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Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018

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Summary

Background: Data regarding incidence, prevalence and long-term outcomes of inflammatory bowel diseases in the UK are limited or outdated.

Aims: To investigate incidence and prevalence of Crohn's disease and ulcerative colitis and risk of colorectal cancer and all-cause mortality in these diseases.

Methods: Inflammatory bowel disease cases between 2000 and 2018 were identified from a national primary care database. Inflammatory bowel disease prevalence was forecast until 2025. The association between inflammatory bowel disease and colorectal cancer and all-cause mortality was investigated using age/sex-matched retrospective cohort studies. Hazard ratios were adjusted for age, sex, deprivation, comorbidity, smoking status and body mass index.

Results: Ulcerative colitis prevalence increased from 390 to 570 per 100 000 population from 2000 to 2017. Prevalence of Crohn's disease increased from 220 to 400 per 100 000. In 2017 male Crohn's disease prevalence was 0.35% (95% confidence interval 0.34-0.36); female prevalence was 0.44% (0.43-0.45). Prevalence of inflammatory bowel disease is predicted to be 1.1% by 2025. Incidence of ulcerative colitis and Crohn's disease was 23.2 (22.8-23.6) and 14.3 (14.0-14.7) per 100 000 person-years respectively. Subjects with ulcerative colitis were more likely to develop colorectal cancer than controls (adjusted Hazard Ratio 1.40 [1.23-1.59]). Colorectal cancer rates remained stable in inflammatory bowel diseases over time. Ulcerative colitis and Crohn's disease were associated with increased risk of all-cause mortality (1.17 [1.14-1.21] and 1.42 [1.36-1.48] respectively).

Conclusions: The UK prevalence of inflammatory bowel disease is greater than previous reports suggest and we predict an 11% increase in prevalence by the year 2025. Mortality risk in inflammatory bowel disease and colorectal cancer risk in ulcerative colitis are increased compared to matched controls.

1 | INTRODUCTION

Inflammatory bowel diseases are characterised by chronic and relapsing inflammation of the bowel. They can affect any age group, have a significant impact on working age populations and lead to a considerable societal and economic burden.[1,2] Inflammatory bowel disease largely consists of two sub-phenotypes: Crohn's disease and ulcerative colitis. The global epidemiology of inflammatory bowel disease has changed substantially over time, with a recent review demonstrating an increasing incidence of inflammatory bowel disease in developing nations and a stabilising incidence in developed nations.[3,4] Similarly, all-cause mortality rates within the inflammatory bowel disease cohort have improved significantly, with recent research suggesting rates similar to those of the general population.[5] Historically a key risk factor for mortality in the inflammatory bowel disease cohort was thought to be the association between inflammatory bowel disease and colorectal cancer (CRC)[6]; however, recent evidence suggests that this risk is now much lower than previously thought.[7,8]

Inflammatory bowel disease can lead to hospitalisation and time off work, and its management is costly. Given the individual and societal impact of these diseases, accurate and up-to-date data on prevalence and outcomes are important for service planning. Published United Kingdom (UK) inflammatory bowel disease epidemiology data are out of date or based on small or regional datasets which may not be representative of the United Kingdom as a whole.[4,9-12]

The primary aim of this study was to provide an up-to-date description of the incidence and prevalence of inflammatory bowel diseases in the UK and forecast the expected prevalence of these conditions. The secondary aim was to quantify the risk of all-cause mortality and colorectal cancer (CRC) in the inflammatory bowel disease cohort.

2 | MATERIALS AND METHODS

2.1 | Data source

This study utilised The Health Improvement Network primary care (THIN) database. This is derived from 787 general practices across the UK and incorporates data from approximately 15 million subjects. It is generalisable to the UK population.[13] Longitudinal patient-level data including medication use, primary and secondary care investigations and diagnoses are uploaded electronically using a hierarchy of clinical (Read) codes.[14] Diagnoses of inflammatory bowel disease are derived from general practitioners who receive this data from secondary and tertiary centres where the diagnosis would have been established. Practices were included in the study if they had achieved an acceptable mortality recording threshold and at least one year had elapsed since the installation of the electronic medical record system.[15] Inclusion only after attainment of an acceptable level of data recording (assessed by acceptable mortality recording) reduces the risk of under-recording.

2.2 | Study design

Cross-sectional and retrospective cohort studies were carried out to identify the annual point prevalence and incidence rates, respectively, of ulcerative colitis and Crohn's disease among adults aged 18 years and over between 1 January 2000 and 31 December 2017. Incident cases were defined as new cases during the study period without a previous diagnosis before entry date. Prevalent cases were defined as cases diagnosed/recorded before the annual point prevalence calculation for the year of interest.

The prevalence of ulcerative colitis and Crohn's disease was projected forward to 2025 using Holt-Winters' double exponential smoothing model with 80 and 95% prediction intervals (PI). For the model validation, the dataset was separated into two portions: training (from 2000 to 2012) and test (from 2013 to 2017) data. The model was fitted to the training data and predicted prevalence up to 2017 compared with test data.

The incidence of colorectal cancer was determined in the whole adult, THIN database population and in those with ulcerative colitis and Crohn's disease. Mortality and colorectal cancer incidence rates were quantified using matched cohort studies between 1 January 2000 and the date of the latest data available at the time of study (17 January 2018). Four controls, unexposed to either ulcerative colitis or Crohn's disease, were directly matched for each ulcerative colitis or Crohn's disease subject by age, sex, Townsend deprivation level[16] and index date. Index date was defined as the date of diagnosis of ulcerative colitis or Crohn's disease for incident cases and one year after joining an eligible practice for prevalent cases. If individuals in the colorectal cancer study had a previous record of colorectal cancer prior to the study start date, they were excluded. Subjects with a colectomy code prior to cancer diagnosis were excluded from the colorectal cancer study. Subjects were followed up until the outcome of interest, death or the earlier of a subject leaving the practice or the final collection of data on a subject. If subjects were coded for both ulcerative colitis and Crohn's disease, the later of the two was considered the diagnosis while the earliest diagnosis date was retained.

