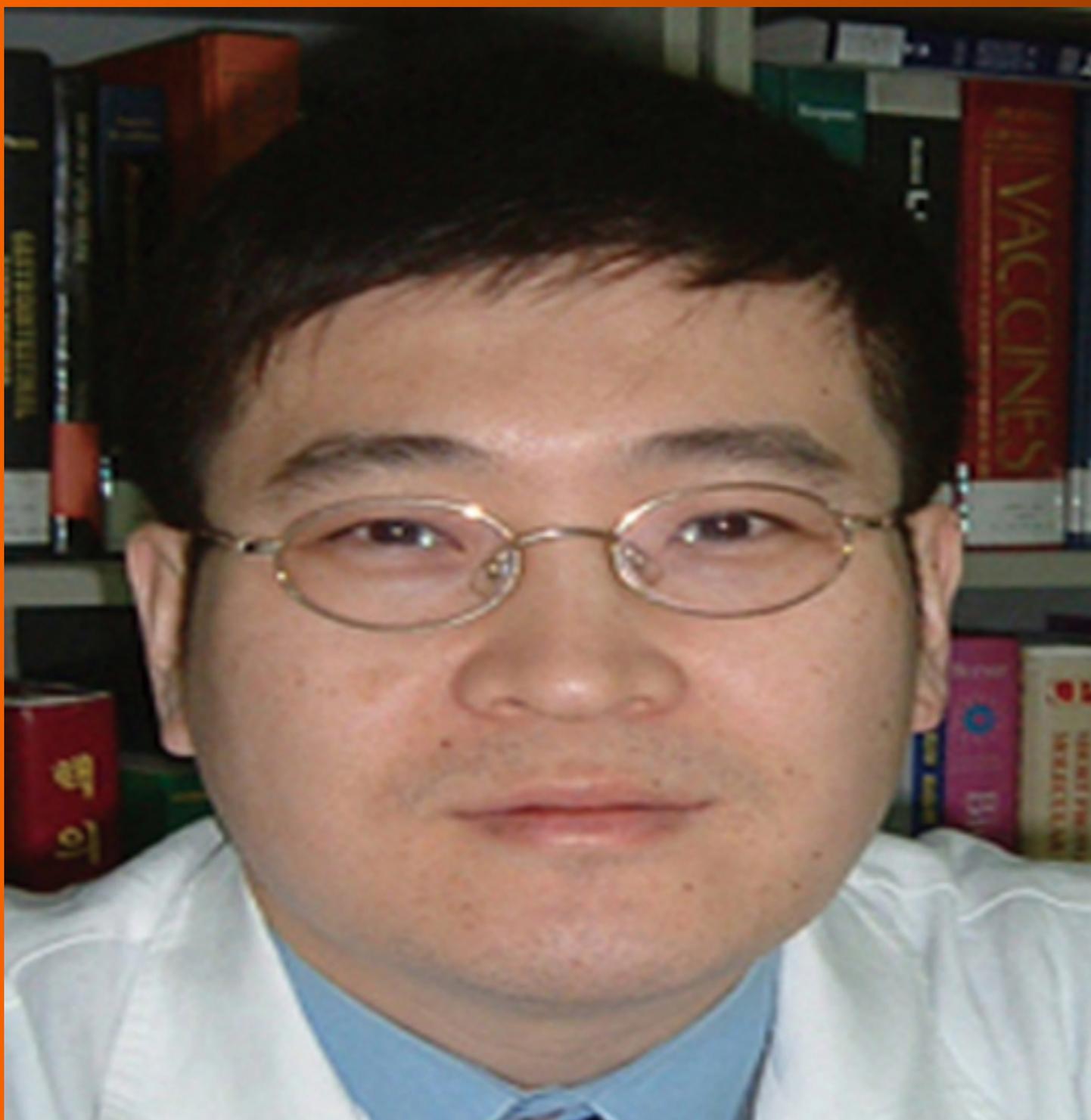


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Retrospective Cohort Study

Prevalence of anal fistula in the United Kingdom

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Abstract

BACKGROUND

Anal fistula is a pathological connection between the anal canal and perianal skin, which most commonly develops from an infected anal crypt. While the majority of anal fistulas are idiopathic, they are also associated with Crohn's disease (CD) and other inflammatory conditions. The prevalence of anal fistula is estimated to be 1-2 per 10000 patients, but population-based studies on anal fistula epidemiology are limited and outdated.

