STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ok
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ok
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ok
Objectives	3	State specific objectives, including any prespecified hypotheses ok
Methods		
Study design	4	Present key elements of study design early in the paper ok
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ok
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ok
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed ok
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ok
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ok
Bias	9	Describe any efforts to address potential sources of bias ok
Study size	10	Explain how the study size was arrived at ok
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ok
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ok
		(*b*) Describe any methods used to examine subgroups and interactions ok
		(*c*) Explain how missing data were addressed ok
		(*d*) If applicable, explain how loss to follow-up was addressed ok
		(*e*) Describe any sensitivity analyses ok
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ok
		(b) Give reasons for non-participation at each stage ok
		(c) Consider use of a flow diagram ok
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ok
		(b) Indicate number of participants with missing data for each variable of interest ok
		(c) Summarise follow-up time (eg, average and total amount) ok
Outcome data	15*	Report numbers of outcome events or summary measures over time ok
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ok
		(*b*) Report category boundaries when continuous variables were categorized ok

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ok
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ok
Discussion		
Key results	18	Summarise key results with reference to study objectives ok
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ok
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ok
Generalisability	21	Discuss the generalisability (external validity) of the study results ok
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ok

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Supplementary Table S1. ICD codes defining inflammatory bowel disease (IBD)

	ICD-7	ICD-8	ICD-9	ICD-10
	1964-1968	**1969-1986**	**1987-1996**	**1997-**
Ulcerative colitis (UC)	572,20 ; 572,21; 578,03	563,10 ; 563,99 ; 569,02	556	K51
Crohn's disease (CD)	572,00 ; 572,09	563,00	555	K50
IBD unclassified (IBD-U)	UC+CD	UC+CD	UC+CD	UC + CD, or K52.3

Supplementary Table S2a: ICD codes associated with Crohn's disease.

SURGERY CODES	**5/6th edition**	**7th edition (KKÅ97)**
Years	**1963-1996**	**1997-2016**
Resection of small bowel		
Small bowel resection	4630-4631	JFB00-01
Entero-anastomosis	4631	JFC00-01
Stricture-plasty to the small bowel		JFA60
Partial resection of the colon		
Left-sided hemicolectomy	4640	JFB43-44
Right-sided hemicolectomy	4641	JFB30-31
Ileocecal resection	4642	JFB20-21
Resection of the transverse colon	4643	JFB40-41
Resection of the colon sigmoideum	4644	JFB46-47,
Ileocolonic re-resection	4648	
Other type of partial colon resection	4649	JFB50-51
Other type of partial colon or small bowel resection		JFB33-34, JFB96-97
Other colon resection with colostomy and distal closure		JFB63-64, JGB10-11
Resection of the sigmoid colon with sigmoidostomy and closure of the rectum.	4713	JFB60-61
Fistula treatment		
Lay open or excision of perianal fistula	4922	JHD20-33, JHD50-63 JHD63, JHA00,
Other anal or perianal surgery (e.g., examination under anesthesia)	4923, 4999	JHW96,
Closure of fistula of the small intestine		JFA76
Closure of fistula of the colon		JFA86
Other fistulas	616,629	KCH30-33, LEE30
Perianal abscess		
Incision abscess, hematoma	4970, 4860	JAJ00
Dilatation		
Dilatation of the duodenum		JDH32
Endoscopic dilatation of the small bowel		JFA38
Endoscopic dilatation of the colon		JFA58
Endoscopic dilatation of the rectum		JGA58
Ultrascan of the anus/rectum		

Transanal endoscopic ultrascan		XJH00
ICD codes not compatible with ulcerative colitis	**ICD-10**	
Crohn's disease of the small bowel	K50.0	
Perianal disease modifier	Crohn's disease AND any of: (K60.3, K60.4, K60.5, K61.0, K61.1, K61.2, K61.3, K61.4, K62.4) OR any of the following surgical procedure codes: (JHD20, JHD30, JHD33, JHD50, JHD60, JHD63, JHA00, JHA20, JHW96)	

Supplementary Table S2b. Childhood-onset inflammatory bowel disease (IBD)
ROWS: classification using the first two diagnoses (used in Table 2 and all measures of incidence). Counts and percent in rows represent the proportion of e.g. patients defined as CD based on the first two diagnoses, who were defined as CD, IBD-U and UC when all information at end of follow-up was available.
COLUMNS: the reclassification (describing phenotype at end of follow-up, as described in Table 3).