2.3 | Data validation

Clinical codes used to identify ulcerative colitis, Crohn's disease and colorectal cancer are listed in Appendix S1. Code lists used to identify patients with inflammatory bowel disease have been previously validated.[17,18] For internal validity, 88 practices were examined during the study time period. Subjects coded with ulcerative colitis were assessed to ascertain whether they had ever had medical treatment (thiopurine [azathioprine or mercaptopurine] or mesalazine) or definitive surgical

treatment in the form of colectomy or both. This methodology was replicated in subjects with Crohn's disease; however, all bowel resection surgeries and perianal surgical procedures were also included.

2.4 | Statistical analysis

2.4.1 | Incidence and prevalence

Annual point prevalence of ulcerative colitis and Crohn's disease was calculated on 31 December each year per 100 000 population and was stratified by sex. Point prevalence for ulcerative colitis and Crohn's disease in 2000 and 2017 was standardised to an adult UK age-sex standardised population for these years derived from the Office for National Statistics data (ONS).[19] Incidence rates per 100 000 person-years (py) were calculated from 1 January to 31 December annually. Incidence was stratified by sex and 10-year age bands over the study period and annually. Multivariable Poisson regression models were used to calculate incidence rate ratios (IRR) for ulcerative colitis and Crohn's disease, adjusting for age band, sex and year of study.

2.4.2 | Mortality and colorectal cancer outcomes

Baseline characteristics were compared using Chi-squared tests for categorical variables and Student t-tests for continuous variables. A multivariable Cox proportional hazards model was used to quantify colorectal cancer risk, adjusting for sex, body mass index (BMI) at index date, Townsend deprivation quintile, Charlson comorbidity score and smoking status. A further multivariable Cox proportional hazard model was used to derive adjusted hazard ratios (aHR) to quantify risk of mortality, adjusting for the same variables.[16,20] The proportional hazards assumption was tested using log-log plots. Missing values were included as separate categories. Kaplan-Meier survival analyses for all-cause mortality were performed in ulcerative colitis and Crohn's disease subjects and their controls. Poisson regression models adjusting for year, age at index date and sex were used to assess trends in colorectal cancer in ulcerative colitis and Crohn's disease. Standardised mortality ratios (SMR) annually and overall were produced for both ulcerative colitis and Crohn's disease using UK standardised mortality rates for each year of the study, derived from the Office for National Statistics data.[21] Analyses were performed using Stata version 15.0[22] and $P < 0.05$ were considered statistically significant.

2.5 | Sensitivity analysis

The impact of age on the risk of mortality and colorectal cancer was assessed through sensitivity analysis excluding subjects over 70 years old at index date. This analysis may improve internal validity due to the reduced proportion with inflammatory bowel disease drugs or inflammatory bowel disease surgery observed in older age bands. The colorectal cancer and mortality studies were performed with a combination of incident and prevalent cases. A sensitivity analysis including only incident cases of ulcerative colitis or Crohn's disease and their respective controls was undertaken.

3 | RESULTS

3.1 | Validation

Within the validation cohort there were 2578 subjects with ulcerative colitis (median age 47 [IQR 33-62] years, 49.6% female). Eighty-nine percent of subjects with a diagnostic code for ulcerative colitis had a record of either an inflammatory bowel disease drug or a colectomy. The Crohn's disease validation cohort consisted of 1943 subjects (median age 41 [IQR 27-56] years, 56.3% female). Eighty-seven percent of Crohn's disease subjects had a code with an inflammatory bowel disease drug or an appropriate surgery recorded. When ulcerative colitis or Crohn's disease and an inflammatory bowel disease drug, excluding surgical codes, were examined, co-coding was observed in 87.6% and 81.0% of cases respectively (Appendix S2).

3.2 | Cohort for prevalence and incidence studies

Seven hundred and eighty-seven general practices are included in The Health Improvement Network database. The 787 practices contributed 8 486 415 subjects to the study based on the study period, population age and data quality requirements as previously described. 71.6% of subjects came from English primary care practices, 3.6% from Northern Irish practices, 14% from Scottish practices and 10.8% from Welsh practices.

3.3 | Prevalence of ulcerative colitis and Crohn's disease

The annual point prevalence of ulcerative colitis over the study period increased from 390 per 100 000 population in 2000 to 570 per 100 000 in 2017 (Figure 1), with an average increase of 2.5% per annum. Prevalence of ulcerative colitis was similar among males and females. In 2000, age-sex standardised point prevalence of ulcerative colitis was 365 per 100 000 population for adult males, 372 for adult females and 369 per 100 000 overall. In 2017 the standardised rates were 662 for males, 615 for females and 637 per 100 000 population overall. The prevalence of Crohn's disease increased from 220 to 400 per 100 000 over the 18 years studied, an average rise of 3.5% per annum. When stratified by sex, there were more female subjects with Crohn's disease (Figure 1). The standardised point prevalence of Crohn's disease was 189 for males, 235 for females and 213 per 100 000 population overall. In 2017, Crohn's disease point prevalence for

males was 354 and for females 448 per 100 000, with an overall adult prevalence of 403 per 100 000 population in 2017.

Using Holt-Winters' double exponential smoothing model, ulcerative colitis and Crohn's disease prevalence were forecast forward to the year 2025. Ulcerative colitis prevalence in 2025 was forecast to be 592.6 (95% PI 490.3-694.9) per 100 000 and Crohn's disease prevalence was forecast to be 487.2 (95% PI 470.7-503.8) per 100 000. Time series graphs with actual and forecasted prevalence of ulcerative colitis and Crohn's disease are shown in Appendix S3.