AIM

To assess the prevalence of anal fistula and relevant comorbidities, with and without CD in the United Kingdom and Europe.

METHODS

A retrospective population-representative observational cohort study was performed in The Health Improvement Network (THIN), a United Kingdom primary care database. Mid-year point prevalence of anal fistula was calculated on the first of July for each year between 2014 and 2017. Estimates were calculated for anal fistula overall and by CD status and standardized to the United Kingdom and European population. Prevalence of relevant comorbidities including lymphogranuloma venereum, hidradenitis suppurativa, anal presentation of sexually transmitted diseases, diabetes mellitus, and radiation in the pelvic area was reported.

RESULTS

STROBE statement: Guidelines of the STROBE statement have been adopted.

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The United Kingdom-standardized overall point prevalence of anal fistula was 1.80 (95%CI: 1.65-1.94) per 10000 patients in 2017, while the Europe standardized estimate was 1.83 (95%CI: 1.68-1.98) per 10000 patients. Both these standardized point prevalence estimates ranged from 1.89 to 2.36 between 2014-2016. The United Kingdom-standardized point prevalence of anal fistula without CD was 1.35 (95%CI: 1.23-1.48) per 10000 patients, while the Europe-standardized estimate was 1.39 (95%CI: 1.26-1.52) per 10000 patients. In contrast, the standardized point prevalence estimate of anal fistula with CD was lower for both United Kingdom and Europe (0.44; 95%CI United Kingdom: 0.37-0.52, 95%CI Europe: 0.37-0.51) per 10000 patients in 2017. In 2017, 19% of anal fistula patients without CD and 13% of anal fistula patients with CD had at least one relevant comorbidity. These results show that anal fistulas are infrequent in the general population. 24.5% of prevalent anal fistulas are associated with CD, but other potentially etiological comorbidities are rare.

CONCLUSION

This real-world evidence study estimated the United Kingdom-standardized prevalence of anal fistula was 1.80 per 10000 patients in 2017. Approximately 25% of cases may be associated with CD, while other comorbidities are rare.

Key words: Anal fistula; United Kingdom; Europe; Crohn's disease; Comorbidities; Prevalence

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Core tip: There is no recent data on the prevalence of anal fistula in Europe. The frequency of underlying risk conditions in anal fistula is also poorly understood. This real-world evidence study aimed to estimate United Kingdom and Europe-standardized prevalence of anal fistula, with and without Crohn's disease (CD), and describe the prevalence of relevant comorbidities among patients with anal fistula. Data was derived from the The Health Improvement Network database. Overall, the United Kingdom and Europe-standardized prevalence of anal fistula were 1.80 and 1.83 per 10000 patients respectively in 2017 (1.89-2.36 in 2014-2016). Approximately 25% of anal fistula cases may be associated with CD, while other comorbidities are rare.

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INTRODUCTION

An anal (or perianal) fistula is defined as an external abnormal anatomical connection between the anorectal canal and the perianal skin^[1]. Symptoms of anal fistulas include perianal cellulitis, anorectal pain, pruritus ani, smelly or bloody drainage of pus, and in some cases difficulty controlling bowel movements^[2,3].

Most anal fistulas are idiopathic (approximately 90% of cases), and arise from an infected anal crypt^[1]. Men are more commonly affected than women^[4], and the mean age of first presentation is reported to be 40 years^[5]. Management of anal fistula usually requires surgery including fistulotomy^[6], as very few heal without intervention. In Crohn's disease (CD) patients, first-line treatment with anti-tumor necrosis factor α antibody is recommended^[3].

The prevalence of anal fistula is reported to be approximately 1-2 per 10000 patients in European population studies^[7]. The mean incidence of anal fistula is estimated to be 8.6 per 100000 people, 1.04 per 10000 people, and 2.32 per 10000 people in Finland, Spain and Italy, respectively^[4,7]. However, being more than 10 years old, these reports may be outdated. A recent systematic review estimates the prevalence of anal fistula in Europe as 1.69 per 10000 patients^[8].

