Degree of urbanisation				
Population density, inhabitants per km^2				
≤49	86 (7)	380 (7)	23 (9)	20 (8)
50-99	347 (29)	1664 (30)	83 (31)	86 (32)
100-199	265 (22)	1258 (23)	68 (25)	60 (22)
≥200	165 (14)	516 (9)	23 (9)	24 (9)
Copenhagen suburbs	236 (20)	1244 (22)	47 (18)	62 (23)
Copenhagen	112 (9)	483 (9)	24 (9)	16 (6)
Comorbid disease[a]				
Gastrointestinal				
Intestinal surgery	132 (11)	551 (10)	30 (11)	25 (9)
Intestinal-/anal-/rectal fissure/fistula/abscess	96 (8)	255 (5)	29 (11)	14 (5)
Cardiovascular disease	83 (7)	318 (6)	13 (5)	112 (5)

Chronic pulmonary disease	49 (4)	214 (4)	5 (2)	11 (4)
Diabetes	78 (6)	274 (5)	9 (3)	12 (5)
Renal disease	10 (1)	37 (1)	1 (<1)	1 (<1)
Liver disease	9 (1)	63 (1)	2 (1)	3 (1)
Rheumatic disease	216 (18)	173 (3)	8 (3)	10 (4)
Cancer	26 (2)	84 (2)	1 (<1)	1 (<1)
Prior infections[b]	108 (9)	466 (8)	24 (9)	26 (10)
Non-IBD drugs[a]				
Cardiovascular	185 (15)	886 (16)	24 (9)	21 (8)
Antianemic	210 (17)	670 (12)	35 (13)	47 (18)
Pulmonary antiobstructive	104 (9)	556 (10)	14 (5)	25 (9)
Antimicrobials	598 (49)	2470 (45)	118 (44)	123 (46)
Prescription drugs used in last 6 months, No.				
0	68 (6)	3829 (69)	59 (22)	59 (22)
1-2	163 (14)	168 (3)	18 (7)	21 (8)
3-4	192 (16)	247 (5)	36 (13)	36 (13)
≥5	788 (65)	1301 (24)	155 (58)	152 (57)
IBD drugs[a]				
5-ASA/sulfasalazine	632 (52)	3514 (63)	132 (49)	151 (56)
Intestinal corticosteroids	332 (27)	2159 (39)	85 (32)	89 (33)
Methotrexate/Cyclosporine/Cyclophosphamide	105 (9)	40 (1)	3 (1)	2 (1)
Oral corticosteroids	606 (50)	3794 (68)	138 (52)	199 (74)
Health care use in past year				
No of hospital admissions				
0	397 (33)	2209 (40)	75 (28)	91 (34)
1-2	647 (53)	2721 (49)	156 (58)	141 (53)
≥3	167 (14)	615 (11)	37 (14)	36 (13)
No of outpatient contacts				
0	159 (13)	931 (17)	34 (13)	35 (13)
1-2	803 (66)	3765 (68)	180 (67)	187 (70)
≥3	249 (21)	849 (15)	54 (20)	46 (17)

Abbreviations: 5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease; SD, standard deviation; TNF, tumour necrosis factor.

All characteristics are as current at cohort entry unless stated otherwise.

*Not matched on propensity scores but matched on fixed factors including sex, age, disease duration and IBD subtype.
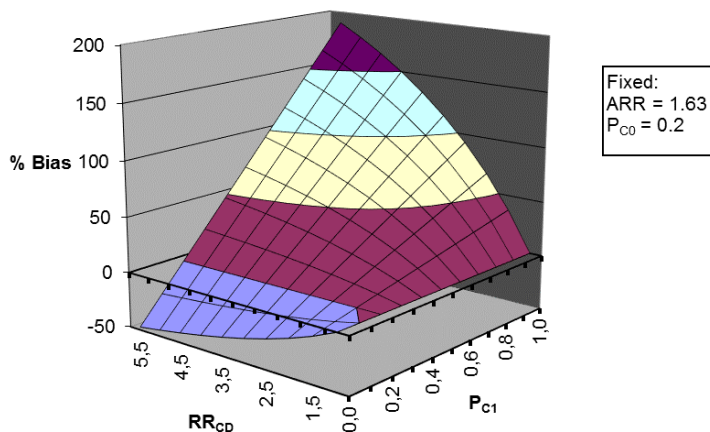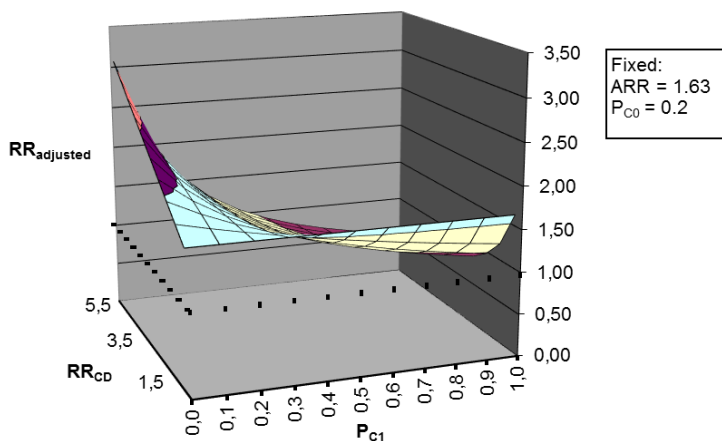
[a]As registered within 1 year prior cohort entry.