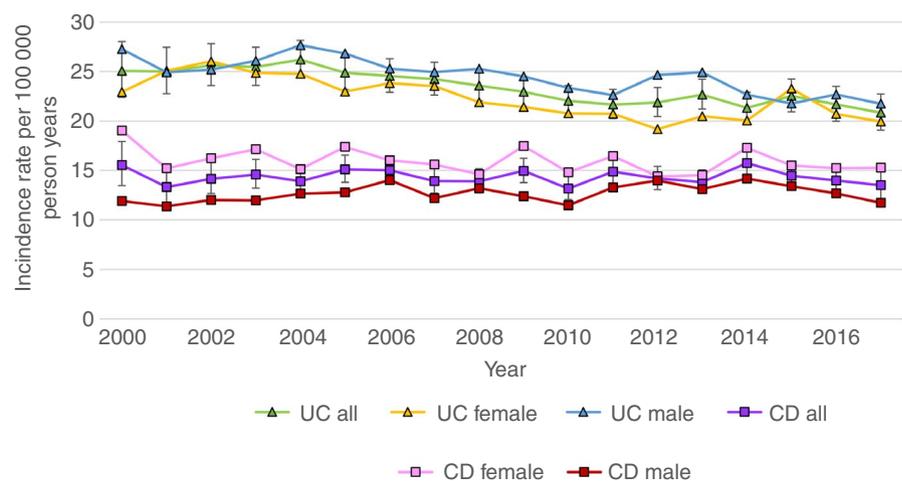## 3.4 | Incidence of ulcerative colitis and Crohn's disease

Between 2000 and 2018, in the study of incidence, 12 787 incident cases of ulcerative colitis were identified, with an overall incidence rate of 23.2 (95% CI 22.8-23.6) per 100 000 person-years (py). A bimodal profile of incidence rates by age was identified, with peaks in the 30-40 and 60-80 age groups (Appendix S4). Incidence was higher in males compared to females (24.4 [23.9-25.0] and 22.1 [21.5-22.6] per 100 000 person-years respectively). Adjusting for year and sex, females had a 10% lower risk of developing ulcerative colitis compared

to males between 2000 and 2018 (incidence rate ratio 0.90 [0.87-0.93], $P < 0.001$). The overall incidence of ulcerative colitis fell during the study period from 25 per 100 000 person-years in 2000 to 20 per 100 000 person-years in 2017, an average of 1.6% per annum, incidence rate ratio 0.98 (95% CI 0.98-0.99), $P < 0.001$. Incidence remained stable in those aged under 50 years of age (incidence rate ratio 1.02 [95% CI 1.01-1.02], $P < 0.001$) but fell in those aged 50 and over (incidence rate ratio 0.93 [0.93-0.94], $P < 0.001$). Trends in incidence rates overall and among males and females are shown in Figure 2. 7904 incident cases of Crohn's disease were identified in the study of incidence, with an overall incidence rate of 14.3 (14.0-14.7) per 100 000 py. A bimodal incidence rate age profile was again demonstrated, with a higher peak in the 18-30-year age category and a smaller peak in the 60-70 age group (Appendix S4). Crohn's disease incidence rates were stable over the study period with a higher incidence of Crohn's disease in females compared to males (12.8 [12.4-13.2] and 15.8 [15.4-16.3] respectively) (Figure 2). Adjusting for year, females had a 23% higher incidence of Crohn's disease compared to males (incidence rate ratio 1.23 [1.18-1.29], $P < 0.001$). The overall incidence of Crohn's disease, adjusting for year of study, remained stable over the study period (incidence rate ratio 0.99 [0.99-1.00], $P = 0.590$). In those aged under 50 years, the incidence increased slightly over time (incidence rate

FIGURE 1 Annual point prevalence of ulcerative colitis and Crohn's disease per 100 000 population. CD, Crohn's disease; UC, ulcerative colitis
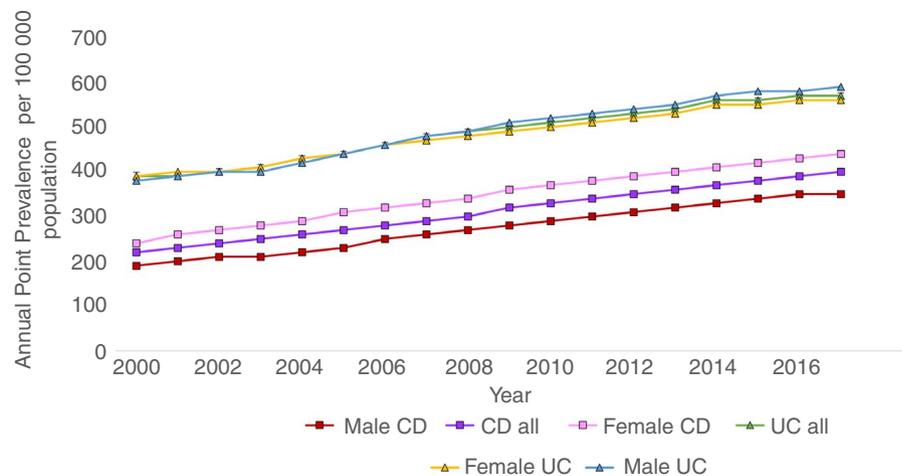
FIGURE 2 Annual incidence rate of ulcerative colitis and Crohn's disease per 100 000 person-years. CD, Crohn's disease; UC, ulcerative colitis

ratio 1.03 [1.03-1.04], P < 0.001), but in those aged 50 and over, the incidence fell by 5% (incidence rate ratio 0.95 [0.94-0.96], P < 0.001).

3.5 | Colorectal cancer risk in ulcerative colitis and Crohn's disease

The colorectal cancer (CRC) incidence rate for the whole adult THIN population was 64.6 (95% CI 63.9-65.3) per 100 000 py over the study period. The rate in females was 57.3 (56.4-58.2) and in males 72.1 (71.1-73.1) per 100 000 py.

In the matched ulcerative colitis colorectal cancer cohort study, 37 793 subjects with ulcerative colitis (12 319 (33%) incident cases and 25 474 (67%) prevalent cases) were matched to 148 126 control subjects contributing 242 407 and 966 522 person-years at risk respectively. Baseline demographic characteristics are shown in Table 1 and a comparison of incident and prevalent case demographics is shown in Appendix S5. Three hundred and twenty-eight (0.87%) new cases of colorectal cancer were observed in the ulcerative colitis group and 917 (0.62%) new cases in the control group. The incidence rate of colorectal cancer in ulcerative colitis subjects was 135.3 (121.2-150.9) per 100 000 py compared to 94.9 (85.9-97.7) in