Anal fistulas are also associated with CD, lymphogranuloma venereum, hidradenitis suppurativa, surgery, radiotherapy^[9], and sexually transmitted diseases^[10], as these

can result in deep rectal/anal mucosal damage, which facilitates the development of fistula. Epidemiological reports on these and other etiologically relevant comorbid conditions in anal fistula are sparse. In CD, the cumulative incidence of anal fistula ranges between 17% and 50%, with about 35% of patients having at least one anal fistula during the course of the disease^[11-14]. Anal fistulas reported to be associated with tuberculosis are 0.2%, and 3.3% are associated with trauma^[4]. After surgery, between 1.2% of patients and 0.3% of patients develop anal fistula^[15-18]. Approximately 7% of patients with lymphogranuloma venereum^[19] and 80%-91% of patients with anorectal tuberculosis present with anal fistula^[20].

Patients with chronic diseases like diabetes mellitus are also discussed to be at increased risk of anal fistula, due to their susceptibility to skin lesions and systemic infections^[21], and increased risk for perianal abscesses^[22].

There is no recent data on the prevalence of anal fistula in the European or United Kingdom. The frequency of underlying risk conditions in anal fistula is also poorly understood, and no comprehensive estimate of their prevalence within the population of anal fistula patients exists. Although there is an established association between CD and anal fistula, there remains a lack of current prevalence estimates as well as estimates of relevant risk comorbidities.

This observational study aimed to generate population-based real-world evidence on the epidemiology of anal fistula within a United Kingdom primary healthcare database. The study hopes to improve our understanding of the prevalence of anal fistula, with and without CD, as well as the prevalence of relevant comorbidities among anal fistula patients.

MATERIALS AND METHODS

Study design

A retrospective observational database cohort study was conducted in The Health Improvement Network (THIN) database. The mid-year point prevalence of anal fistula was reported on the 1st of July for each year of 2014-2017. Estimates were standardized to United Kingdom and Europe populations.

Data source

THIN is a large United Kingdom primary care database containing electronic medical records (EMR). As of September 2015, THIN contained pseudonymised primary care medical records from over 14 million patients, of which over 3.5 million are currently registered and actively contributing to the database, representing almost 6% of the United Kingdom population. THIN data have been shown to be generally representative of the United Kingdom in terms of age and gender composition, and chronic disease prevalence^[23,24].

Medical diagnoses in THIN are recorded using Read codes, the standard classification system in the United Kingdom^[25]. Data from all active patients collected via the Vision software from registration through to September 2017 was used for analysis in this study. The study protocol was reviewed and approved by the THIN Scientific Review Committee (SRC 18THIN006). In accordance with data protection rules, patient counts of 1-5 are masked.

Study population

All subjects registered in a primary care general practice, submitting data to THIN with an acceptable record were considered (permanently registered, contained no out of sequence year of birth or registration date, registered a transfer out date that was not missing or invalid, registered a year of birth, and had recorded information on sex). Patients were excluded from the study if they registered in the database prior to the date that practice started using the Vision management software, and if their first recorded sign of anal fistula in THIN was prior to the date of registration.

All diagnoses were based on the presence of a Read code (supplementary Table 1) in the patient's EMR. Firstly, prevalent cases of anal fistula, regardless of underlying disease etiology, were identified. If a CD diagnosis occurred prior to, or up to 4 years after the anal fistula diagnosis, the patient was considered to have anal fistula with CD. This permitted the inclusion of patients for whom anal fistula was the first manifestation of CD^[26-28]. To accommodate the slower healing of anal fistula in patients with CD^[6], the patient was considered prevalent for 4 years following an anal fistula diagnosis. Patients without CD were expected to have healed faster, thus considered prevalent for 12 mo following diagnosis.

Study parameters

Anal fistula Read codes were divided into two categories: (1) Direct codes which

Table 1 Overall prevalence of anal fistula with and without Crohn's disease

	2014	2015	2016	2017
Prevalence of AF, <i>n</i>	1143	938	688	579
Prevalence of AF, <i>n</i> /10000 patients	2.34	2.22	1.93	1.82
Standardization to				
UK (95%CI)	2.31 (2.18-2.44)	2.19 (2.05-2.33)	1.89 (1.75-2.03)	1.80 (1.65-1.94)
EU (95%CI)	2.36 (2.22-2.50)	2.23 (2.08-2.37)	1.94 (1.79-2.08)	1.83 (1.68-1.98)

AF: Anal fistula; *n*: Number; CI: Confidence interval; UK: United Kingdom; EU: European Union.

specify anal fistula (*e.g.*, anal fissure and fistula, and fistula-in-ano), and (2) Indirect codes which are explicitly related to anal fistula, such as procedures or surgeries (*e.g.*, excision of fistula in ano, and anal fistula operations) (supplementary Table 1).