[b]Defined as prior infections associated with hospital admission within 1 year prior to cohort entry.

eTable 6: Array approach testing the impact of unmeasured confounding

$$RR_{adj.} = \dfrac{ARR}{\left[\dfrac{P_{C1}(RR_{CD}-1)+1}{P_{C0}(RR_{CD}-1)+1} \right]}$$

% Bias = [(ARR-RR$_{adj.}$)/RR$_{adj.}$]*100

ARR	RR$_{CD}$	P$_{C1}$	P$_{C0}$	RR$_{adjusted}$	%Bias
1,63	5,5	0,1	0,2	2,14	-23,68
1,63	5,0	0,1	0,2	2,10	-22,22
1,63	4,5	0,1	0,2	2,05	-20,59
1,63	4,0	0,1	0,2	2,01	-18,75
1,63	3,5	0,1	0,2	1,96	-16,67
1,63	3,0	0,1	0,2	1,90	-14,29
1,63	2,5	0,1	0,2	1,84	-11,54
1,63	2,0	0,1	0,2	1,78	-8,33
1,63	1,5	0,1	0,2	1,71	-4,55
1,63	1,0	0,1	0,2	1,63	0,00
1,63	5,5	0,2	0,2	1,63	0,00
1,63	5,0	0,2	0,2	1,63	0,00
1,63	4,5	0,2	0,2	1,63	0,00
1,63	4,0	0,2	0,2	1,63	0,00
1,63	3,5	0,2	0,2	1,63	0,00
1,63	3,0	0,2	0,2	1,63	0,00
1,63	2,5	0,2	0,2	1,63	0,00
1,63	2,0	0,2	0,2	1,63	0,00
1,63	1,5	0,2	0,2	1,63	0,00
1,63	1,0	0,2	0,2	1,63	0,00
1,63	5,5	0,3	0,2	1,32	23,68
1,63	5,0	0,3	0,2	1,33	22,22
1,63	4,5	0,3	0,2	1,35	20,59
1,63	4,0	0,3	0,2	1,37	18,75
1,63	3,5	0,3	0,2	1,40	16,67
1,63	3,0	0,3	0,2	1,43	14,29
1,63	2,5	0,3	0,2	1,46	11,54
1,63	2,0	0,3	0,2	1,50	8,33
1,63	1,5	0,3	0,2	1,56	4,55
1,63	1,0	0,3	0,2	1,63	0,00
1,63	5,5	0,4	0,2	1,11	47,37
1,63	5,0	0,4	0,2	1,13	44,44
1,63	4,5	0,4	0,2	1,15	41,18
1,63	4,0	0,4	0,2	1,19	37,50
1,63	3,5	0,4	0,2	1,22	33,33
1,63	3,0	0,4	0,2	1,27	28,57
1,63	2,5	0,4	0,2	1,32	23,08
1,63	2,0	0,4	0,2	1,40	16,67
1,63	1,5	0,4	0,2	1,49	9,09
1,63	1,0	0,4	0,2	1,63	0,00
1,63	5,5	0,5	0,2	0,95	71,05
1,63	5,0	0,5	0,2	0,98	66,67
1,63	4,5	0,5	0,2	1,01	61,76
1,63	4,0	0,5	0,2	1,04	56,25
1,63	3,5	0,5	0,2	1,09	50,00
1,63	3,0	0,5	0,2	1,14	42,86
1,63	2,5	0,5	0,2	1,21	34,62
1,63	2,0	0,5	0,2	1,30	25,00
1,63	1,5	0,5	0,2	1,43	13,64
1,63	1,0	0,5	0,2	1,63	0,00
1,63	5,5	0,6	0,2	0,84	94,74
1,63	5,0	0,6	0,2	0,86	88,89
1,63	4,5	0,6	0,2	0,89	82,35
1,63	4,0	0,6	0,2	0,93	75,00
1,63	3,5	0,6	0,2	0,98	66,67
1,63	3,0	0,6	0,2	1,04	57,14
1,63	2,5	0,6	0,2	1,12	46,15
1,63	2,0	0,6	0,2	1,22	33,33
1,63	1,5	0,6	0,2	1,38	18,18
1,63	1,0	0,6	0,2	1,63	0,00
1,63	5,5	0,7	0,2	0,75	118,42
1,63	5,0	0,7	0,2	0,77	111,11
1,63	4,5	0,7	0,2	0,80	102,94
1,63	4,0	0,7	0,2	0,84	93,75
1,63	3,5	0,7	0,2	0,89	83,33
1,63	3,0	0,7	0,2	0,95	71,43
1,63	2,5	0,7	0,2	1,03	57,69
1,63	2,0	0,7	0,2	1,15	41,67
1,63	1,5	0,7	0,2	1,33	22,73
1,63	1,0	0,7	0,2	1,63	0,00