TABLE 1 Colorectal cancer study: cohort demographics

	Ulcerative colitis (%)	Ulcerative colitis controls (%)	Crohn's disease (%)	Crohn's disease controls (%)
N	37 793 (20.33)	148 126 (79.67)	26 160 (20.27)	102 881 (79.73)
Male	18 860 (49.90)	73 840 (49.86)	11 534 (44.09)	45 327 (44.06)
Female	18 933 (50.10)	74 286 (50.14)	14 626 (56.91)	57 554 (55.94)
Age, median (IQR)	51 (37-65)	50 (37-64)	43 (31-58)	43 (31-58)
Age, n (%)				
18-30	4723 (12.50)	18 609 (12.56)	5817 (22.24)	22 887 (22.25)
30-40	6519 (17.25)	25 866 (17.46)	5532 (21.15)	22 095 (21.48)
40-50	6793 (17.97)	27 045 (18.26)	4777 (18.26)	18 968 (18.44)
50-60	6896 (18.25)	27 326 (18.45)	3922 (14.99)	15 497 (15.06)
60-70	6088 (16.11)	23 685 (15.99)	3087 (11.80)	12 059 (11.72)
70-80	4328 (11.45)	16 746 (11.31)	1999 (7.64)	7699 (7.48)
>80	2446 (6.47)	8849 (5.97)	1026 (3.92)	3676 (3.57)
Deprivation score				
1 (least deprived)	8672 (22.95)	34 175 (23.07)	5367 (20.52)	21 201 (20.61)
2	7613 (20.14)	29 940 (20.21)	4915 (18.79)	19 400 (18.86)
3	7077 (18.73)	27 841 (18.8)	4915 (18.79)	19 402 (18.86)
4	5592 (14.80)	21 948 (14.82)	4180 (15.98)	16 386 (15.93)
5 (most deprived)	3353 (8.87)	12 894 (8.70)	2970 (11.35)	11 470 (11.15)
Missing	5486 (14.52)	21 328 (14.40)	3813 (14.58)	15 022 (14.60)
Charlson comorbidity score				
0	24 469 (64.74)	103 970 (70.19)	17 344 (66.30)	75 238 (73.13)
1	8134 (21.52)	28 044 (18.93)	6085 (23.26)	19 187 (18.65)
2	2889 (7.64)	8939 (6.03)	1568 (5.99)	4859 (4.72)
3	1282 (3.39)	4185 (2.83)	693 (2.65)	2128 (2.07)
4+	1019 (2.70)	2988 (2.02)	470 (1.80)	1469 (1.43)
Smoking status				
Smoker	4660 (12.33)	29 648 (20.02)	6795 (25.97)	22 259 (21.64)
Nonsmoker	20 492 (54.22)	76 393 (51.57)	12 078 (46.17)	52 991 (51.51)
Ex-smoker	9964 (26.36)	27 056 (18.27)	5417 (20.71)	16 651 (16.18)
Missing	2677 (7.08)	15 029 (10.15)	1870 (7.15)	10 980 (10.67)
Body mass index				
<25 kg/m^2	14 547 (38.49)	50 565 (34.14)	11 422 (43.66)	36 315 (35.3)
25-30 kg/m^2	10 660 (28.21)	39 871 (26.92)	6105 (23.34)	24 640 (23.95)
>30 kg/m^2	5497 (14.55)	23 857 (16.11)	3391 (12.96)	16 095 (15.62)
Missing	7089 (18.76)	33 833 (22.84)	5242 (20.04)	25 831 (25.11)

the control group, giving an unadjusted incidence rate ratio of 1.43 (1.25-1.62), P < 0.001. After adjusting for age, year, sex, deprivation quintile, comorbidity, body mass index and smoking status, aHR was 1.40 (1.23-1.59), P < 0.001 (Table 2). In a sensitivity analysis, excluding subjects aged > 70, aHR was 1.56 (1.33-1.83), P < 0.001. The absolute risk of colorectal cancer in ulcerative colitis subjects was 0.87%. In the incident only analysis, 54 cases of colorectal cancer were observed among 12 319 incident cases contributing 67 334

person-years at risk, compared to the control group where 222 cases were observed in 48 514 control subjects contributing 264 791 person-years at risk. This is lower than was seen in the prevalent and incident data with a crude incidence rate ratio of 0.97 (0.70-1.29), P = 0.390 and an adjusted Hazard ratio of 0.91 (0.68-1.23), P = 0.553 (incident only data presented in Appendix S8).

In the Crohn's disease colorectal cancer matched cohort study, 26 160 subjects with Crohn's disease (8115 [31%] incident cases and

TABLE 2 Multivariable Cox proportional hazard model of factors associated with colorectal cancer