Relevant infectious risk comorbidities (anal/rectal tuberculosis, lymphogranuloma venereum, anal/rectal syphilis, anal/rectal chlamydia, anal/rectal gonorrhoea, and proctitis), and chronic risk comorbidities [human immunodeficiency virus (HIV), anal carcinoma, radiation administered to the pelvic area, diabetes mellitus type 1 and 2, diverticulitis of the large intestine/colon/rectum, and hidradenitis suppurativa] were identified through Read codes (supplementary Table 1). Patients were defined as having the infectious comorbidities if they were recorded up to two years prior to the anal fistula diagnosis, and chronic comorbidities at any time in patient history prior to anal fistula diagnosis. Congenital anal fistula was identified independently from comorbidities (supplementary Table 1).

Statistical analysis

Mid-year point prevalence was calculated for anal fistula with and without CD as crude numbers and rates per 10000 patients on 1st July of each year 2014-2017 by dividing the number of identified prevalent anal fistula cases by the number of active patients in the database (per 10000). Prevalence was calculated for both Direct and Indirect codes together as well as separately, with further stratification by age, gender, and CD status.

Overall point prevalence results were standardized to the United Kingdom and Europe population by sex and age group, and are reported as point prevalence rates per 10000 patients with corresponding 95%CI. For the standardization, the latest available national mid-year population statistics for the United Kingdom (2016)^[29] and Europe (2013)^[30] were used.

The mid-year prevalence of relevant comorbidities in patients with anal fistula are reported for each year 2014-2017 as prevalent anal fistula with any comorbidity per 10000 patients, and individually by comorbidity as proportion of affected anal fistula patients. Analyses were stratified by CD status.

The statistical methods of this study were reviewed by Catrina Richards of IQVIA.

RESULTS

Overall point prevalence of anal fistula

The overall crude point prevalence of anal fistula (with and without CD) in THIN per 10000 patients was 1.82 in 2017, and ranged from 1.93 to 2.34 in 2014-2016 (Table 1). The United Kingdom-standardized point prevalence estimate was 1.80 (95%CI: 1.65-1.94) per 10000 patients in 2017, and the Europe-standardized estimate was 1.83 (95%CI: 1.68-1.98) per 10000 patients. United Kingdom- and Europe-standardized point prevalence estimates ranged from 1.89 to 2.36 in 2014-2016.

Point prevalence of anal fistula without CD

The overall crude point prevalence of anal fistula without CD in THIN per 10000 patients was 1.38 in 2017, and ranged from 1.44 to 1.83 in 2014-2016 (Table 2).

Consistently, throughout the period 2014-2017, fewer females were diagnosed with anal fistula (44%-45%), and most patients were aged between 40 and 59 years (39%-45%) or between 20 and 39 years (31%-35%). The United Kingdom-standardized point prevalence estimate of anal fistula was 1.35 (95%CI: 1.23-1.48) per 10000 patients in 2017, and the Europe-standardized estimate was 1.39 (95%CI: 1.26-1.52) per 10000 patients. United Kingdom- and Europe- standardized point prevalence estimates ranged from 1.41 to 1.84 in 2014-2016 (Table 2).

