

Emerging trends and risk factors for perianal surgery in Crohn's disease: A twenty year national population-based cohort study

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Abstract

Introduction

Little is known about rates of perianal surgery (PAS) in Crohn's disease (CD). Our aim was to determine trends in PAS, the timing of surgery relative to diagnosis of CD and to identify subgroups at risk of PAS.

Methods

We identified 9391 incident cases of CD between 1989-2009. We defined 3 era: era 1 (1989-1995), era 2 (1996-2002), era 3 (2003-2009) and determined trends in procedure type and the time to first PAS relative to the date of diagnosis. We used Kaplan-Meier analysis to demonstrate the rate of first PAS and performed Cox regression to determine subgroups at risk of PAS.

Results

Among the 9391 incident cases of CD, 405 (4.3%) underwent PAS. The overall rate of PAS was 5.5% (95% CI: 4.9 – 6.2%) 10 years after diagnosis. 34% (n=137) of all patients undergoing PAS had surgery in the 5 years before CD diagnosis. Abscess drainage increased from 34% to 58% whilst proctectomy decreased from 16% to 6% between era 1 and 3 respectively. Men (HR 1.51, 95% CI: 1.24-1.84), those aged 17-40 years (HR 1.69, 95% CI: 1.09-2.02 vs those aged >40 years) and those with a history of previous intestinal resection (HR: 28.5, 95% CI: 22.2–36.5) were more likely to have PAS.

Conclusion

Around a third of patients have a PAS 5 years preceding their diagnosis of CD. Surgical practice has changed over twenty years with a decrease in proctectomy and a concurrent increase in abscess drainage. PAS should alert clinicians to consider a possible underlying diagnosis of CD.

Short running title

Trends in perianal surgery in Crohn's disease

Keywords

Crohn's disease

Perianal disease

Perianal surgery

Seton

Fistula

Abscess

CPRD

Introduction

Perianal problems in Crohn's disease (CD) causing perianal pain, discharge and faecal incontinence have a debilitating effect on quality of life and carries a considerable emotional burden [1, 2]. Manifestations include perianal skin tags, anal canal lesions including anal strictures, anal fissures and ulcers, abscesses and perianal and recto-vaginal fistulae [3–5]. If not treated promptly and optimally, lesions can progress requiring recurrent surgery and ultimately proctectomy [6–8].

Estimates of the lifetime risk of perianal CD vary, with rates of perianal fistulisation reported by referral centres ranging from 17 to 43% [2]. A single population-based study from New Zealand suggests a frequency of 27% for the presence of symptomatic perianal disease with fistulae accounting for up to half of all lesions present [9]. Estimates vary but up to 40% of CD patients develop perianal CD lesions by 20 years, among which perianal fistulae are the most commonly occurring lesions in a third of all cases [9–12]. The wide ranging estimates of perianal disease may be accounted for by the previous lack of a definitive classification system for perianal CD which has been addressed in an American Gastroenterological Association Technical Review [3]. The presence of perianal lesions in CD is a well-recognised marker of a severe disease phenotype [13, 14] and may also presage the onset of CD itself.

Avoidance of surgical intervention, often considered a hard endpoint in CD, is now considered a more appropriate therapeutic goal than steroid sparing. This is particularly relevant to perianal CD since there is no evidence for the efficacy of steroids in this context [3, 15]. Intestinal surgery rates have declined by a third in the past 2 decades associated with increased thiopurine use [16, 17]. We have also recently described the associated benefit of sustained thiopurine therapy in reducing the risk of perianal surgery (PAS) in CD, demonstrating a decline in the modern era reflecting the more widespread use of these agents and anti-tumour necrosis factors (anti-TNFs) [18]. It is therefore likely that improvements in diagnosis and increased and earlier use of medical therapies have impacted favourably on the need for surgical intervention in perianal disease. However, studies of

trends and risk factors for PAS particularly in relation to the formal diagnosis of CD are limited. We therefore aimed to characterise the rate and temporal trends of PAS, the timing of surgery relative to the formal diagnosis of CD and to identify subgroups at risk of PAS using the UK nationally representative Clinical Practice Research Datalink (CPRD).

