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Risk of dementia in patients with inflammatory bowel disease: a Danish population-based study

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Summary

Background: Inflammatory bowel disease (IBD) may be associated with increased dementia risk, but the literature is conflicting.

Aim: To investigate dementia risk in patients with IBD.

Methods: We conducted a nationwide population-based cohort study in Denmark (1977–2018) including all patients with incident IBD matched with up to 10 general population comparators without IBD by sex, year of birth and region of residence. We calculated cumulative incidence proportions (CIPs) of dementia treating death as a competing risk, and adjusted hazard ratios (HRs) comparing IBD patients with matched comparisons. In a nested case–control analysis, we investigated the impact of IBD severity, steroid use, colorectal and small bowel surgery, and healthcare system contacts on dementia risk.

Results: Of 88,985 patients with IBD (69.6% with ulcerative colitis [UC], 30.4% with Crohn's disease [CD]) and 884,108 comparisons, 2076 patients (78.1% with UC) and 23,011 comparisons (76.6% UC comparisons) developed dementia. The 40-year CIP of all-cause dementia was 7.2% for UC patients and 5.8% for CD patients. UC patients had a slightly increased HR of all-cause dementia (HR = 1.07 [95% confidence interval (CI): 1.01;1.12]) and Alzheimer's disease (HR = 1.10 [95% CI: 1.01–1.19]). CD patients had an increased HR of all-cause dementia (HR = 1.15 [95% CI: 1.05–1.27]) and frontotemporal dementia (HR = 2.70 [95% CI: 1.44–5.05]). Dementia in IBD patients was associated with frequent healthcare system contacts.

Conclusions: UC and CD are associated with slightly increased all-cause dementia risk, particularly frontotemporal dementia in CD patients. Frequent healthcare system contacts by patients with IBD and detection bias may play a role in the association.

1 | INTRODUCTION

Worldwide, 10 million incident cases of dementia are reported annually.[1] The World Health Organisation expects a threefold increase before the year 2050,[1] threatening to escalate the already high economic societal burden.[1,2] Mounting evidence suggests an involvement of the intestinal microbiota in neurocognitive decline mediated through a microbiota–gut–brain axis.[3,4] Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), are chronic intestinal diseases with inflammation of varying intensity, which may feature alterations in the composition of the microbiota.[5–7] The degree of microbiota alterations is associated with the severity of intestinal inflammation.[8]

Interestingly, several studies show that IBD patients are at increased risk of various brain disorders, including multiple sclerosis,[9] anxiety disorders and depression,[10–13] schizophrenia[13] and Parkinson's disease,[14] supporting the potential clinical importance of the microbiota–gut–brain axis in IBD. Moreover, increased cardiovascular comorbidity in IBD patients,[15,16] could elevate the risk of dementia as well.[17,18] Finally, characteristics related to IBD severity, including hospitalisation,[19,20] surgical intervention[19] and potentially steroid exposure[21] may increase risk of dementia. However, the results of studies investigating the association between IBD and dementia are conflicting.[22–26]

A Taiwanese population-based cohort study showed a 2.5-fold increased risk of dementia in IBD patients,[22] whereas a German study of IBD patients followed in general practices found an only 1.2-fold increase.[23] Both studies had limited follow-up time and restricted age groups of IBD patients.[22,23] Contrasting these studies, a Swiss cross-sectional study found an approximately 20% lower dementia prevalence in IBD patients, estimated, however, with low statistical precision.[24] Finally, two recent studies from the United Kingdom[26] and Canada[25] found no overall association between IBD and dementia. The Canadian study had over 30 years of follow-up[25]. None of the abovementioned studies investigated the risk of dementia subtypes other than Alzheimer's disease (AD) and vascular dementia (VaD).[22–26]

An association between IBD and dementia could prove important for early detection and intervention against dementia in IBD patients[27] and foster new understanding of the long-term effects of intestinal inflammation. With access to wide longitudinal data from Danish healthcare registries, we therefore performed a nationwide population-based cohort study to investigate risk of all-cause dementia in patients with IBD (UC or CD). We also examined the risk of less common dementia subtypes. In a nested case–control analysis, we also examined the impact of IBD severity, colorectal or small bowel surgery, steroid use and frequency of healthcare system contacts on dementia risk.