Table 2 Prevalence of anal fistula without Crohn's disease

	2014	2015	2016	2017
Prevalence of AF, <i>n</i>	891	726	514	437
Prevalence of AF, <i>n</i> /10000 patients	1.83	1.72	1.44	1.38
Gender Female, <i>n</i> (%)	365 (43.7)	288 (44.6)	197 (44.4)	180 (44.9)
Age 0-19, <i>n</i> (%)	53 (5.9)	29 (4.0)	24 (4.7)	21 (4.8)
20-39, <i>n</i> (%)	314 (35.2)	249 (34.3)	162 (31.5)	137 (31.4)
40-59, <i>n</i> (%)	344 (38.6)	320 (44.1)	230 (39.5)	197 (45.1)
60-79, <i>n</i> (%)	147 (16.5)	112 (15.4)	112 (21.8)	70 (16.0)
80+, <i>n</i> (%)	33 (3.7)	16 (2.2)	13 (2.5)	12 (2.7)
Standardization to				
UK (95%CI)	1.80 (1.68-1.92)	1.69 (1.57-1.81)	1.41 (1.29-1.53)	1.35 (1.23-1.48)
EU (95%CI)	1.84 (1.72-1.97)	1.73 (1.60-1.85)	1.45 (1.32-1.58)	1.39 (1.26-1.52)
Direct AF Read codes ¹				
Prevalence of Direct AF, <i>n</i>	586	466	347	265
Prevalence of Direct AF, <i>n</i> /10000 patients	1.20	1.10	0.97	0.84
Standardization to				
UK (95%CI)	1.18 (1.09-1.28)	1.09 (0.99-1.19)	0.96 (0.86-1.06)	0.83 (0.73-0.92)
EU (95%CI)	1.21 (1.11-1.31)	1.11 (1.01-1.21)	0.98 (0.87-1.08)	0.84 (0.74-0.94)
Most commonly used Read codes:				
Anal fissure and fistula, <i>n</i>	360	245	186	139
Fistula-in-ano, <i>n</i>	250	224	167	141
Indirect AF Read codes ²				
Prevalence of Indirect AF, <i>n</i>	391	324	214	199
Prevalence of Indirect AF, <i>n</i> /10000 patients	0.80	0.77	0.60	0.63
Standardization to				
UK (95%CI)	0.79 (0.71-0.87)	0.75 (0.67-0.83)	0.60 (0.58-0.50)	0.61 (0.52-0.69)
EU (95%CI)	0.81 (0.73-0.89)	0.77 (0.69-0.86)	0.61 (0.53-0.69)	0.63 (0.54-0.72)
Most commonly used Read codes:				
Anal fistula operations, <i>n</i>	135	98	65	69
Laying open of anal fistula NEC, <i>n</i>	106	87	59	41
Excision of fistula in ano, <i>n</i>	94	74	61	55

AF: Anal fistula; *n*: Number; CI: Confidence interval; UK: United Kingdom; EU: European Union; NEC: Not elsewhere classified;

¹Direct codes: Read codes directly identifying anal fistula (e.g. anal fissure and fistula, and fistula-in-ano);

²Indirect codes: Read codes identifying procedures or surgeries related specific to anal fistulas (e.g., excision of fistula in ano, and anal fistula operations); One patient can have multiple Direct and Indirect anal fistula codes.

Direct Read codes identified the majority of prevalent anal fistula cases (Direct codes: *n* = 265 *vs* Indirect codes: *n* = 199 in 2017; Table 2). A patient could have been assigned multiple Direct and/or Indirect codes. The most commonly used Direct codes were "Anal fissure and fistula" (*n* = 139/265 in 2017) and "fistula-in-ano" (*n* = 141/265 in 2017). The most common Indirect codes were "anal fistula operations" (*n* = 69/199) and "excision of fistula in ano" (*n* = 55/199 in 2017) (Table 2).

Point prevalence of anal fistula with CD

The overall crude point prevalence of anal fistula with CD in THIN per 10000 patients was 0.45 in 2017, and ranged from 0.49 to 0.52 in 2014-2016 (Table 3). Consistently, throughout the period 2014-2017, fewer females were diagnosed with anal fistula (42%-47%), and most patients were aged between 20 and 39 years (43%-56%) or between 40 and 59 years (32%-42%). The standardized point prevalence estimate of anal fistula with CD was 0.44 for both United Kingdom and Europe (95%CI United

Kingdom: 0.37-0.52, 95%CI Europe: 0.37-0.51) per 10000 patients in 2017. United Kingdom- and Europe-standardized point prevalence estimates ranged from 0.48 to 0.52 in 2014-2016 (Table 3).

Comorbidities in anal fistula with and without CD

Patients with an anal fistula without CD consistently presented more frequently with an anal fistula-related comorbidity than anal fistula patients with CD over the period 2014-2017. In 2017, 19% ($n = 82/437$) of anal fistula patients without CD had at least one comorbidity of interest, compared to 13% ($n = 18/142$) anal fistula patients with CD (Table 4). As no anal fistula patients were identified with the sexually transmitted diseases of interest (anal/rectal syphilis, anal/rectal gonorrhoea, anal/rectal chlamydia, and lymphogranuloma venereum) or anal/rectal tuberculosis, counts are not included in Table 4.