		Phenotype at end of follow-up		
		CD	**IBD-U**	**UC**
Phenotype at start of follow-u	**CD**	3420 (90.8%)	229 (6.1%)	119 (3.2%)
	IBD-U	357 (36.1%)	442 (44.7%)	190 (19.2%)
	UC	495 (10.6%)	471 (10.1%)	3682 (79.2%)

Crohn's disease=CD; IBD unclassified=IBD-U; Ulcerative colitis=UC.

Supplementary Table S3. Definitions and diagnostic codes used to define ulcerative colitis and Crohn's disease according to the Paris classifications since the start of ICD-10 (1997).

Ulcerative colitis	**Extent**	**Diagnostic codes**
E1	Ulcerative proctitis	K51.2
E2	Left-sided UC	K51.3; K51.5
E3 or E4	Extensive UC	K51.0
EX	Extent not defined	K51.4; K51.8; K51.9
Crohn's disease	**Location/Behavior**	
L1 (Location)	Small bowel disease or terminal ileitis	K50.0
L2	Colon	K50.1
L3/LX	Ileocecal Crohn's disease or location not defined	K50.8, K50.9
B1 (Behavior)	Non-stricturing, non-penetrating	None of the ICD-codes for B2 or B3.
B2	Stricturing	Crohn's disease AND any of the following codes (K56.5; K56.6; K56.7; K62.4)
B3	Penetrating	Crohn's disease AND any of the following diagnostic codes (K63.0, K63.2, K31.6, N82.3, N82.3, N82.4) OR any of the following surgical procedure codes (JFA76, JFA86).
B2B3	Both stricturing and penetrating disease	Crohn's disease AND ICD codes (or procedure codes) for B2 and B3 at the same time or at different occasions.
P	Perianal disease modifier	Crohn's disease AND any of the following diagnostic codes: (K60.3, K60.4, K60.5, K61.0, K61.1, K61.2, K61.3, K61.4, K62.4) OR any of the following surgical procedure codes: (JHD20, JHD30, JHD33, JHD50, JHD60, JHD63, JHA00, JHA20, JHW96)

Supplementary Table S4. Extra-intestinal manifestations and primary sclerosing cholangitis in patients with inflammatory bowel disease (IBD) as defined by ICD-9 and ICD-10 codes.

	ICD-9	ICD-10
Complication	**1987-1996**	**1997-**
Primary sclerosing cholangitis	576B	K83.0
Extra-intestinal manifestations		
Erythema nodosum	695C	L52
Pyoderma gangrenosum	-	L88
Sweet syndrome	-	L98.2
Iridocyclitis	364	H20
Arthropathy in Crohn's disease	713B	M07.4
Arthropathy in Ulcerative colitis	713B	M07.5
Other defined arthropathy in gastrointestinal disorders	-	M07.6
Juvenile arthritis in Crohn's disease	-	M09.1
Juvenile arthritis in Ulcerative colitis	-	M09.2
Bechterew's disease	720A	M45
Spondylarthritis, inflammatory NOD	720C, 720W, 720X	M460, M461, M468, M469
Arthritis NOD	-	M139, M255

Supplementary Table S5. Surgery codes included in the definitions of "inflammatory bowel disease-related bowel surgery and perianal surgery" (since 1964).