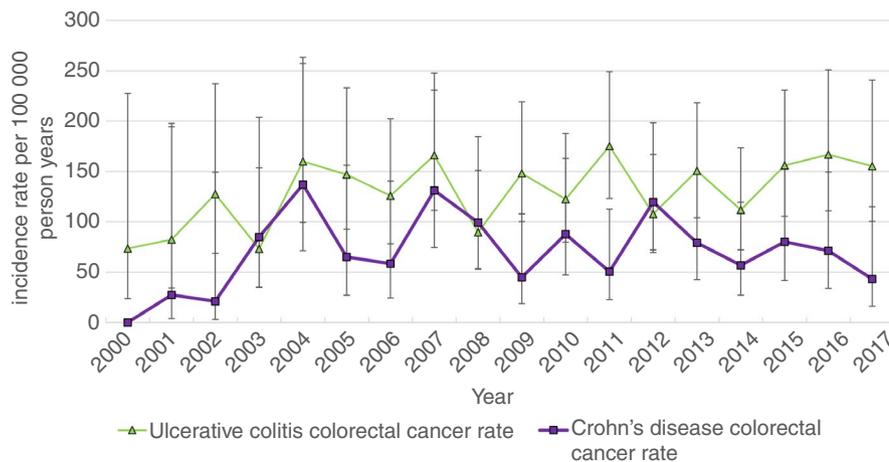|	Ulcerative colitis					Crohn's disease			
	Hazard ratio	[95% Conf. interval]		P		Hazard Ratio	[95% Conf. Interval]		P
Ulcerative colitis	1.40	1.23	1.59	<0.001	Crohn's disease	1.19	0.97	1.46	0.096
Age band									
Reference 18-30	1.00					1.00			
30-40	1.45	0.73	2.89	0.290		4.06	1.55	10.61	0.004
40-50	3.64	1.95	6.79	<0.001		9.30	3.72	23.24	<0.001
50-60	7.97	4.34	14.60	<0.001		23.07	9.40	56.61	<0.001
60-70	15.11	8.27	27.60	<0.001		40.53	16.57	99.16	<0.001
70-80	22.57	12.34	41.28	<0.001		65.65	26.75	161.10	<0.001
>80	25.22	13.56	46.90	<0.001		76.55	30.30	193.39	<0.001
Sex									
Reference Male	1.00					1.00			
Female	0.75	0.67	0.84	<0.001		0.77	0.65	0.92	0.003
Smoking status									
Reference Nonsmoker	1.00					1.00			
Smoker	0.96	0.81	1.14	0.618		0.83	0.65	1.07	0.159
Ex-smoker	1.03	0.89	1.18	0.727		1.05	0.85	1.31	0.644
Missing	1.03	0.83	1.29	0.782		1.00	0.73	1.37	0.986
Body mass index kg/m^2									
Reference <25	1.00					1.00			
25-30	1.02	0.88	1.17	0.804		1.04	0.83	1.29	0.741
>30	1.08	0.91	1.28	0.362		1.03	0.79	1.34	0.835
Missing	0.95	0.79	1.15	0.608		1.21	0.93	1.59	0.161
Charlson Score									
Reference 0	1.00					1.00			
1	1.10	0.96	1.27	0.176		0.99	0.80	1.23	0.954
2	1.21	1.01	1.46	0.044		1.02	0.76	1.38	0.883
3	1.39	1.08	1.78	0.011		0.65	0.38	1.11	0.114
4+	1.47	1.09	2.00	0.012		1.27	0.78	2.07	0.333
Deprivation score									
Reference 1	1.00					1.00			
2	1.06	0.90	1.24	0.500		1.09	0.84	1.42	0.508
3	1.03	0.87	1.22	0.715		1.15	0.89	1.50	0.285
4	1.03	0.85	1.24	0.774		1.16	0.87	1.53	0.308
5 (most deprived)	1.11	0.89	1.39	0.346		1.14	0.83	1.57	0.422
Missing	0.89	0.73	1.10	0.281		1.01	0.74	1.38	0.954

18 045 [69%] prevalent cases) were matched to 102 881 control subjects contributing a total of 158 906 and 647 624 person-years at risk respectively. Baseline demographic characteristics are shown in Table 1 and a comparison of incident and prevalent case demographics is shown in Appendix S5. One hundred and twenty (0.46%) cases of colorectal cancer were observed in the Crohn's disease group and 423 (0.41%) in the control group. The incidence rate of colorectal cancer in Crohn's disease subjects was 75.5 per 100 000 py (62.6-90.3) compared to 65.3 (59.2-71.8) in the control group, giving an unadjusted incidence rate ratio of 1.16 (0.93-1.42), P = 0.082. Following adjustment for covariates, aHR was 1.19 (0.97-1.46), P = 0.096. The absolute risk of colorectal cancer in Crohn's disease cases was 0.46%. Increased risk of colorectal cancer in younger subjects with Crohn's disease was seen in a sensitivity analysis, excluding subjects aged over 70 years old: aHR 1.29 (1.01-1.65), P = 0.043. Adjusting for age and sex, both the Crohn's disease colorectal cancer rate (incidence rate ratio 0.99 (0.96-1.04), P = 0.960) and the ulcerative colitis colorectal cancer rate (1.02 (0.99-1.04), P = 0.158), were stable over time. Trends in colorectal cancer rates among the ulcerative colitis and Crohn's disease cohorts are graphically represented in Figure 3. In the incident only analysis, 39 cases of colorectal cancer were observed among 8115 incident Crohn's disease cases accounting for 42 627 person-years at risk. This compared to 117 cases in the unexposed group of 31 946 control subjects which accounted for 169 221 person-years at risk. This gives a crude incidence rate ratio of 1.32 (0.90-1.92), P = 0.068. An adjusted hazard ratio for incident Crohn's disease cases was 1.34 (0.93-1.93), P = 0.118 (incident only data are presented in Appendix S8).

3.6 | Mortality in ulcerative colitis and Crohn's disease

In the matched ulcerative colitis cohort study addressing mortality risk, 42 179 subjects with ulcerative colitis were matched to 166 083 control subjects contributing 276 312 and 1 099 868 person-years at risk respectively. During the study period 4807 (11.4%) ulcerative colitis subjects and 16 098 (9.7%) matched controls died. The

absolute risk difference between ulcerative colitis and control subjects was 1.7%. Cohort characteristics are shown in Appendix S6. Ulcerative colitis subjects were more likely to die than matched controls: aHR 1.17 (95% CI 1.14-1.21), P < 0.001 (Table 3 and Appendix S7). In sensitivity analysis, excluding subjects age >70, aHR was 1.13 (1.07-1.20), P < 0.001. The factors associated with death in subjects with ulcerative colitis when assessed separately were age above 18-30, P < 0.001, current and ex-smoking (1.58 [1.43-1.74], P < 0.001 and 1.09 [1.02-1.16], P = 0.017 respectively), deprivation levels greater than level 2 and additional comorbidities. The factors associated with a reduced risk of mortality among subjects with ulcerative colitis were female sex (0.77 [0.73-0.82], P < 0.001) and body mass index in the range of 25-30 kg/m^2 when compared to those <25 kg/m^2 (0.86 [0.80-0.93], P < 0.001). When adjusting for age and sex, ulcerative colitis mortality remained unchanged over the duration of the study period with an incidence rate ratio of 0.99 (0.99-1.00), P = 0.309. The standardised mortality ratio for ulcerative colitis subjects was 0.96 (0.93-0.99) and annual standardised mortality ratios for ulcerative colitis are presented in Figure 4. In the incident only analysis, 1134 deaths were observed among 13 122 ulcerative colitis subjects accounting for 73 069 person-years at risk compared to 3533 deaths among 51 927 control subjects contributing 287 404 person-years at risk. This provides a crude incidence rate ratio of 1.26 (1.18-1.35), P < 0.001, an adjusted HR of 1.31 (1.23-1.41), P < 0.001 and an absolute risk difference of 1.84% (incident only data presented in Appendix S8).