Materials and Methods

Clinical Practice Research Database (CPRD)

The CPRD, is a primary care database containing anonymised patient records for approximately 8% of the UK population. It is one of the world's largest sources of longitudinal data from primary care and currently contains 3.6 million active patients from 450 general practices from all over the UK [19]. Data accuracy and completeness of data recording by participating practices is subject to regular quality control in the 'up to standard practice' (UTS) audit before inclusion in the CPRD [19].

Our dataset provides details on basic demographics, registration dates, diagnosis dates, surgical procedure types and dates, and IBD related prescriptions issued during the registration period with the exception of anti-TNF therapy, ciclosporin and methotrexate.

Cohort construction

We defined an incident case as any patient with a new diagnosis of CD using previously validated Read or Oxford Medical Indexing System (OXMIS) codes [19, 20]. Patients were included between 01/01/1989 and 31/12/2009 and had to be registered with an 'up to standard' (UTS) practice for 12 months before diagnosis. All patients with a diagnosis code of ulcerative colitis or inflammatory bowel disease were excluded. We excluded patients with co-morbid inflammatory conditions including asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, temporal arteritis and polymyalgia rheumatica or solid organ transplants since they may have been prescribed steroids for another indication and we wished to use exposure to steroids as a proxy indicator of CD severity [21]. We established our cohort of incident cases and searched the dates of PAS including operations before the date of diagnosis.

We grouped patients according to their age at diagnosis according to the Montreal classification; ≤ 16 years (A1), 17-40 years (A2) and >40 years (A3) [22]. We also grouped patients according to the era

in which they were diagnosed with CD; era 1 (1989 – 1995), era 2 (1996 – 2001) and era 3 (2002 – 2009) to explore changes in trends in the different types of PAS.

Outcomes

The primary outcome was first PAS defined using procedure codes for laying open of an anal fistula, insertion of a Seton, perianal abscess surgery or drainage, excision of a perianal fistula, excision of anus, excision of the rectum and proctectomy.

Confounders and exposure variables

We considered age at diagnosis, sex, current smoking status, history of appendectomy, history of previous intestinal surgery and early steroid use, within 3 months of diagnosis to be potential confounders that have been associated with a more severe course of disease and could therefore influence the risk of having PAS [23–26].

Statistical analysis

We determined trends in the type of PAS performed and evaluated the time to and rate of first PAS relative to the time of diagnosis. We calculated the rate of PAS at 1, 5 and 10 years after diagnosis. We calculated means and standard deviations for Gaussian distributions and medians and interquartile ranges for non-Gaussian distributions. χ^2 test was used for comparing groups of categorical data. We used Kaplan-Meier survival analysis to demonstrate the 5 year cumulative probability of first PAS over time and used the log-rank test to compare survival outcomes between groups. We performed a univariable analysis to evaluate the influence of age at diagnosis, sex, appendectomy, smoking status, previous intestinal surgery and early steroid use on the risk of first PAS and performed a multivariable analysis using the Cox proportional hazards model to determine the relative hazard for each subgroup and determine risk predictors for first PAS adjusted for confounders. All data management and statistical analysis was conducted using STATA v12 (Statacorp LP, College Station, TX, USA) with p values of <0.05 being considered significant.

Results

We identified a cohort of 9391 incident cases of CD between 1989 and 2009 (figure 1), contributing 54,376 patient-years of follow up time with a mean duration of 5.8 years per patient. 56% of patients were female and the median age at diagnosis was 33.9 years (IQR: 24.0 – 51.8 years)(table 1).

Trends in perianal surgery

In all 405/9391 (4.3%) patients had a perianal surgical procedure. After adjusting for follow up time using the Kaplan-Meier method, the overall cumulative rate of PAS was 2.6% (95% CI: 2.3 – 2.9%), 4.0% (95% CI: 3.6 – 4.4%) and 5.5% (95% CI: 4.9 – 6.2%) at 1, 5 and 10 years after diagnosis (figure 2). This included patients with a PAS prior to CD diagnosis. The median time to PAS was 4 months (IQR: -1.3 – 2.7 years) after diagnosis. A significant proportion of patients had a PAS prior to CD diagnosis with 13% (n=53), 17% (n=69) and 34% (n=137) of patients having PAS in the 6 months, 1 year and 5 years prior to diagnosis respectively (figure 3). 59% (n=238) of all patients undergoing PAS had this performed in the first year after CD diagnosis.

