The risk of inflammatory bowel disease in subjects presenting with perianal abscess

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Title: The risk of inflammatory bowel disease in subjects presenting with perianal abscess: findings from the THIN database

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ABSTRACT

Background

Perianal abscess (PA) is associated with inflammatory bowel disease (IBD). The incidence of IBD after a diagnosis of PA and potential predictors of a future diagnosis of IBD are unknown.

Methods

The Health Improvement Network (THIN) is a primary care database representative of the UK population. Incident cases of PA were identified between 1995 and 2017. Subjects with PA were matched to controls within the same general practice. Primary outcome was subsequent diagnosis of Crohn's Disease (CD) or ulcerative colitis (UC). A Cox regression model was used to assess potential predictors of a new diagnoses of CD or UC following PA.

Results

The risk of CD was higher in the PA cohort compared to controls; adjusted HR 7.51(95%CI 4.86-11.62), p<0.0001. The risk of UC was also higher in the PA cohort compared to controls; adjusted HR 2.03 (1.38-2.99), p<0.0001. Anaemia in men (HR 2.82(1.34-5.92), p=0.002), and use of antidiarrheal medications (HR 2.70(1.71-4.25), p<0.0001) were associated with an increased risk of CD following PA. Anaemia in men (HR 2.58(1.09-6.07), p=0.03), diarrhoea (HR 2.18(1.23-3.85), p=0.007) and use of anti-diarrhoeal medication (HR 2.27(1.19-4.30), p=0.012) were associated with an increased risk of UC following PA.

Conclusion

Subjects with PA are at an increased risk of subsequent diagnosis of CD and UC. Clinicians should strongly consider investigation for IBD in young patients presenting with diarrhoea and anaemia (in

men) following PA. Future research should discern appropriate screening strategies for this high-risk cohort.

Key Words: Perianal Abscess, Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis

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Abbreviations: Inflammatory Bowel Disease (IBD), Crohn's Disease (CD), Ulcerative Colitis (UC), Body-Mass Index (BMI), The Health Improvement Network (THIN), Hazard Ratio (HR), interquartile range (IQR)

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BACKGROUND AND AIMS

Perianal abscesses are caused by an infection of obstructed anal crypt glands resulting in a collection of pus. A previous cohort study[1] conducted in Sweden estimated the incidence of perianal abscesses to be around 16.1 per 100,000 people per year. Perianal abscesses can be complicated by fistulation, and systemic infection[2]. The primary management of perianal abscesses is surgical drainage.

Perianal abscess has been identified as a potential early indicator of Crohn's Disease (CD)[3]. The National Health Service conducted over 12,300 operations on perianal abscesses in 2016-2017. Perianal abscess surgery in an incident CD population in the United Kingdom (UK) was reported in a third of patients prior to their diagnosis of CD[4]. Perianal abscesses can also be associated with ulcerative colitis (UC) [5]. It has therefore been suggested that cases of perianal abscesses be carefully followed up to monitor for the development of inflammatory bowel disease (IBD).

The incidence of IBD in the West is slowing but a rapid increase in the Far East has been noted[6]. The advent of thiopurine and biologic therapy[7] and their potential to alter disease course through mucosal healing[8] has marked a shift in the therapeutic goals of IBD management. Perianal involvement in IBD (CD specifically), has been identified as an independent predictor of rapid

progression to ileocolonic disease and stricturing and penetrating behaviour[9]. Early identification of these patients would enable consideration of more effective medical treatment strategies such as thiopurines and biologics at an earlier disease stage and thereby potentially reduce the need for intestinal resection[10] in this high-risk cohort. However, no study to-date has examined the incidence of IBD subsequent to a diagnosis of perianal abscess and risk characterization of predictors of a future diagnosis of IBD within this cohort has not been attempted.

Therefore, this study aims to assess the future risk of an IBD diagnosis, as well as identifying potential predictors for an IBD diagnosis following a presentation of perianal abscess with the intention of reducing diagnostic delay in IBD.