Classification of surgical procedures	**6th revision**	**7th revision**
Colectomy		
1) Subtotal colectomy with end ileostomy		
Colectomy and ileostomy with closure of the rectum	4651	JFH10
Laparoscopic colectomy and ileostomy		JFH11
Other colectomy		JFH96
2) Colectomy with IRA (ileorectal anastomosis)		
Colectomy with ileorectal anastomosis	4650	JFH00
Laparoscopic colectomy with ileorectal anastomosis		JFH01
Ileorectal anastomosis		JFC40
Laparoscopic ileorectal anastomosis		JFC41
Closure of enterostomy with anastomosis to the rectum		JFG29
Closure of enterostomy with anastomosis to the colon		JFG26
3) Partial colectomies		
Right-sided colectomy	4641	JFB30, JFB31
Resection of the colon transversum	4643	JGB40, JFB41
Left-sided colectomy	4640	JFB43, JFB44
Resection of the sigmoid colon	4644	JFB46, JFB47
Other colon resection	4649	JFB50, JFB51
4) Proctocolectomy with IPAA (ileal pouch-anal anastomosis)		

Colectomy, rectal mucosectomy and ileoanal anastomosis *without* ileostomy.		JFH30
Colectomy, rectal mucosectomy and ileoanal anastomosis *and* ileostomy.		JFH33
Mucosectomy and ileoanal anastomosis after previous colectomy.	4654	JGB50
Extirpation of rectum or making of an ileoanal anastomosis after previous colectomy.		JGB60
5) Continent ileostomy at time of colectomy		
Proctocolectomy with continent ileostomy, Kock	4653	JFH40
Converting a conventional ileostomy to a continent ileostomy		JFG60
6) Proctocolectomy		
Proctocolectomy with ileostomy	4652	JFH20
Other bowel surgery	**1964-96**	**1997-**
Strictureplasty to the small bowel		JFA60
Strictureplasty to the colon		JFA63
Closure the small intestinal fistula		JFA76
Closure of the fistula of the colon		JFA86
Colonic and/or small bowel resection	4630, 4631, 4640-4649	JFB
Formation of the stoma		JFF
Operations on the intestinal stoma or reservoir		JFG
Other operation of the small bowel and/or colon	4660-4668, 4700-4739, 4790-4798	JFW96
Other laparoscopic operation of the small bowel and/or colon		JFW97
Rectal resection	4820-4828	JGB
Perianal surgery		
Perianal incision and drainage	4900	JHA00
Dilatation of the anal sphincter	4960	JHD00
Lay open or excision of perianal fistula	4920, 4922-4924	JHD20
Partial lay open or excision of perianal fistula (including seton placement)	4970-4971	JHD30
Completion lay open or excision of perianal fistula		JHD33
Excision of perianal fistula with advancement flap		JHD50
Occlusion of perianal fistula with collagen plug		JHD60
Occlusion of perianal fistula with fibrin glue		JHD63
Other anal or perianal surgery (e.g., examination under anesthesia)	4999	JHW96

Supplementary Table S6. ATC codes representing inflammatory bowel disease (IBD) treatment.

Drug group	Substance	ATC-code
Immune modulators	Azathioprine	L04AX0 1
	Mercaptopurine	L01BB02
	Methotrexate	L04AX03/L01BA01
Anti-TNF treatment	Infliximab	L04AB02 (L04AA12 before 2008)
	Adalimumab	L04AB04 (L04AA17 before 2008)
	Golimumab	L04AB06
	Vedolizumab	L04AA33
Systemic corticosteroids	Betamethasone	H02AB01
	Dexamethasone	H02AB02
	Methylprednisolone	H02AB04
	Prednisolone	H02AB06
	Prednisone	H02AB07
	Hydrocortisone	H02AB09
	Cortisone	H02AB10
Systemic Aminosalicylates (5-ASA)	Sulfasalazine	A07EC01
	Mesalazine	A07EC02
	Olsalazine	A07EC03
	Balsalazide	A07EC04
Rectal Aminosalicylates (5-ASA)	Mesalazine	A07EC02
Corticosteroids acting locally	Hydrocortisone	A07EA02
	Budesonide	A07EA06
IBD-related antibiotics	Metronidazole	P01AB01
	Ciprofloxacin	J01MA02