Type of procedure

The commonest forms of PAS performed were abscess drainage (51%); laying open of fistula (20%) and proctectomy (11%). Between era 1 and era 3, the proportion of abscess drainage procedures nearly doubled from 17 out of 50 (34%) to 101 out of 172 (58%); whereas proctectomy more than halved from 8 out of 50 (16%) to 10 out of 172 (6%). Fistula and seton surgery remained relatively stable across the era (figure 4). Of the 405 patients undergoing PAS, 75% (305) had a single surgery, 16% (63) required 2 surgeries, 6% (26) required 3 surgeries and 3% (11) required 4 or more surgeries during follow up (figure 5).

Predictors of perianal surgery

The 5 year rate of PAS was 4.9% (95% CI: 4.3 – 2.9%) and 3.2% (95 % CI: 2.7 – 3.8%) for men and women respectively (log-rank $p<0.001$). The 5 year rate of PAS was 2.8% (95% CI: 1.7 – 4.5%), 4.8% (95% CI: 4.2 – 5.5%) and 3.0% (95% CI: 2.5 – 3.7%) for those aged <17, 17-40, >40 years respectively (log-rank $p<0.001$). PAS was not more common amongst early steroid users within 3 months of diagnosis, a surrogate marker for severe disease (early 98/2083 vs late 307/7308, $p=0.32$).

After adjusting for age at diagnosis, sex, prior appendectomy and prior intestinal resection, we found that men with CD had a 51% higher risk of PAS compared with women (HR 1.51, 95% CI: 1.24 – 1.84, $p<0.001$) (table 3). Patients aged 17 – 40 years at diagnosis (Montreal class A2) also had a 62% increased risk of PAS compared with those aged >40 years at diagnosis (Montreal class A3) (HR 1.62, 95% CI: 1.29 – 2.02, $p<0.001$) whilst there was no difference for Montreal class A1 (<17 years) compared to A3 (HR 1.09, 95% CI: 0.73 – 1.63, $p=0.67$). An appendectomy prior to CD diagnosis did not increase the risk of PAS (HR: 2.04, 95% CI: 0.89 – 4.70, $p=0.09$) whereas the risk of PAS increased by 30 times for those undergoing prior intestinal resection (HR 28.5, 95% CI: 22.2 – 36.5%, $p<0.001$). Neither smoking (unadjusted HR 1.09, 95% CI: 0.88 – 1.34, $p=0.45$) nor early steroid use within 3 months of diagnosis (unadjusted HR 1.18, 95% CI: 0.94 – 1.48, $p=0.16$) increased the risk for first PAS.

Discussion

Main findings

Amongst a national incident CD cohort derived from a large representative primary care dataset, studied over a twenty year period, around 5% of patients underwent a PAS within 10 years of diagnosis. The rate of proctectomy has halved whereas abscess drainage has nearly doubled over the twenty year study period. The majority of procedures were performed at or within the first 4 months of diagnosis but, importantly, around one third were undertaken in the 5 years before a formal diagnosis of CD was made. Surgery was more common in men aged 17-40 years. Prior intestinal surgery was associated with a marked increase in risk of PAS, whilst neither early steroid use nor smoking was associated with an increased risk PAS [16, 27]. These findings reflect a significant burden of perianal disease requiring surgery amongst patient with CD and clinicians need to be aware that a requirement for PAS may often precede the diagnosis of CD by months or years.

Findings in relation to other studies

Limited data is available with respect to rates of PAS most of which derives from referral centre studies published in the 1980s and 1990s and as such are subject to bias [28–30]. Keighley *et al* previously reported a 54% prevalence of perianal disease in their cohort [29]. Other small studies of perianal CD report fistula repair and abscess drainages to be the commonest form surgery performed [30, 31]. Reported proctectomy rates from referral centre studies vary between 9% and 38% [28, 30]. A single previous population-based cohort study from New Zealand reports the overall rate of PAS to be 18% in a cohort followed between 2003 and 2005 of which perianal abscess drainage and fistula repair were the most common procedures with 60% of these performed in the first year of diagnosis [32]. The lower overall rate of PAS reported in our cohort of 5.5% over 10 years, likely reflects the origin of our data derived from a primary care setting, a more restricted range of perianal procedures studied as well as recent advances in therapy. In keeping with the

findings of Eglington *et al* we found a quarter of patients required 2 or more perianal procedures and some patients many more [32].