METHODS

Data Source: The Health Improvement Network

The Health Improvement Network (THIN) is a primary care database consisting of electronically recorded person-level medical records derived from a population of 3.6 million patients actively contributing to the dataset (sourced from 750 general practices), and deemed to be representative of the UK population[11,12]. Details of routine care including clinical diagnoses are recorded through use of a hierarchical coding system known as READ codes. Practices were eligible for inclusion in the study from the latest of the two following dates: either one year after the date of installation of the electronic medical record (EMR) system or after the practice's acceptable mortality recording date. This ensured that the practice was making full use of the EMR system. To ensure baseline co-morbidities data was recorded, individual subjects were eligible for inclusion from the date their practice became eligible for inclusion in the study or one year after registration with their practice if this date was later.

The risk of future development of inflammatory bowel disease following perianal abscess

Incident cases of perianal abscess diagnosed from 01 January 1995 to 01 December 2017 in the THIN network were identified by READ codes. Index date was assigned six months after presentation with perianal abscess to ensure a diagnosis of CD or UC was not made preceding presentation. Subjects with perianal abscess were matched to up to 2 controls of the same age (+/- 1 year), gender, smoking and Body Mass Index (BMI) within the same general practice. Controls were defined as subjects who had never had a recorded diagnosis of perianal abscess at time of the study. Controls were assigned the same index date as their corresponding exposed subject to avoid immortality time bias. The primary outcome was the diagnosis of IBD (either CD or UC). The corresponding READ codes (appendix B) were identified in matched groups from the index date until the first of the following outcomes occurred (exit date); subject died, subject left practice, last data collection from practice or the subject was diagnosed with CD or UC. Any subjects with the outcome of interest prior to the index date were excluded from the study.

Statistical Analysis

Categorical baseline characteristics of the perianal abscess cohort and corresponding control group was assessed with the chi squared ($\chi 2$) test and are expressed in proportions. Parametric continuous variables such as age and body mass index (BMI) were assessed using two-sample t-tests and are expressed as mean (standard deviation). Non-parametric continuous variables were assessed with Mann-Whitney U test (person-years). Cox regression was used to provide an adjusted hazard ratio to estimate the likelihood of a diagnosis of CD or UC following a diagnosis of perianal abscess. The following co-variates were adjusted for: age, sex, BMI, diabetes, smoking and Townsend deprivation index (measure of material deprivation within a population derived from variables including unemployment, car and home ownership as well as household overcrowding)[13]. Cumulative hazard curves were derived for both CD and UC.

A cox regression model was used to assess potential predictors of a diagnosis of CD or UC following a diagnosis of perianal abscess. These were selected a-priori for inclusion in the regression model. The following factors were considered according to their presence closest in proximity to the index date: anaemia in males and females, abdominal pain, diarrhoea, lower gastrointestinal bleeding, and use of anti-diarrhoeal medication. Gonen and Heller's K concordance statistic was computed to assess the ability of the cox regression model in predicting a diagnosis of CD, or UC following a diagnosis of perianal abscess. The median and interquartile range (IQR) of time from the diagnosis of perianal abscess to diagnosis of CD, or UC respectively was also reported. Hazard ratios were calculated with 95% confidence intervals and a statistical significance threshold of $p<0.05$. Statistical analysis was performed on Stata v14.0 software.

The THIN data collection scheme received multi-centre research ethics committee (MREC) approval in 2003 with scientific committee approval of this particular study in April 2018 (18THIN018) from 'IQVIA' (data provider).