In the Crohn's disease matched cohort study addressing mortality risk, 27 870 subjects with Crohn's disease were matched to 110 005 control subjects contributing 171 906 and 700 975 person-years at risk respectively. During the study period, 2612 (9.4%) Crohn's disease subjects and 7137 (6.5%) matched control subjects died. The absolute risk difference between Crohn's disease and control subjects was 2.88%. Crohn's disease subjects were more likely to die than matched controls: aHR 1.42 (1.36-1.48), P < 0.001 (Table 3 and Appendix S7). This risk increased when those > 70 were excluded in the sensitivity analysis to 1.49 (1.40-1.60), P < 0.001. The factors associated with mortality in Crohn's disease when assessed separately were age greater than 18-30, current and ex-smoking (1.87


FIGURE 3 Colorectal cancer rates in ulcerative colitis and Crohn's disease subjects over the study period

TABLE 3 Multivariable Cox proportional hazard model of factors associated with all-cause mortality

	Ulcerative colitis					Crohn's disease			
	Hazard ratio	**[95% Conf. interval]**		**P**		**Hazard ratio**	**[95% Conf. interval]**		**P**
Ulcerative colitis	**1.17**	**1.14**	**1.21**	**<0.001**	**Crohn's disease**	**1.42**	**1.36**	**1.48**	**<0.001**
Age band									
Reference 18-30	1.00					1.00			
30-40	2.21	1.69	2.88	<0.001		2.78	2.11	3.65	<0.001
40-50	4.78	3.72	6.14	<0.001		6.20	4.80	8.02	<0.001
50-60	11.76	9.22	15.01	<0.001		16.22	12.65	20.79	<0.001
60-70	29.34	23.04	37.36	<0.001		37.29	29.17	47.68	<0.001
70-80	75.71	59.49	96.36	<0.001		95.99	75.13	122.64	<0.001
>80	196.94	154.68	250.76	<0.001		244.55	191.16	312.86	<0.001
Sex									
Reference Male	1.00					1.00			
Female	0.79	0.77	0.81	<0.001		0.80	0.77	0.83	<0.001
Smoking status									
Reference Nonsmoker	1.00					1.00			
Smoker	1.81	1.74	1.88	<0.001		1.95	1.85	2.06	<0.001
Ex-smoker	1.12	1.08	1.16	<0.001		1.22	1.16	1.28	<0.001
Missing	1.14	1.08	1.20	<0.001		1.28	1.19	1.39	<0.001
Body mass index kg/m^2									
Reference < 25	1.00					1.00			
25-30	0.85	0.82	0.88	<0.001		0.82	0.78	0.87	<0.001
>30	0.95	0.91	0.99	0.011		0.94	0.88	1.00	0.036
Missing	1.25	1.20	1.30	<0.001		1.21	1.14	1.29	<0.001
Charlson Score									
Reference 0	1.00					1.00			
1	1.61	1.56	1.67	<0.001		1.69	1.60	1.78	<0.001
2	2.01	1.93	2.10	<0.001		2.20	2.07	2.33	<0.001
3	2.46	2.34	2.59	<0.001		2.63	2.44	2.83	<0.001
4+	3.68	3.50	3.87	<0.001		3.82	3.54	4.13	<0.001
Deprivation score									
Reference 1	1.00					1.00			
2	1.08	1.03	1.12	0.001		1.11	1.04	1.19	0.002
3	1.23	1.18	1.29	<0.001		1.18	1.11	1.26	<0.001
4	1.35	1.29	1.41	<0.001		1.32	1.24	1.41	<0.001
5 (most deprived)	1.43	1.36	1.51	<0.001		1.42	1.32	1.52	<0.001
Missing	1.17	1.11	1.23	<0.001		1.17	1.09	1.27	<0.001

[1.69-2.07], P < 0.001 and 1.17 [1.06-1.29], P < 0.001 respectively), deprivation and additional comorbidities. As with ulcerative colitis, the factors associated with a reduced risk of mortality in subjects with Crohn's disease were female sex (0.87 [0.81-0.95], P < 0.001) and body mass index in the range of 25-30 kg/m^2 when compared to those <25 kg/m^2 (0.88 [0.78-0.99], P = 0.045). Over the study period, adjusting for age and sex, Crohn's disease mortality fell slightly; incidence rate ratio was 0.99 (0.98-0.99), P = 0.009. Over the study period the standardised mortality ratio (SMR) for Crohn's disease subjects was 1.26 (1.21-1.30), annual standardised mortality ratios for Crohn's disease are presented in Figure 4. In the incident only analysis, 689 deaths were observed among 8442 Crohn's disease subjects, contributing 44 856 person-years at risk, compared to 1711 deaths observed in 33 371 control subjects contributing 178 235 person-years at risk. This gives a crude incidence rate ratio of 1.60 (1.46-1.75), P < 0.001, an absolute risk difference of 3.0% and an adjusted HR of 1.50 (1.37-1.64), P < 0.001 (incident only data presented in Appendix S8).
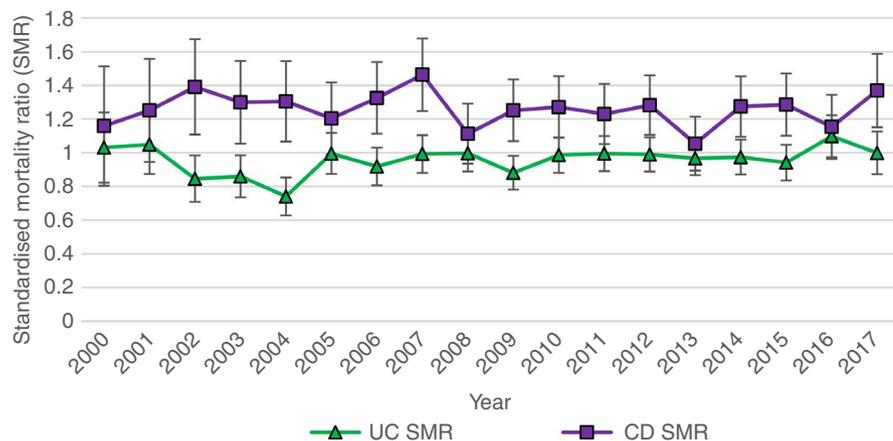
FIGURE 4 Annual standardised mortality ratio for ulcerative colitis and Crohn's disease. CD, Crohn's disease; SMR, standardised mortality ratio; UC, ulcerative colitis