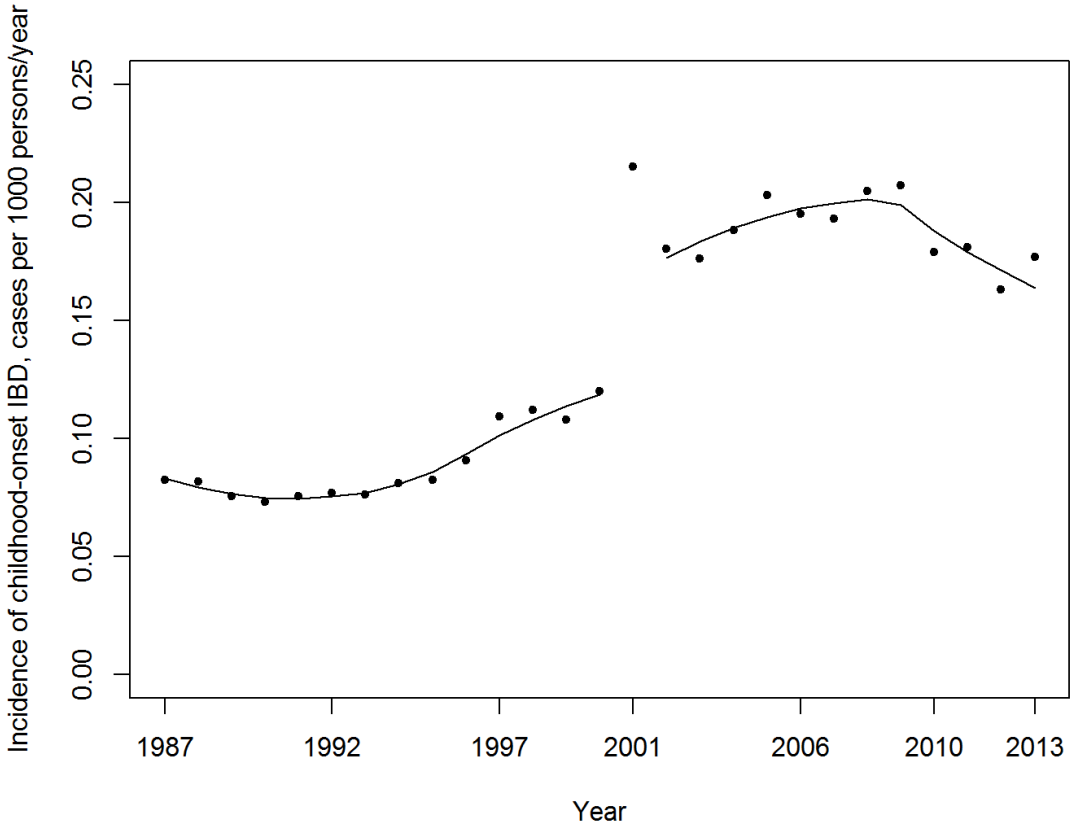
Supplementary Table S7. ICD-codes used to define different cancers in the study.

Group of cancers	Cancers	ICD-7
All gastrointestinal cancer		150-159
Colorectal cancer	Colon, Rectum	153-154*
Small bowel cancer	Small bowel	152
Liver cancer	Primary, gallbladder	155-156
All hematological cancer		200-209
Lymphomas including ALL and Myeloma	HL, NHL, ALL	200-202, 203,204
Myeloid malignancies	AML, MDS	205-209
Skin cancer	Melanoma	190
	Non-melanoma	191
Breast cancer	Breast cancer	170
Genital organs, female	Uterus, cervix, ovarian cancer	171-176
Genital organs, male	Prostate, testis, etc.	177-179
CNS	Eye, brain and rest of CNS	192-193
Thyroid and endocrine cancers		194-195
All other cancers	Excluding the above	All but the above

* Anal cancer and appendix cancer were not included in the colorectal cancers, but in the term "all gastrointestinal cancer" (and in "All cancer").
HL=Hodgkin lymphoma; NHL=Non Hodgkin lymphoma; ALL=Acute lymphatic leukemia; AML=Acute Myeloid Leukemia; MDS=Myelodysplastic Syndrome; CNS=Central nervous system.

Supplement 12: A description of the reasons behind a one year look back period to ensure true incident cases since 2002.

When the outpatient register started in 2001, the register-based incidence of childhood-onset IBD increased sharply, because some patients had never been cared for in the inpatient setting, and were hence misclassified as "incident cases" when the outpatient register started. Already in 2002 (i.e. after 1 year of "look back") the incidence of childhood-onset IBD was back on a stable level (i.e. basically the same as for the following years), indicating that as little as one year of look back is enough to ensure that new cases are true incident cases since start of the outpatient register.