RESULTS

Demographics and co-morbidity in the matched perianal abscess and control groups

There were 17,854 perianal abscess cases matched to 27,111 controls within the THIN database. There was a mean of 5.6(SD 4.2) and 5.4(SD 4.1) person years follow-up for perianal abscess subjects and controls respectively. The perianal abscess cohort contained a lower proportion of males compared to the control population; 11,857(66.4%) vs 17,333(63.9%), $p<0.0001$. Perianal abscess cases were slightly younger than controls as they were matched to within 2 years (45.8 vs 46.9 years,

p<0.0001). Both cohorts displayed no significant difference in current smoking or former smoker rates. The perianal abscess cohort had a higher mean BMI (28.1(SD 6.2) vs 27.2(SD 4.9), p<0.0001), increased use of oral steroid medication (2608(14.6%) vs 3112(11.5%), p<0.0001), an increased prevalence of anaemia (1121(6.3%) vs 1384(5.1%), a higher prevalence of diabetes mellitus (1700(9.5%) vs 1619(6%), p<0.0001) and had a higher proportion of the most deprived category of subjects (2607(14.6%) vs 3690(13.6%), p<0.0001) compared to the control population. Seventy-two patients were documented to have recurrent episodes of perianal abscess between the index date and exit date, and no patients were identified to have developed peri-anal fistulae or extra-intestinal manifestations including; ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, episcleritis, scleritis, uveitis or aphthous ulcers prior to diagnosis of IBD. Prior to the diagnosis of PA, 60 patients had seen their GP on more than one occasion for symptoms of diarrhoea and 36 patients received anti-diarrhoeal medication on more than one occasion. All demographic and baseline characteristics data for both perianal abscess cases and controls are presented in *Table 1*.

The risk of Crohn's disease and ulcerative colitis in the matched perianal abscess and control groups

Following adjustment for potential confounding factors, the risk of CD was higher in the perianal abscess cohort compared to the control population; adjusted HR 7.51(95%CI 4.86-11.62), p<0.0001(*Table 2*). Mean age at CD diagnosis within the perianal abscess cohort was 38.51(SD 15.92) years. The median time from perianal abscess diagnosis to CD was 1.72(IQR 0.93-3.70) years. Cumulative hazard curve for CD is presented in *Figure 1A*.

The risk of a subsequent diagnosis of UC was higher in the perianal abscess cohort compared to control population; adjusted HR 2.03(95%CI 1.38-2.99), p<0.0001(*Table 2*). Mean age at UC diagnosis

within the perianal abscess cohort was 50.46(SD 14.89) years. Median time from perianal abscess diagnosis to ulcerative colitis was 4.04(IQR 1.80-6.51) years. Cumulative hazard curve for UC is presented in *Figure 1B*.

Subjects with diagnoses of CD or UC was pooled and the risk of IBD was found to be higher in the perianal abscess cohort compared to the control population; adjusted HR 3.86(95%CI 2.92-5.10), p<0.0001.

Predictive variables of future development of Crohn's Disease in perianal abscess subjects

Cox regression was used to assess features that might indicate a future diagnosis of CD. Anaemia in men (HR 2.82(95%CI 1.34-5.92), p=0.002), and use of antidiarrheal medications (HR 2.70(95%CI 1.71-4.25), p<0.0001) within 180 days of a diagnosis of perianal abscess were found to be associated with an increased likelihood of a diagnosis of CD in the future (*Table 3*).

Similarly, several factors were found to be negatively associated with a future diagnosis of CD. These were: BMI>30(HR 0.43(95%CI 0.24-0.78), p=0.005), and increasing age (HR 0.97(95%CI 0.96-0.98), p<0.0001). On further investigation, the following age categories in particular were negatively associated with a future diagnosis of CD; 40-60 years (HR 0.32(95%CI 0.14-0.71), p=0.005) and 60-80 years (HR 0.39(95%CI 0.16-0.95), p=0.04). The predictive accuracy of this regression model was assessed and a Gonen and Heller's K value of 0.71 was derived. For individuals who developed Crohn's disease in the exposed group, 43 (30.7%), 40 (28.6%), 19 (13.6%) patients experienced abdominal pain, diarrhoea or lower GI bleeding respectively at any point prior to diagnosis of perianal abscess at index date of study.