4 | DISCUSSION

This study has examined in detail the UK epidemiology of ulcerative colitis and Crohn's Disease using a large, population-based dataset. Previous reports of the epidemiology of ulcerative colitis and Crohn's disease in the UK have used comparatively small datasets or focused on regional areas which may not be generalisable to the UK population as a whole or are now largely historic.[9,11,12] As with other high-prevalence areas,[3,4] this study shows that ulcerative colitis and Crohn's disease prevalence in the UK have been increasing over the past two decades at a rate of 2%-3% per annum. This is in keeping with a recent study from Canada which has forecast a 35% increase in those living with inflammatory bowel disease over the next decade.[23] The UK population in mid-2017 was estimated at 66 million.[24] Applying the findings of this study, an unadjusted estimate of the number of people living with ulcerative colitis in the UK in 2017 would be 376 000 and with Crohn's disease 264 000. This translates to an inflammatory bowel disease prevalence of 640 000 people or 0.97% of the population. The UK population in 2025 is predicted to be 68.9 million.[25] This study has forecast a combined inflammatory bowel disease prevalence of 1080 per 100 000 by 2025, equating to 744 120 living with inflammatory bowel disease in the UK or 1.1% of the population. How novel therapeutics, surgery, an older population and multidisciplinary management of these conditions might mitigate such an increase in prevalence is uncertain,[26,27] but these findings are fundamental for future planning of services in inflammatory bowel disease. The increasing prevalence of inflammatory bowel disease likely represents a reduction in mortality over time, given the slight decrease observed in incidence rates for these diseases. The cautious forecasting undertaken in this study represents a realisation that prevalence is likely to stabilise as, in due course, life expectancy plateaus.

The incidence of both ulcerative colitis and Crohn's disease is relatively stable, with an observed reduction in ulcerative colitis incidence rates over the study period. This is mainly driven by a more significant reduction in those over 50 years while little change was observed in those under 50 years old. Inflammatory bowel disease diagnosis in the elderly can be challenging due to a range of differential diagnoses and phenotypic differences when compared to younger groups.[28] The internal validation work presented in this study has sought to examine miscoding bias among subjects with inflammatory bowel disease. It was found that the prescription of medication unique to inflammatory bowel disease and surgical procedures commonly utilised in the management of inflammatory bowel disease were highly consistent in THIN but with lower consistency in the oldest age groups. Some studies have previously demonstrated a bimodal, age-stratified distribution of incidence rates, which this study has also documented. However, this is not universal among inflammatory bowel disease epidemiological profiles, and when present, the second peak is often only modest.[3] A higher subsequent peak in ulcerative colitis incidence has been previously demonstrated in a North American cohort [29] and more recently in a Korean study.[30] This has also been replicated in this study and is largely driven by male subjects in the older age group. Stable or slight declines in overall incidence have been demonstrated in a few other studies from the developed world.[4,31,32] The finding of a reduced incidence rate over time in those over 50 is novel, although a study from Québec observed a statistically significant time-trend decline in annual incidence in both ulcerative colitis and Crohn's disease in 40-49-year-olds and among ulcerative colitis subjects aged 20-29 and 50-69 between 2001 and 2008.[33] However, a bimodal peak in age-specific incidence was not reported and it was suggested that a migration effect had changed the nature of the epidemiology of inflammatory bowel disease in Québec.[33] Migration and second generation changes in inflammatory bowel disease risk may also be playing a role in our observations. Previous studies have suggested that second generation migrants to the West have a higher risk of inflammatory bowel disease than first generation migrants (either comparable or greater than the native population risk).[34-36] Disease course in inflammatory bowel disease differs with age, with a more aggressive disease pattern and extensive gastrointestinal involvement in the young.[37]

The differences in the female and male incidence and prevalence of Crohn's disease has been demonstrated previously.[38-40] A hormonal theory based on a reverse in incidence rates between male and female subjects at the time of puberty, as well as an association seen with hormone based medications is hypothesised.[39,41]

The colorectal cancer rate in the THIN population over the study period was comparable to the estimated rate of 64.2 per 100 000 persons for colorectal cancer in 2015 for the UK (age standardised: 69.9 [95% CI 69.2-70.6]).[42] This study found no decline in colorectal cancer rates in ulcerative colitis or Crohn's disease over the study period, despite a significant increase in the available medications used to manage inflammatory bowel disease, however studies going forward may well find improvement. The matched cohort designs allowed for comparison of inflammatory bowel disease subjects with age and sex-matched non-inflammatory bowel disease populations, while further adjusting for residual confounding factors. A significantly increased relative colorectal cancer risk in ulcerative colitis, demonstrates that this condition remains an important risk factor for colorectal cancer. However, in the incident only sensitivity analysis, there was no difference in risk between cases and controls. This most likely reflects a longer follow-up period in prevalent compared to incident cases (Appendix S5). It may also reflect that with newer diagnoses there is better surveillance, and more active and improved treatments, thereby reducing the risk of colorectal cancer in this group.

Ulcerative colitis has consistently been associated with colorectal cancer when compared with the non-inflammatory bowel disease population, this association is not, however, consistently observed in Crohn's disease.[8,43] It should be acknowledged that the potentially differing influence of Crohn's disease colitis and Crohn's disease small bowel disease on colorectal cancer risk were not specifically assessed in this study and the differing frequencies of these phenotypes are relevant in assessing colorectal cancer risk in Crohn's disease. While in this study colectomy was excluded in both ulcerative colitis and Crohn's disease subjects, in Crohn's disease, partial colectomy may precede the development of colorectal cancer and therefore some cases may be missed. More recent population studies and meta-analyses [7,8] have reappraised the very high historic colorectal cancer estimates in these conditions.[6] Although beyond the scope of this study, there remain particular inflammatory bowel disease phenotypes that pose significant risks, as well as inflammatory bowel disease medications that may mitigate colorectal cancer risk in Crohn's disease and ulcerative colitis.[8]