Our analysis of the temporal trends in surgery indicates that PAS may occur up to 30 years in advance of a formal diagnosis of CD, with around one third of all procedures undertaken in the 5 years before a formal diagnosis of CD; but the majority of surgeries occurred at or within the first 4 months of the incident diagnosis of CD. To our knowledge this is the first study to describe the relationship between the timing of PAS in relation to a formal diagnosis of CD. Eglington *et al* previously report a temporal relationship between the onset of perianal lesions and CD diagnosis and found 17% of patients developed perianal lesions within 6 months prior to the diagnosis of CD [9]. We have previously demonstrated a temporal trend in the requirement for PAS with a reduced risk in the modern era [18]. In the current study we have shown the rate of proctectomy approximately halved between the earliest and the most recent era studied whilst in contrast the rate of abscess drainage nearly doubled. This may reflect evolution in medical practice, in particular the increasing use of anti-TNFs in the modern era, which may promote the formation of perianal abscess formation potentially due to premature closure of draining fistulae [33]. This emphasizes the need for a combined surgical and medical approach with early placement of a Seton in tandem with anti-TNF therapy [34].

A variety of risk factors were associated with a requirement for PAS in our study. We have demonstrated male sex to be associated with an increased risk and this is supported by other studies [9, 18] although other studies have suggested females to be at a greater risk of perianal disease [9, 35, 36]. We found an age between 17-40 years (Montreal class A2) was associated with an increased risk of PAS. This relationship between age and perianal disease is not consistently reported, for example a population-based study reported rates of PAS were twice as high amongst patients under 17 year [32]. We also found prior intestinal resection was associated with a greatly increased risk of subsequent PAS reflecting the more severe disease phenotype of these patients. Other studies have reported conflicting evidence regarding the association of distal colonic and ileal disease locations

and the risk of perianal disease and this may reflect difference in the definition of perianal lesions and referral centre bias [11, 32]. We were not able to evaluate the importance of disease location in our cohort since CPRD does not record these details.

Study strengths and limitation

Our population based study is the largest to date to assess trends in PAS and assess risk of first PAS in CD over twenty years. The strengths include the size and nationally representative sample of incident cases derived from the CPRD, a validated primary care research database which is free from referral centre bias and linked with hospital coding [19, 20]. The cohort consisted of 9391 patients drawn from 13 million patients attending their primary care practitioner. However, our study is subject to some limitations. Biases include the exclusion of patients who had co-morbid inflammatory conditions requiring steroids. Clinical and biochemical markers of severity are not available in CPRD and are potential confounders. However, we attempted to adjust for severity by adjusting for early steroid use, a validated proxy marker [26]. Details of disease location are not documented in CPRD which prevented assessment in this respect [32, 36]. Coding inaccuracies and misclassification are potential biases in database analyses, although the CPRD is regularly validated and has stringent data quality criteria [19, 37]. We were not able to determine the overall occurrence of perianal CD and clearly not all patients in this group require PAS although Eglington *et al* suggest around one third of CD patients have symptomatic perianal disease [9]. Furthermore, given the nature of our study we cannot assume all PAS performed prior the diagnosis of CD related directly to that subsequent diagnosis, but nevertheless there appears to be a strong relationship. Neither were we able to quantify the background risk of PAS in the general population without an established subsequent diagnosis of CD. However, we did exclude surgeries for commonly presenting perianal conditions such as skin tags and haemorrhoids limiting the repertoire of procedures evaluated to those more commonly required in CD than the general population as well as examination under anaesthesia (EUA) due to the non-specific nature of the procedure.