Predictive variables of future development of ulcerative colitis in perianal abscess subjects

Cox regression was also used to screen for potential predictors of a future diagnosis of UC. Anaemia in men (HR 2.58(95%CI 1.09-6.07), p=0.03), diarrhoea (HR 2.18(95%CI 1.23-3.85), p=0.007) and use of anti-diarrhoeal medication (HR 2.27(95%CI 1.19-4.30), p=0.01) within 180 days of index date, were found to indicate an increased risk of future diagnosis of UC. In the perianal abscess cohort, BMI>30 was associated with a reduced risk of future diagnosis of UC (HR 0.41(95%CI 0.19-0.87), p=0.02) (Table 3). The predictive ability of this model was assessed and a Gonen and Heller's K value of 0.70 was derived. For individuals who developed ulcerative colitis in the exposed group, 16 (24.2%), 25 (37.9%), 11 (16.7%) patients experienced abdominal pain, diarrhoea or lower GI bleeding respectively at any point prior to diagnosis of perianal abscess at index date of study.

Sensitivity Analysis

Sensitivity analysis was carried out to ensure coding within the general practice was accurate and that the exposure was coded prior to the outcome. A latency period of 180 days was reduced to 0 to assess the effect on the future risk of IBD within the perianal abscess population. The risk of CD and UC in this analysis was: HR 10.49(95%CI 6.71-16.4), p<0.0001 and HR 2.54(95%CI 1.69-3.82), p<0.0001 respectively.

DISCUSSION

This study has identified that a diagnosis of perianal abscess confers an increased risk of a subsequent diagnosis of CD and UC. The current study also identified predictors of a subsequent diagnosis of IBD in the perianal abscess population. Anaemia in men and prescription of anti-diarrhoeal medication around the time of diagnosis of perianal abscess were found to indicate an increased risk of a future diagnosis of both inflammatory bowel diseases within this cohort. The median time from a diagnosis of perianal abscess to CD and UC was found to be 1.7 years and 4 years respectively.

The marked disparity between the risk ratios for developing CD and UC supports the traditional association between perianal abscess and predominantly Crohn's disease. This study suggests that older subjects with perianal abscess are less likely to have a future diagnosis of CD compared to their younger counterparts, particularly those within the 40-60 and 60-80 age groups. This is similar to previous findings suggesting that older subjects, particularly those greater than 40 years of age, are at lower risk of complex perianal disease than their younger counterparts. Hamadani et al[14] identified the age category of <40 as being at higher risk of chronic perianal fistula following the initial presentation of perianal abscess; HR 2.12(95%CI 1.22-3.68), p<0.01. As the outcomes of this cohort study were limited to chronic anal fistula and recurrent anal sepsis, it is unclear whether any of these recurrent cases were actually manifestations of inflammatory bowel diseases. The elevated risk of complex perianal disease noted in the younger age category has also has been replicated in Chhaya et al[4]. In this cohort study, the Montreal A2(17 to 40-year-old) category conferred an increased risk of perianal abscess surgery within the CD cohort compared to the A3 category (>40 years old); HR 1.62(95%CI 1.29-2.02, p<0.001). No statistically significant association between increasing age and a future diagnosis of UC was discerned in the current study. Gender, diabetes and smoking status were not shown to be a statistically significant predictor of either of the inflammatory bowel diseases.

The present study suggests that subjects in the perianal abscess cohort with BMI > 30 were less likely to be diagnosed with CD and UC in the future. It has been previously shown that by Chan et al[15] that obesity as measured by BMI is not associated with the development of incident ulcerative colitis or Crohn's disease. This is in contrast to a similar large population-based prospective cohort study carried out in the Danish National Birth Cohort which suggested that obesity(BMI>30kg/m2) was a risk factor for Crohn's disease[16]. Both Dong et al[17] and Staborth-Akil[18] suggest that high BMI had an association with a favourable prognosis, whereas low BMI was associated with a more severe disease course. In the context of this study, subjects with undiagnosed IBD could potentially have had low BMI due to the pathological processes underlying IBD, leading to a perceived decrease in risk of a future diagnosis of IBD in subjects with high BMI.