The most common comorbidity among both anal fistula patients with and without CD was diabetes mellitus type 1 or 2, with 5% and 9% of patients affected in 2017, respectively. Diverticulitis of the colon or rectum was also a common comorbidity in anal fistula patients without CD (5% affected in 2017), while hidradenitis suppurativa was the second most common comorbidity in anal fistula patients with CD (4% affected in 2017) (Table 4).

Upon stratification, anal fistula patients with the highest frequency of comorbidities were men and patients over 65 years of age. In 2017, 23% ($n = 58/257$) of male and 13% ($n = 24/180$) of female anal fistula patients without CD had at least one comorbidity of interest. The frequency was comparable between male (12%, $n = 9/78$) and female (14%, $n = 9/64$) anal fistula patients with CD. Among anal fistula patients without CD aged over 65 years, 62% ($n = 33/53$) presented with at least one comorbidity of interest – most frequently with diabetes mellitus (34%, $n = 18/53$). There were too few patients in this age category with anal fistula with CD to report ($n = 1-5$).

DISCUSSION

This observational real-world evidence study is the first to report comprehensive prevalence estimates of anal fistula in patients with and without CD, and the frequency of concomitant comorbidities in a United Kingdom population-based study. We report the United Kingdom-standardized overall prevalence of anal fistula to be 1.80 cases per 10000 patients.

Most anal fistula patients identified in this study were idiopathic. This finding is consistent with previous studies^[4,31,32] and a recently conducted systematic literature review on anal fistula prevalence^[8]. As the fistula duration is longer for patients with CD than for patients without^[33-36], we adjusted the look-back period for prevalence estimates accordingly, which allowed for accurate prevalence estimate.

Reported population-based incidence estimates for anal fistula in CD patients range between 1.2%^[37] to 7.5%^[38]. Based on these values, a systematic review calculated anal fistula prevalence among CD patients to be 3.4%-6.0% in the Europe^[8]. Our study's prevalence estimates of anal fistula patients with CD (0.44/10000 patients, United Kingdom standardized) are not directly comparable to these results, as the denominators represent different patient populations (we used the number of total patients instead of number of CD patients). However, while literature typically suggests 90% of anal fistula to be idiopathic^[2,3], the proportion of anal fistula patients with a diagnosis of CD in the THIN database was 25%. This may be explained by the different methods applied, as well as characteristics of the databases: We included a look-back period for CD at any time in the patient's history as well as a four-year prospective period from the index anal fistula diagnosis to account for the possibility that anal fistula are the first manifestation of CD. This is likely to have increased the proportion of CD patients within anal fistula patients compared to studies that did not allow for a prospective follow-up time.

In line with previous studies^[4], we found men to be more frequently affected by anal fistula than women, in both patients with and without CD. This is attributable to the substantially higher prevalence of anal abscesses in men^[39].

In THIN, both Direct (capturing anal fistula diagnoses) and Indirect (capturing procedures explicitly related to anal fistula) anal fistula Read codes are used – Direct codes being more frequent than Indirect ones. This was expected, because procedures associated with anal fistula therapy are commonly conducted in a secondary care setting. Although diagnoses are reported back from secondary care to the general practitioner (GP) in the United Kingdom, this data transfer is often facilitated by letters; therefore, it is possible that not all procedures may have been transcribed into