Fixed:
ARR = 1.63
P$_{C0}$ = 0.2

Fixed:
ARR = 1.63
P$_{C0}$ = 0.2

RR	"True" or fully adjusted exposure relative risk
ARR	Apparent (or observed) exposure relative risk
RR$_{CD}$	Association between confounder and disease outcome
P$_{C1}$	Prevalence of confounder in the exposed
P$_{C0}$	Prevalence of confounder in the unexposed

Reference:
Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Safety, 2006;15:291-303.

eTable 7. Hazard ratios for any serious infection comparing current and past TNF-α inhibitor users with non-users based on a propensity score matched sub-cohort[a].

Risk periods	TNF-α inhibitor non-users	TNF-α inhibitor users	
		Current	past
90 days			
Patients, No	1457[b]	1457[b]	345
Events, No	74	46	0
HR (95% CI)	1 (Reference)	1.70 (1.03 to 2.81)	n/a
365 days			
Patients, No	1472	1472	980
Events, No	74	74	26
HR (95% CI)	1 (Reference)	1.29 (0.90 to 1.85)	1.20 (0.74 to 1.95)

Abbreviations: HR, hazard ratio; n/a, not applicable; TNF, tumour necrosis factor.

[a]The sub- cohort included 1472 TNF-α inhibitor users and 1472 non-users and was based on data on drug exposure from the National Patient Registry restricted to a study period from 2005 to 2012.

[b]In a minority of patients, data on specific TNF-α inhibitors was not available for the first dose(s). These patients could enter the analysis later during follow-up. Hence, the number of patients included in the 365-day risk period is larger than the number in the 90-day risk period.

eTable 8: Hazard ratios for any serious infection comparing TNF-α inhibitor users and non-users *not* matched on propensity scores, within a 90 days and 365 days risk period and according to sex and inflammatory bowel disease subtype.

Risk periods	TNF-α inhibitor users		TNF-α inhibitor non-users		HR (95% CI)
	Patients	Events	Patients	Events	
90 days					
Main analysis	4216	132	46 091	602	2.38 (1.97 to 2.88)
Sex					
Men	1820	51	20 609	283	2.02 (1.50 to 2.73)
Women	2396	81	25 482	319	2.69 (2.11 to 3.43)
IBD subtype					
Ulcerative colitis	1992	71	31 891	363	3.12 (2.42 to 4.02)
Crohn's disease	2224	61	14 200	239	1.62 (1.22 to 2.15)
365 days					
Main analysis	4216	325	46 091	1732	1.99 (1.77 to 2.24)
Sex					
Men	1820	122	20 609	758	1.78 (1.47 to 2.15)
Women	2396	203	25 482	974	2.14 (1.84 to 2.49)
IBD subtype					
Ulcerative colitis	1992	168	31 891	1067	2.46 (2.09 to 2.89)
Crohn's disease	2224	157	14 200	665	1.47 (1.24 to 1.75)

TNF-α inhibitor users and non-users were matched on fixed factors (age, sex, IBD subtype and disease duration).