Anaemia was shown to be a strong predictor of both inflammatory bowel diseases in the current study but only among men. The presence of anaemia at the time of diagnosis of IBD is a well-recognised feature[19]. The prevalence of anaemia in an IBD inception cohort has been reported be as high as 48.8% in CD patients and 20.2% in UC patients [20]. A gender difference in the prevalence of anaemia in IBD was also described with a higher proportion of males being affected than females in both of the inflammatory bowel diseases. The present study confirms this distribution with men affected more than women in both CD and UC; 8.5% vs 7.7% and 12.5% vs. 0% respectively.

Prescription of anti-diarrhoeal medication around the time of diagnosis of perianal abscess was associated with a subsequent diagnosis of inflammatory bowel disease. Reporting diarrhoea was also associated with a future diagnosis of UC alone. In the context of this study, this finding suggests that reporting diarrhoea is a key marker of undiagnosed IBD. Hence this symptom would merit

further investigation, e.g. faecal calprotectin testing. However, symptoms such as abdominal pain, lower gastrointestinal tract bleeding at the time of diagnosis of perianal abscess were not associated with a future diagnosis of either IBD.

Diagnostic delay remains a significant global challenge in the management of IBD, particularly CD[21]. This is known to have a significant adverse effect on disease course[22]. Recent cohort studies suggest the median time from symptoms to diagnosis of CD has been shorter than 1 year[23,24]. In contrast, median time from a diagnosis of perianal abscess to CD and UC in the current study was found to be 1.7 and 4 years respectively. This delay might potentially represent an opportunity for early detection and early therapeutic intervention of IBD in a potentially high-risk cohort.

The findings of this study rely upon accurate coding of the diagnosis of perianal abscess and the other baseline variables. The perianal abscess cohort in the present study resembles previous descriptions of subjects with this disease in the literature. The male predominant gender ratio of 2:1 (M: F) and relatively high proportion of smokers(40.87%) is similar to the gender ratio (2.4:1) in Adamo et al[1] and proportion of smokers(48.6%) in Devaraj et al[25] respectively. IBD has also been well-validated in the General Practice Research Database (GPRD) – a precursor to the THIN database[26]. The inability of this study to conclusively discern whether perianal abscess was in fact the initial manifestation of underlying undiagnosed inflammatory bowel disease itself, as opposed to a stand-alone condition is a significant limitation. However, this does not affect one of the key objectives of this study; enabling a reduction in diagnostic delay of IBD. This study adjusts for the varied role of smoking, however there may yet be unknown confounders that may affect the development of IBD. It is also clear from the baseline data that the exposed cohort had a higher prevalence of patients using oral steroids prior to index date. As we were unable to quantify the

indications for this prescription it is possible that patients in this cohort had comorbidities that necessitated steroid prescription.

The findings of this study in addition to knowledge that diagnostic delay[22] and perianal involvement in IBD can be a prognostic indicator of a severe disease course[27] confers great onus on the physician for early identification of IBD. Physicians should have a low threshold for investigation to screen for IBD in the PA cohort, particularly in the younger cohort (<40 years of age), males with anaemia and patients using antidiarrhoeals around the time of the diagnosis of perianal abscess.

This is the first study to report the incidence of IBD in patients who have had a prior diagnosis of perianal abscess. The results suggest that patients with a diagnosis of perianal abscess are at an increased risk of having a subsequent diagnosis of Crohn's disease and ulcerative colitis. This study was also able to establish predictive features of inflammatory bowel disease to assist in the risk-stratification of this patient population in the clinical setting.