Implications and future research

A significant proportion of patients with CD require PAS and more than one third of perianal procedures were performed prior to the diagnosis of CD. This is an important observation and more research is required to assess the associated risk of PAS in predicting a subsequent diagnosis of CD. It has been reported that cryptoglandular abscess formation can occur in CD but we recognise that this is not the case for all patients with perianal disease [38]. Although not all patients undergoing a PAS will develop CD, we recommend that a diagnosis of CD should be considered in any patient requiring fistula surgery or abscess drainage and should be assessed accordingly and followed-up carefully thereafter. Developments in medical therapy particularly the long term impact of combination therapy of anti-TNFs and immunomodulators may have impacted on the changing requirement for and the type of PAS performed [33, 39]. A recent systematic review has highlight the use of anti-TNFs is associated with an increase in perianal abscess formation and this is in keeping with our findings and underscores the need for a co-ordinated joint surgical and medical approach to the management of perianal CD [34].

Conclusions

This nationally representative study of patient with CD indicates around one in twenty patients undergo PAS. There has been a decrease in proctectomy rates which coincide with an increase in abscess drainage procedures which may reflect changes in medical therapy. Men, those aged 17-40 years and those with a history of appendectomy or prior intestinal resection are at increased risk of PAS. A third of patients who had PAS underwent the procedure in the 5 years preceding their diagnosis of CD. A requirement for PAS should alert clinicians to consider a possible underlying diagnosis of CD.

References

1. Mahadev S, Young JM, Selby W, Solomon MJ: **Quality of life in perianal Crohn's disease: what do patients consider important?** *Dis Colon Rectum* 2011, **54**:579–85.
2. Schwartz DA, Herdman CR: **Review article: The medical treatment of Crohn's perianal fistulas.** *Aliment Pharmacol Ther* 2004, **19**:953–67.
3. Sandborn W, Fazio V, Feagan B, Hanauer S: **AGA Technical Review on Perianal Crohn's Disease.** *Gastroenterology* 2003, **125**:1508–1530.
4. Hughes LE: **Surgical pathology and management of anorectal Crohn's disease.** *J R Soc Med* 1978, **71**:644–651.
5. Buchmann P, Alexander-Williams J: **Classification of perianal Crohn's disease.** *Clin Gastroenterol* 1980, **9**:323–330.
6. Schwartz DA: **What is the optimal maintenance treatment for perianal Crohn's disease?** *Inflamm Bowel Dis* 2008, **14 Suppl 2**:S269–70.
7. Williams J, Rothenberger D, Nemer F, Goldberg S: **Fistula-in-ano in Crohn's disease. Results of aggressive surgical treatment.** *Dis Colon Rectum* 1991, **34**:378–384.
8. Levien D., Surrell J, Mazier W.: **Surgical treatment of anorectal fistula in patients with Crohn's disease.** *Surg Gynecol Obs* 1989, **169**:133–136.
9. Eglinton TW, Barclay ML, Gearry RB, Frizelle FA: **The spectrum of perianal Crohn's disease in a population-based cohort.** *Dis Colon Rectum* 2012, **55**:773–7.
10. Schwartz DA, Loftus E V., Tremaine WJ, Panaccione R, Scott Harmsen W, Zinsmeister AR, Sandborn WJ: **The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota.** *Gastroenterology* 2002, **122**:875–880.
11. Tang LY, Rawsthorne P, Bernstein CN: **Are perineal and luminal fistulas associated in Crohn's disease? A population-based study.** *Clin Gastro Hep* 2006, **4**:1130–4.
12. Lapidus A: **Crohn's disease in Stockholm County during 1990-2001: An epidemiological update.** *World J Gastroenterol* 2006, **12**:75–81.
13. Lakatos P-L: **Perianal disease, small bowel disease, smoking, prior steroid or early azathioprine/biological therapy are predictors of disease behavior change in patients with Crohn's disease.** *World J Gastroenterol* 2009, **15**:3504–3510.
14. Beaugerie L, Sokol H: **Clinical, serological and genetic predictors of inflammatory bowel disease course.** *World J Gastroenterol* 2012, **18**:3806–13.
15. Rieder F, Reinisch W: **Thiopurines and the natural course of Crohn's disease: did we finally find the right therapeutic target?** *Am J Gastroenterol* 2014, **109**:1037–40.