Table 3 Prevalence of anal fistula with Crohn's disease

	2014	2015	2016	2017
Prevalence of AF, <i>n</i>	252	212	174	142
Prevalence of AF, <i>n</i> /10000 patients	0.52	0.50	0.49	0.45
Gender Female, <i>n</i> (%)	66 (43.3)	53 (42.4)	51 (46.8)	42 (43.8)
Age 0-19, <i>n</i> (%)	###	###	###	###
20-39, <i>n</i> (%)	115 (45.6)	96 (45.3)	75 (43.4)	79 (55.6)
40-59, <i>n</i> (%)	89 (35.3)	81 (38.2)	73 (42.2)	45 (31.7)
60-79, <i>n</i> (%)	32 (12.7)	23 (10.8)	16 (9.2)	13 (9.2)
80+, <i>n</i> (%)	###	###	###	###
Standardization to				
UK (95%CI)	0.51 (0.45-0.57)	0.50 (0.43-0.56)	0.48 (0.41-0.55)	0.44 (0.37-0.52)
EU (95%CI)	0.52 (0.45-0.58)	0.50 (0.43-0.57)	0.48 (0.41-0.56)	0.44 (0.37-0.51)
Direct AF Read codes ¹				
Prevalence of Direct AF, <i>n</i>	149	125	109	96
Prevalence of Direct AF, <i>n</i> /10000 patients	1.31	1.30	0.31	0.30
Standardization to				
UK (95%CI)	0.30 (0.25-0.35)	0.29 (0.24-0.34)	0.30 (0.24-0.36)	0.30 (0.24-0.36)
EU (95%CI)	0.30 (0.26-0.35)	0.29 (0.24-0.35)	0.30 (0.25-0.36)	0.30 (0.24-0.36)
Indirect AF Read codes ²				
Prevalence of Indirect AF, <i>n</i>	147	125	102	70
Prevalence of Indirect AF, <i>n</i> /10000 patients	0.30	0.30	0.29	0.22
Standardization to				
UK (95%CI)	0.30 (0.25-0.34)	0.29 (0.24-0.34)	0.28 (0.23-0.34)	0.22 (0.17-0.27)
EU (95% CI)	0.30 (0.25-0.35)	0.29 (0.24-0.35)	0.28 (0.23-0.34)	0.22 (0.17-0.27)

AF: Anal fistula; *n*: Number; CI: Confidence interval; UK: United Kingdom; EU: European Union;

¹Direct codes: Read codes directly identifying anal fistula (*e.g.*, anal fissure and fistula, and fistula-in-ano);

²Indirect codes: Read codes identifying procedures or surgeries related specific to anal fistulas (*e.g.*, excision of fistula in ano, and anal fistula operations); One patient can have multiple Direct and Indirect anal fistula codes; ### masking due to small patient numbers (*n*: 1-5).

the fields of the data source. A small subset of anal fistula cases may also be treated without invasive methods^[40].

In addition to the well-established connection between CD and anal fistula, anal fistula has been associated with anal/rectal infectious diseases^[4,19,20], anal carcinoma^[41], and systemic diseases^[42,43]. We report diabetes mellitus to be the most common comorbidity of interest within anal fistula patients with and without CD, and elderly patients to be most frequently affected by comorbidities. This is not surprising, as diabetes is common in the general population, with a reported United Kingdom prevalence of 4.3% in 2005^[44]. Diabetic patients are more susceptible to skin lesions and systemic infections^[21], and are reported to be at increased risk for anal abscesses^[22]. It is also possible that diabetic patients are more likely to be diagnosed instead of remaining undetected, as they are more frequently clinically assessed. They may thus be at increased risk for anal fistula. Diverticulitis is regarded as a risk factor for anal fistula, if a low sigmoid diverticular infection or abscess damages all mucosal layers.

However, typically, diverticulosis is associated with fistulas between the colon and bladder or the colon and vagina in women^[45,46]; not anal fistula. Other comorbid conditions included in our study are very rare. However, it is to be noted that sexually transmitted diseases are under-recorded in THIN, as patients in the United Kingdom are frequently treated at specialized sexual health clinics, and data are not always conveyed to the GP, or transcribed into the fields of the data source if they are conveyed. We may also have missed cases with radiation to the pelvic area as a comorbidity, as procedure codes from secondary care may not all be transcribed into THIN.

A decline in the number of practices using Vision software has led to a decline in active patients in THIN. This may contribute to the observed decline in anal fistula prevalence 2014-2017. It is unclear to what extent differential changes in patient

Table 4 Prevalence of comorbidities in anal fistula with and without Crohn's disease