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FIGURE LEGENDS

Fig 1A: Cumulative hazard curve for Crohn's disease

Fig 1B: Cumulative hazard curve for ulcerative colitis

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TABLES

Table 1: The Health Improvement Network perianal abscess and matched control group characteristics

		Perianal Abscess Cases	Control
Number of outcomes		17,854	27,111
Person years of follow-up (SD)		5.6 (4.2)	5.4 (4.1)
Age (SD)		45.8 (15.6)	46.9 (15.2)
Male Sex		11,857 (66.4%)	17,333 (63.9%)
Body mass index (SD)		28.1 (6.2)	27.2 (4.9)
Current smoker		7297 (40.9%)	11156 (41.2%)
Ex-Smoker		3,451 (19.3%)	5,363 (19.8%)
Anaemia		1121 (6.3%)	1384 (5.1%)
Diabetes mellitus		1700 (9.5%)	1619 (6%)
Townsend index*	**1**	3497 (19.6%)	5800 (21.4%)
	2	3230 (18.1%)	5084 (18.8%)
	3	3461 (19.4%)	5178 (19.1%)
	4	3312 (18.6%)	4733 (17.5%)
	5	2607 (14.6%)	3690 (13.6%)

Not available	1747 (9.8%)	2626 (9.7%)

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Standard Deviation (SD)

Table 2: The incidence of Crohn's Disease and Ulcerative colitis among the perianal abscess subjects and controls

	Crohn's Disease		Ulcerative Colitis	
	Perianal Abscess	**Control Population**	**Perianal Abscess**	**Control Population**
Number of Outcomes	140	25	66	49

Person-years	99,802.8	147,088.1	100,156.5	147,034.2
Incidence Rate **(per 100,000 person-years)**	0.0014	0.0008	0.0007	0.0003
Incidence Rate Ratio **(95% CI)**	8.25 (5.39-12.63)		2.02 (1.39-2.93)	
***p*-value**	<0.0001		<0.0001	
Adjusted* Hazard Ratio **(95% CI)**	7.51 (4.86-11.62)		2.03 (1.38-2.99)	
***p*-value**	<0.0001		<0.0001	

* Adjusted for age, sex, BMI, diabetes, smoking and Townsend deprivation score

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Table 3: The predictive variables for future development of Crohn's Disease and ulcerative colitis within the perianal abscess cohort

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		Crohn's Disease			Ulcerative Colitis		
		HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Gender	Male	1	ref	ref	1	ref	ref
	Female	1.31	0.89-1.92	0.17	0.88	0.50-1.55	0.66
Age (Continous)		**0.97**	**0.96-0.98**	**<0.0001**	1.00	0.98-1.01	0.64
Age (Categorical)	20 < x <= 40 years	0.78	0.37-1.64	0.52			
	40 < x <= 60 years	**0.32**	**0.14-0.71**	**0.005**			
	60 < x <= 80 years	**0.39**	**0.16-0.95**	**0.04**			
	80 to max years	0.14	0.02-1.17	0.07			
BMI	<25	1	ref	ref	1	ref	ref
	25-30	0.82	0.52-1.28	0.38	0.59	0.31-1.11	0.1
	>30	**0.43**	**0.24-0.78**	**0.005**	**0.41**	**0.19-0.87**	**0.02**
Diabetes		0.42	0.15-1.16	0.1	0.85	0.33-2.22	0.74
Smoking	Never Smoker	1	ref	ref	1	ref	ref
	Current Smoker	0.90	0.60-1.34	0.59	1.18	0.66-2.11	0.57
	Ex-Smoker	1.15	0.70-1.89	0.58	1.15	0.57-2.32	0.71
Abdominal Pain		1.33	0.91-1.93	0.14	0.71	0.39-1.29	0.26
Anaemia	**Men**	**2.82**	**1.34-5.92**	**0.002**	**2.58**	**1.09-6.07**	**0.03**
	Women	1.24	0.52-2.93	0.63	*calculation not feasible due to low number of outcomes		
Diarrhoea		1.33	0.87-2.02	0.18	**2.18**	**1.23-3.85**	**0.007**
Lower GI Bleed		1.60	1.00-2.56	0.05	1.83	0.98-3.43	0.06
Use of Anti-Diarrhoeals		**2. 70**	**1.71-4.25**	**<0.0001**	**2.27**	**1.19-4.30**	**0.01**
Townsend	**1**	1	ref	ref	1	ref	ref
	2	0.56	0.31-1.01	0.05	1.45	0.71-3.00	0.31
	3	0.91	0.55-1.51	0.71	1.24	0.59-2.61	0.58