16. Chatu S, Saxena S, Subramanian V, Curcin V, Yadegarfar G, Gunn L, Majeed A: **The impact of timing and duration of thiopurine treatment on first intestinal resection in Crohn's disease: National UK population-based study 1989-2010.** *Am J Gastroenterol* 2014, **109**:409–16.
17. Frolkis AD, Dykeman J, Negrón ME, Debruyn J, Jette N, Fiest KM, Frolkis T, Barkema HW, Rioux KP, Panaccione R, Ghosh S, Wiebe S, Kaplan GG: **Risk of Surgery for Inflammatory Bowel Diseases Has Decreased Over Time: A Systematic Review and Meta-analysis of Population-Based Studies.** *Gastroenterology* 2013, **145**:996–1006.
18. Chhaya V, Saxena S, Cecil E, Subramanian V, Curcin V, Majeed A, Pollok R: **Impact of Timing and Duration of Thiopurine Treatment on First Perianal Surgery in Crohn's Disease: UK Population-based.** *Inflamm Bowel Dis* 2015, **21**:385–91.
19. Khan NF, Harrison SE, Rose PW: **Validity of diagnostic coding within the General Practice Research Database: a systematic review.** *Br J Gen Pr* 2010, **60**:e128–136.
20. Lewis JD, Brensinger C, Bilker WB, Strom BL: **Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease.** *Pharmacoepidemiol Drug saf* 2002, **11**:211–218.
21. Lewis JD, Aberra FN, Lichtenstein GR, Bilker WB, Brensinger C, Strom BL: **Seasonal variation in flares of inflammatory bowel disease.** *Gastroenterology* 2004, **126**:665–673.
22. Satsangi J, Silverberg MS, Vermeire S, Colombel J-F: **The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications.** *Gut* 2006, **55**:749–754.
23. Cosnes J, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre J: **Effects of cigarette smoking on the long-term course of Crohn's disease.** *Gastroenterology* 1996, **110**:424–431.
24. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP: **Smoking cessation and the course of Crohn's disease: An intervention study.** *Gastroenterology* 2001, **120**:1093–1099.
25. Cosnes J, Seksik P, Nion-Larmurier I, Beaugerie L, Gendre J: **Prior appendectomy and the phenotype and course of Crohn's disease.** *World J Gastroenterol* 2006, **12**:1235–1242.
26. Ramadas A, Gunesh S, Thomas G, Williams G, Hawthorne A: **Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates.** *Gut* 2010, **59**:1200–6.
27. Chatu S, Subramanian V, Saxena S, Pollok RC: **The role of thiopurines in reducing the need for surgical resection in Crohn's disease: A systematic review and meta-analysis.** *Am J Gastroenterol* 2014, **109**:23–34.
28. Buchmann P, Keighley M, Allan R, THompson H, Alexander-Williams J: **Natural History of Perianal Crohn's Disease Ten Year Follow-Up : A Plea for Conservatism.** *Am J Surg* 1978, **140**:642–644.
29. Keighley M, Allan R: **Current status and influence of operation on perianal Crohn's disease.** *Int J Color Dis* 1986, **1**:104–7.

30. Michelassi F, Melis M, Rubin M, Hurst RD: **Surgical treatment of anorectal complications in Crohn's disease.** *Surgery* 2000, **128**:597–603.
31. Williamson P, Hellinger M, Larach S, Ferrara A: **Twenty-year review of the surgical management of perianal Crohn's disease.** *Dis Colon Rectum* 1995, **38**:389–392.
32. Eglinton T, Reilly M, Chang C, Barclay M, Frizelle F, Gearry R: **Ileal disease is associated with surgery for perianal disease in a population-based Crohn's disease cohort.** *Br J Surg* 2010, **97**:1103–9.
33. Bouguen G, Siproudhis L, Gizard E, Wallenhorst T, Billioud V, Bretagne J-F, Bigard M-A, Peyrin-Biroulet L: **Long-Term Outcome of Perianal Fistulizing Crohn's Disease Treated with Infliximab.** *Clin Gastroenterol Hepatol* 2013:Epub ahead of print.
34. Yassin N, Askari A, Warusavitarne J, Faiz O, Athanasiou T, Phillips R, Hart A: **Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease.** *Aliment Pharmacol Ther* 2014, **40**:741–9.
35. Sangwan Y, Schoetz Jr D, Murray J, Roberts P, Collier J: **Perianal Crohn's disease. Results of local surgical treatment.** *Dis Colon Rectum* 1996, **39**:529–535.
36. Hellers G, Bergstrand O, Ewerth S, Holmstrom B: **Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease.** *Gut* 1980, **21**:525–527.
37. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ: **Validation and validity of diagnoses in the General Practice Research Database: a systematic review.** *Br J Clin Pharmacol* 2010, **69**:4–14.
38. Parks AG: **Pathogenesis and treatment of fistula-in-ano.** *BMJ* 1961:463–469.
39. Cosnes J, Bourrier A, Laharie D, Nahon S, Bouhnik Y, Carbonnel F, Allez M, Dupas J-L, Reimund J-M, Savoye G, Jouet P, Moreau J, Mary J-Y, Colombel J-F: **Early administration of azathioprine versus conventional management of Crohn's disease: A randomized controlled trial.** *Gastroenterology* 2013, **145**:758–765.