The increased risk of death observed in the current study, in both ulcerative colitis and in particular Crohn's disease subjects,

has been previously demonstrated, however previous studies of all-cause mortality in inflammatory bowel disease have been somewhat contradictory; Table 4 summarises the current evidence in this area. Although assessment of cause-specific mortality was beyond the scope of this present study it bears consideration. In a study from Olmsted County, Minnesota, looking at 1970-2016 data, the authors were able to look at disease-specific cause of death and found that gastrointestinal and respiratory causes were increased in Crohn's disease but not in ulcerative colitis. Ulcerative colitis was at a reduced risk of mortality compared to the US population, and when compared to matched, regional controls, the mortality risk was not significantly different; Crohn's disease did not differ from the background population using either methodology. This was a powerful study because all death certificates and ascertainment of cases were based on strict diagnostic criteria. However, comorbidity data were unavailable and it is a uniquely white and wealthy area of the country that may not be generalisable, not least in terms of health access and outcomes.[44]

The use of routinely gathered data from primary care has both limitations and strengths. Many primary care practices contribute to THIN, providing a representative sample of the UK population, and practices were required to achieve a minimum standard of quality with regard to data recording before participating in the study. Furthermore, the internal validation methodology employed has demonstrated that the coding of medications and surgeries commonly utilised in inflammatory bowel disease is frequently co-coded in those with inflammatory bowel disease diagnoses recorded in the THIN database. The inflammatory bowel diseases are generally managed by specialist secondary care physicians. For this reason, several medications will not be prescribed in primary care or coded in THIN (eg anti-TNF therapy). Although this is a potential limitation, it will underestimate the number of subjects with coding of medications rather than implying a true misclassification bias in inflammatory bowel disease diagnosis coding. Nevertheless, miscoding as well as the lack of universal diagnostic definitions for inflammatory bowel disease remain a potential source of bias. This study has demonstrated a high prevalence of inflammatory bowel disease in the UK but did not use codes for indeterminate colitis and may therefore still underestimate the true level of inflammatory bowel disease in the UK. However, a significant rise in

TABLE 4 Studies reporting all-cause mortality risk in inflammatory bowel disease cases compared to matched controls and background populations

Studies reporting increased mortality risk			Studies reporting decrease/equivalent mortality risk		
	Crohn's Disease	Ulcerative Colitis		Crohn's Disease	Ulcerative Colitis
Bewtra 2013[51]	SMR 1.40 (1.34-1.46)	SMR 1.17 (1.14-1.21)	Jess 2007[52]	—	SMR 1.10 (0.90-1.20)
Card 2003[53]	HR 1.73 (1.54-1.96)	HR 1.44 (1.31-1.58)	Manninen 2012[54]	SMR 1.14 (0.84-1.49)	SMR 0.90 (0.77-1.06)
Duricova 2010[55]	SMR 1.39 (1.30-1.49)	—	Aniwan 2018[44]	SMR 1.25 (0.98-1.57)	SMR 0.71 (0.56-0.89)
Jess 2013[56]	HR 1.73 (1.67-1.80)	HR 1.25 (1.22-1.28)	Aniwan 2018[44]	HR 1.26 (0.97-1.63)	HR 0.89 (0.70-1.14)
Olén 2019[57]	HR 1.60 (1.60-1.70)	HR 1.40 (1.40-1.50)			
Canavan 2007[58]	SMR 1.52 (1.32-1.74)	—			

Abbreviations: HR, hazard ratio; SMR, standardised mortality ratio.

prevalence across, in particular, western societies has been previously described.[23,45] This has been attributed to falls in historic levels of mortality in the inflammatory bowel diseases, improved population-wide longevity and high incidence. It is a potential limitation of the use of primary care databases that general practitioners may be improving their coding of prevalent disease over time. However, one would then expect all conditions in these databases to increase in prevalence over time which is not consistently the case.[46-48] Moreover, better coding in and of itself might be expected to lead to a rise in incident cases which was not seen over time.

Eleven percent of ulcerative colitis cases and 13% of Crohn's disease cases did not have a record of an inflammatory bowel disease drug and did not have a record of an inflammatory bowel disease related surgery in the smaller, validation cohort examined. The distribution of ages in this group demonstrated increased nondrug/noncolectomy coding in older age categories. The reasons for this may be multifactorial including medications only prescribed by secondary care: some general practitioners will not prescribe thiopurines due to the risks associated with these medications and biologic agents are not prescribed in general practice. It has been reported that elderly patients are less commonly prescribed medication for their inflammatory bowel disease, and there may be a desire to avoid immunosuppressants by moving early to surgical options, following which recurrence is less common in the elderly.[28,49] It is possible that a milder form of inflammatory bowel disease may also be represented in this group, for instance, a patient who has had a single flare that was managed with induction therapy or steroids prescribed from secondary care could fall into this group. Misclassification of inflammatory bowel disease may be a further risk, with diverticulitis and ischaemic colitis potentially confusing a diagnosis in older age groups.

Although the focus of this study was on the incidence and prevalence of inflammatory bowel disease and the risk of mortality and colorectal cancer in these populations, a significant limitation is in identification of inflammatory bowel disease phenotype. It has previously been shown that disease severity, extent and comorbid primary sclerosing cholangitis are significant factors in the risk of colorectal cancer in inflammatory bowel disease.[6,50] This study has considered all Crohn's disease and all ulcerative colitis as single diseases and the paucity of data in THIN regarding inflammatory bowel disease phenotypic subtypes would not permit a more in-depth analysis of how these factors affect colorectal cancer and mortality risk. The mitigation of potential confounders was considered through matched cohort designs. Unfortunately, ethnicity, exercise and diet were often not coded and so although important factors, could not be included in these analyses.

Prevalence of both ulcerative colitis and Crohn's disease has been increasing in recent decades, while incidence appears to be declining to some extent, particularly in the older population. These conditions remain significant risk factors for early mortality and colorectal cancer, particularly in ulcerative colitis. With an increasing proportion of society affected, research must continue to focus on how best to manage these conditions and prevent adverse outcomes.

AUTHORSHIP

Guarantor of the article: Nicola Adderley.

Author contributions: Study concept and design was jointly conceived by DK, NT, TT, JSC, NA, KN and RR. Data extraction was performed by DK, AS, JC, TT, RT, KG and analysis was performed by DK, RT, RR, NA and NT. Manuscript was drafted by DK. The data and manuscript were critically reviewed, revised and approved by all authors. NA and NT contributed equally and are joint senior authors.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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