	2014		2015		2016		2017	
	without CD	with CD						
Prevalence of AF, <i>n</i>	891	252	726	212	514	172	437	142
Prevalence of AF with any comorbidity	148	39	124	28	96	26	82	18
per 10000 patients	0.30	0.08	0.29	0.07	0.27	0.07	0.26	0.06
per 100 AF patients	16.61	15.48	17.08	13.21	18.68	15.03	18.76	12.68
Prevalence of comorbidities per 100 AF patients ¹								
HIV	0	###	###	###	0	###	###	###
Anal carcinoma	###	0	###	0	###	0	###	0
Radiation in the pelvic area	1.91	###	1.79	###	1.75	###	3.43	###
Diabetes mellitus type 1 or 2	8.98	5.16	8.13	5.19	10.12	5.20	8.92	4.93
Diverticulitis, colon/rectum	4.38	###	4.96	###	5.84	3.47	5.26	###
Hidradenitis suppurativa	0.90	###	1.38	###	1.95	3.47	1.60	4.23
Proctitis	1.46	4.76	2.20	3.77	1.36	4.62	1.83	###
Congenital anal fistula	0	0	###	0	0	0	0	0

AF: Anal fistula; *n*: Number; HIV: Human immunodeficiency virus;

¹No patients with anal tuberculosis, anal syphilis, anal gonorrhoea, anal chlamydia, lymphogranuloma venereum were detected; ### masking due to small patient numbers (*n*: 1-5).

demographics and healthcare structure affect the estimates. New and personalized treatment options for CD and anal abscesses may also affect the trend of anal fistula prevalence. These hypotheses should be explored in further studies.

The main strength of this real-world evidence study is the population-based nature of the data source, which allows results to be generalized to the United Kingdom and Europe populations. Most cases of anal fistula are thought likely to be captured in the THIN database, as fistulas do not heal on their own and need medical intervention, and the gateway to the medical system in the United Kingdom is through primary care. Similarly, it is unlikely that many patients only receive their care in hospital and appear inactive in THIN. Furthermore, we have accounted for the different courses of disease between patients with and without CD, to report the most accurate overall anal fistula prevalence estimates. Standardization of the prevalence estimates to the Europe is considered to be valid, as biological variation across Europe compared to the United Kingdom is minimal.

ARTICLE HIGHLIGHTS

Research background

An anal (or perianal) fistula is defined as an external abnormal pathological connection between the anal canal and perianal skin. The majority of anal (or perianal) fistulas are idiopathic, associated with Crohn's disease (CD) and, to a lesser extent, other inflammatory conditions.

Research motivation

There is no recent data on the prevalence of anal fistula in the United Kingdom or the Europe. The frequency of underlying risk conditions in anal fistula is also poorly understood.

Research objectives

This real-world evidence study aimed to estimate United Kingdom- and Europe-standardized prevalence of anal fistula, with and without CD. Additionally, the study aimed to describe the prevalence of relevant comorbidities among patients with anal fistula.

Research methods

A retrospective population-observational cohort study was performed using a United Kingdom primary care database. The prevalence of anal fistula by overall and CD status was calculated between 2014 and 2017. These estimates were standardized to the United Kingdom and Europe populations. Prevalence of relevant comorbidities was also reported.

Research results

Analysis estimated the United Kingdom- and Europe-standardized prevalence of anal fistula as 1.80 (95%CI: 1.65-1.94) and 1.83 (95%CI: 1.68-1.98) per 10000 patients, respectively in 2017. Between 2014-2016 the standardized point prevalence estimates ranged from 1.89 to 2.36.

Analysis estimated the United Kingdom- and Europe-standardized prevalence of anal fistula without CD as 1.35 (95%CI: 1.23-1.48) and 1.39 (95%CI: 1.26-1.52) per 10000 patients. In contrast, the standardized point prevalence estimate of anal fistula with CD was lower for both United Kingdom and Europe (0.44; 95%CI United Kingdom: 0.37-0.52, 95%CI Europe: 0.37-0.51) per 10000 patients in 2017. Examining data from 2017 showed that 19% of anal fistula patients without CD and 13% of anal fistula patients with CD were associated with at least one relevant comorbidity. Data indicated that 24.5% of prevalent anal fistulas were associated with CD, whereas association with other potential comorbidities was uncommon.

Research conclusions

This real-world evidence study estimated the United Kingdom- and Europe-standardized prevalence of anal fistula were 1.80 and 1.83 per 10000 patients, respectively in 2017. Furthermore, almost 25% of cases appeared to be associated with CD but associations with other comorbidities seemed rare.

Research perspectives

This study presents new recent population-based data on the prevalence of anal fistula in the United Kingdom and Europe. As such, it highlights the significance of this devastating complication associated with CD and other relevant comorbidities. These prevalence estimates for anal fistula indicate a major need for novel therapeutic options for this population of patients.

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