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease; TNF, tumour necrosis factor

eTable 9. Characteristics of 1) TNF-α inhibitor users before propensity score matching, 2) TNF-α inhibitor users included in the propensity score matched cohort and, 3) TNF-α inhibitor users excluded from the propensity score matched cohort.

	All TNF-α inhibitor users (n=4 216) n (%)	TNF-α inhibitor users included (n=1 543) n (%)	TNF-α inhibitor users excluded (n=2 673) n (%)
Age in years, mean (SD)	39.2 (13.8)	44.6 (14.5)	36.2 (12.4)
Sex			
Males	1820 (43)	665 (43)	1164 (44)
IBD subtype			
Crohn's disease	2224 (53)	667 (43)	1557 (58)
Ulcerative colitis	1992 (47)	876 (57)	1116 (42)
Disease duration, years			
<1	1083 (26)	392 (25)	691 (26)
1-4	1433 (34)	530 (34)	903 (34)
5-9	1100(26)	360 (23)	740 (28)
10-19	561 (13)	238 (15)	323 (12)
≥20	39 (1)	23 (2)	16 (1)
Place of birth			
Denmark	4016 (95)	1473 (95)	2543 (95)
Europe	82 (2)	32 (2)	50 (2)
Other countries	118 (3)	38 (3)	80 (3)
Socioeconomic status			
Employment			
Unknown, basic or no qualifications	1738 (41)	560 (36)	1178 (44)
Medium level qualifications	555 (13)	212 (14)	343 (13)
High level qualifications	403 (10)	146 (10)	257 (10)
Self-employed/co-working spouse	152 (4)	68 (4)	84 (3)
Outside labor market	1190 (28)	424 (28)	766 (29)
Pensioned	178 (4)	133 (9)	45 (2)
Degree of urbanisation			
Population density, inhabitants per km2			
≤49	318 (8)	106 (7)	212 (8)
50-99	1273 (30)	465 (30)	808 (30)
100-199	946 (22)	341 (22)	605 (23)
≥200	468 (11)	160 (10)	308 (12)
Copenhagen suburbs	833 (20)	306 (20)	527 (20)
Copenhagen	378 (9)	165 (11)	213 (8)
Comorbidities[a]			
Gastrointestinal			
Intestinal surgery	519 (12)	115 (8)	404 (15)
Intestinal-/anal-/rectal fissure/fistula/abscess	339 (8)	34 (2)	305 (11)
Rheumatic disease	439 (10)	101 (7)	338 (13)

Cardiovascular disease	257 (6)	135 (9)	122 (5)
Chronic pulmonary disease	179 (4)	86 (6)	93 (4)
Diabetes	208 (5)	104 (7)	104 (4)
Liver disease	44 (1)	23 (2)	21 (1)
Renal disease	27 (1)	16 (1)	11 (<1)
Cancer	63 (2)	50 (3)	13 (1)
Prior infections[b]	329 (8)	117 (8)	212 (8)
Non-IBD drugs[a]			
Cardiovascular	703 (17)	347 (23)	356 (13)
Antianemic	900 (21)	231 (15)	669 (25)
Pulmonary antiobstructive	377 (9)	173 (11)	204 (8)
Antimicrobials	2101 (50)	722 (47)	1379 (52)
No of prescription drugs used in last 6 months			
0	150 (4)	110 (7)	4 (2)
1-2	475 (11)	257 (17)	218 (8)
3-4	608 (14)	244 (16)	364 (14)
5+	2983 (71)	932 (60)	2051 (77)
IBD drugs[a]			
5-ASA/sulfasalazine	2021 (48)	670 (43)	1351 (51)
Intestinal corticosteroids	1323 (31)	283 (18)	1040 (39)
Methotrexate/Cyclosporine/Cyclophosphamide	299 (7)	42 (3)	257 (10)
Health care use in past year			
No of hospital admissions			
0	1606 (38)	872 (57)	734 (28)
1-2	1966 (47)	539 (35)	1427 (53)
3+	644 (15)	132 (9)	512 (19)
No of outpatient contacts			
0	610 (15)	371 (24)	239 (9)
1-2	2826 (67)	944 (61)	1882 (70)
3+	780 (19)	228 (15)	552 (21)

Abbreviations: 5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease; SD, standard deviation; TNF, tumour necrosis factor.

All characteristics are as current at cohort entry unless stated otherwise.

[a]As registered within 1 year prior cohort entry.

[b]Defined as prior infections associated with hospital admission within 1 year prior to cohort entry.