Table 1: Patient characteristics of population-based cohort with Crohn's disease between 1989-2009 (n=9391)

	n	%
Sex		
<i>Men</i>	4110	43.8
<i>Women</i>	5281	56.2
Era of diagnosis*		
<i>Era 1 (1989 – 1995)</i>	1291	13.6
<i>Era 2 (1996 – 2001)</i>	3510	37.4
<i>Era 3 (2002 – 2009)</i>	4590	49.0
Age at diagnosis (years)		
<i><17</i>	702	7.5
<i>17-40</i>	4954	52.7
<i>>40</i>	3735	39.8
Smoker		
<i>Current smoker</i>	2787	29.7
<i>Non-smoker</i>	6070	64.6
<i>Missing</i>	534	5.7
GCS use		
<i>Early (within 3 months of diagnosis)</i>	2083	22.2
Appendectomy	184	2.0
Intestinal resection	1714	18.3

*Increasing number of patients by era of diagnosis noted due to increasing number of up to standard practices contributing data to CPRD

Table 2: Crude and adjusted hazard ratios for perianal surgery in incident cases with Crohn's disease. Cohort of 9391 patients from 1989 - 2009

	Number of perianal surgeries	Crude Hazard ratio	95% CI	P-value ^a	Adjusted Hazard Ratio ^b	95% CI	P-value
Sex							
<i>Males</i>	223	1.57	1.29 – 1.91	<0.001	1.51	1.24 – 1.84	<0.001
<i>Females</i> ^d	182	1.0			1.0		
Age at diagnosis (years)							
<17	31	1.37	0.92 – 2.06	0.12	1.09	0.73 – 1.63	0.67
17-40	262	1.71	1.37 – 2.13	<0.001	1.62	1.29 – 2.02	<0.001
>40 ^d	112	1.0			1.0		
Smoker							
<i>Current smoker</i>	128	1.09	0.88 – 1.34	0.45			
<i>Non-smoker</i> ^d	277	1.0					
Steroid use							
<i>Early (within 3 months of diagnosis)</i> ^c	98	1.18	0.94 – 1.48	0.16			
Appendectomy before- perianal surgery	6	35.9	16.0 – 80.4	<0.001	2.04	0.89 – 4.70	0.09
Intestinal resection before- perianal surgery	84	31.1	24.5 – 39.6	<0.001	28.5	22.2 – 36.5	<0.001

^aLog-rank test for trend

^bMultivariable model with significant covariates from univariable model (sex, age at diagnosis, appendectomy prior to perianal surgery and intestinal resection prior to perianal surgery) included in analysis

^cCompared with reference group of no early steroid use, no previous appendectomy or surgery prior to perianal surgery

^dReference group

Figure legends

Figure 1: Cohort construction after initial Clinical Practice Research Database (CPRD) download showing exclusions.

Figure 2: Survival curve showing overall rate of perianal surgery over 10 years. n=9391

Figure 2 footnote: 2% of patients had a perianal surgery prior to or at diagnosis which accounts for initial increment at time=0

Figure 3: Temporal relationship of first perianal surgery relative to year of diagnosis with Crohn's disease.

Figure 4: Trends in type of perianal surgery by era of diagnosis

Figure 4 footnote: *Seton and fistula procedures combined

Figure 5: Proportion of patients undergoing multiple perianal surgeries.

Acknowledgements

CPRD declaration

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Conflict of Interest/Declaration of personal interests:

None declared

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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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed

(e) Describe any sensitivity analyses		
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
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

*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>.