	4	0.71	0.41-1.23	0.22	0.97	0.43-2.18	0.94
	5	1.00	0.59-1.69	0.993	0.72	0.28-1.81	0.48

Hazard Ratio (HR); Body Mass Index (BMI); 95% Confidence Interval (95% CI)

FIGURES

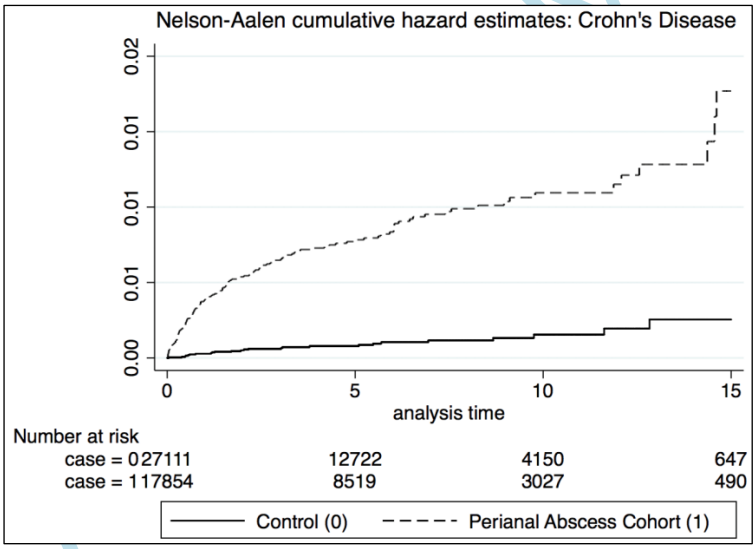

Fig 1A: Cumulative hazard curve for Crohn's disease

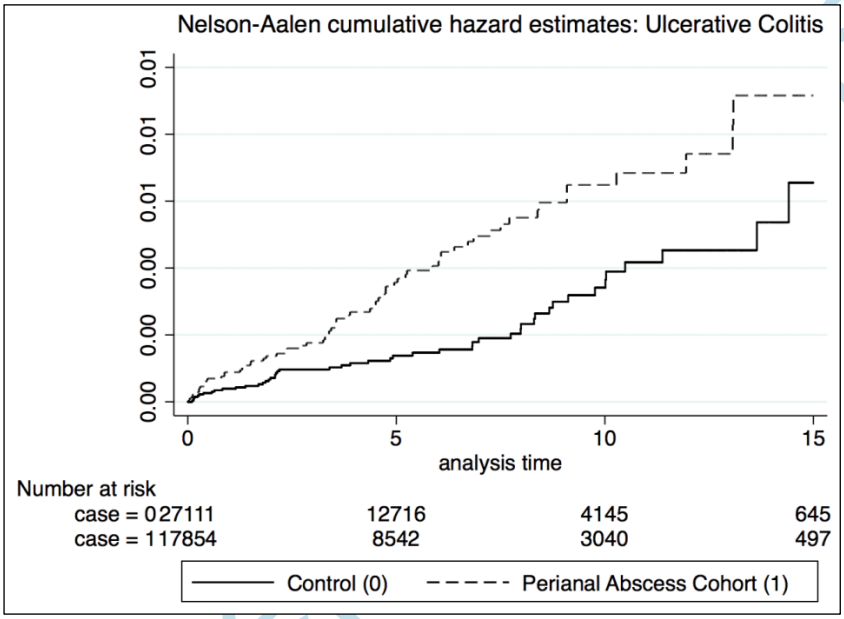

Fig 1B: Cumulative hazard curve for ulcerative colitis