Supplement 13: Explanation of how the missing information for infliximab is distributed in this Swedish dataset and how it might influence the results.

In this dataset, we have identified all cases of childhood-onset inflammatory bowel disease (IBD) in Sweden. Since 1 July 2005 we have information with full coverage of all dispensed prescriptions for all IBD medications in Sweden, except for infliximab (IFX), for which we don't have full coverage.

In Stockholm county (20% of the Swedish population and of this dataset) we have complete coverage of the use of all anti-TNF drugs (including IFX). There were 678 incident cases of childhood-onset IBD in Stockholm since we started monitoring anti-TNF. Of them, 21% (143/678) had ever been exposed to anti-TNF, of which 51% (73/143) had been exposed to IFX as the only anti-TNF drug.

If we translate this information to the entire cohort (3383 incident patients since start of the Prescribed Drug Register) it would equal 710 (0.21*3383) childhood-onset IBD patients ever exposed to anti-TNF instead of the 510 that we were able to identify (even though the use of anti-TNF is slightly higher in Stockholm than in the rest of the country, which means that the true number of misclassified patients is likely lower). In other words, we estimate that we were able to identify at least 72% of all anti-TNF use in Sweden.

That means that about 200 (710 minus 510) patients were likely misclassified as never exposed to anti-TNF in the whole study population, when they in fact were exposed to IFX. Most of these 200 patients were likely misclassified as "thiopurines only", since in Sweden it is very uncommon that patients are exposed to anti-TNF without having tried thiopurines. Thus, the presented analyses of drug exposure and risk of malignancy have likely been affected in the following way for the different strata:

a) "Never thiopurines or anti-TNF": Likely close to true value.
b) "Thiopurines only": Some 12% (200/1606) of patients were in fact also exposed to anti-TNF, which might have increased or decreased HR.
c) "Thiopurines and anti-TNF": Decreased power but likely a true value
(some patients exposed to IFX and thiopurines will be misclassified as thiopurines only).
d) "Anti-TNF only": Decreased power but likely representing true anti-TNF users.
(some patients exposed to IFX only (very few though) misclassified as never thiopurines/anti-TNF).

1. Hazard Ratios for cancer in all Swedish incident cases since the start of the Prescribed drug register (i.e. misclassification of IFX as described above in these analyses):

N incident cases from 1 July 2005	3383
	Number of cancers in IBD/patient-centuries of follow-up, HR (95%CI)
Never thiopurines nor anti-TNF	6/58, 2.7 (1.0-6.2)
Only thiopurine	13/79, 4.2 (2.1-7.9)
Only anti-TNF	too small sample
Thiopurine and anti-TNF	2/28, 1.3 (0.2-4.7)

2. The corresponding results for all incident cases in Stockholm county (complete coverage for all drugs, including IFX):

N incident cases from 1 July 2005	678
	Number of cancers in IBD/patient-centuries of follow-up, HR (95%CI)
Never thiopurines nor anti-TNF	1/14, 2.0 (0.1-12.3)
Only thiopurine	2/11, 4.1 (0.6-19.1)
Only anti-TNF	too small sample
Thiopurine and anti-TNF	1/6, 5.3 (0.2-55.1)

But even if we hadn't had the problem with misclassification of IFX, we would still not have been able to make any firm conclusions regarding IBD medications and risk of cancer because of the lack of power: Our current data gave us approximately 80% power to detect an HR as high as 4.4 for the effect of thiopurines or an HR of

8.2 for the effect of anti-TNF on cancer of any kind among childhood-onset IBD patients followed through adulthood. We would need to observe at least 66 events to have 80% power to detect a more modest HR of 2.0 for thiopurines or at least 142 events for anti-TNF, which would have required 4-9 times more patients or length of follow-up.

In summary, we cannot make any conclusions regarding IBD-medications and risk of cancer. To do that, even larger studies, with longer follow-up, and with complete coverage of all IBD medications, as well as time-dependent analyses stratified by disease phenotypes are needed.