2 | METHODS

2.1 | Setting

We conducted a nationwide cohort study within a source population of the entire Danish population (1 January 1977 until 31 December 2018) and a subsequent nested case–control study (1 January 1996 until 31 December 2018) using Danish healthcare registries.[28–31] In Denmark, unrestricted tax-funded healthcare is provided for all legal residents by the Danish National Health Service, and healthcare services are registered in national registries.[32] Individual level data were linked using the unique 10-digit identifier issued by the Danish Civil Registration System (DCRS).[33] A description of used databases can be found in Table S1.

2.2 | Cohort study

We identified all patients with a first-time inpatient or outpatient diagnosis (primary or secondary) of IBD within the study period recorded in the Danish National Patient Registry (DNPR),[28] and categorised them by IBD subtype as either UC or CD patients (Table S2). The index date was defined as the admission date of the IBD diagnosis. Patients who received a diagnosis of both UC and CD on the index date were excluded.

Using sampling with replacement[34] we constructed a comparison cohort of individuals without IBD using the DCRS and the DNPR. On the index date, each IBD patient was randomly matched with up to 10 individuals from the general population who were alive on that date. Matching factors were sex, year of birth (±1 year) and region of residence (according to municipality). If a comparison received an IBD diagnosis during follow-up, the comparison joined the IBD cohort and was matched with up to 10 new comparisons but also remained in the comparison cohort to avoid informative censoring.

IBD patients and comparisons with a diagnosis of dementia recorded in the DNPR or Danish Psychiatric Central Research Registry (DPCRR)[29] prior to the index date were excluded. For each excluded IBD patient, the matched comparisons were excluded as well.

2.2.1 | Dementia

The outcome of our cohort study was incident all-cause dementia, defined as a first-time inpatient or outpatient diagnosis (primary or secondary) of any dementia recorded in the DNPR or DPCRR after the index (Table S3). We furthermore categorised all-cause dementia in six subgroups of dementia subtypes: AD, VaD, frontotemporal dementia (FTD), Parkinson's disease dementia and dementia with Lewy bodies combined (PDD/DLB), unspecified dementia and other dementias (i.e. all remaining dementia subtypes). The diagnostic codes of dementia subtypes in the DNPR and DPCRR, other than AD, have low positive predictive values (PPVs) or have not been validated.[35] In an attempt to enhance the PPVs, we only regarded primary (not secondary) diagnoses of all-cause dementia in the categorisation of all dementia subtypes except AD. As mixed brain pathology in dementia is common and dementia subtypes often coexist,[36] patients were allowed in multiple outcome groups if they had more than one subtype of dementia recorded on the date of their first-time dementia diagnosis, except unspecified dementia, which was only regarded if this was the sole record.

2.2.2 | Covariates

We categorised IBD patients and comparisons by sex, age and calendar year of index, and for IBD patients also by hospital admission-type at IBD diagnosis (inpatient, outpatient clinic or emergency room). Based on first-time discharge diagnoses recorded prior to the index date, we characterised IBD patients and comparisons according to the following risk factors of dementia: diabetes (type 1 or 2), atrial fibrillation or flutter, hypertension, obesity, chronic obstructive pulmonary disease, depression, hearing impairment and head trauma (Table S4). Likewise, we calculated a modified Charlson Comorbidity Index (CCI) score as a measure of the burden of comorbidity, using diagnoses recorded in the DNPR[37] (Table S5). The CCI was modified to exclude any records of dementia, diabetes (type 1 or 2), and diabetes (type 1 or 2) with end-organ damage. Chronic obstructive pulmonary disease was omitted from the CCI condition *chronic pulmonary disease.*

2.3 | Nested case–control study

In addition to our cohort study, we performed a case–control study nested within the IBD cohort defined above but restricted to patients diagnosed with IBD between 1 January 1996 and 31 December 2018. Cases were defined as those with incident all-cause dementia diagnosed at least 2 years after their first-time IBD diagnosis to achieve a sufficient induction period considering the insidious nature of dementia. Using risk-set sampling with replacement, each IBD case was matched with up to four dementia-free IBD controls on the admission date of the dementia diagnosis. Cases and controls were matched on sex, year of birth (±1 year), year of IBD diagnosis (±1 year) and IBD subtype (UC or CD).

To examine the role of IBD severity, we considered four exposures in the period between the dates of IBD and dementia diagnoses (or dates of matching). First, we calculated the number of steroid prescriptions redeemed at Danish pharmacies, recorded in the Danish National Prescription Registry (NPR),[31] including steroid treatment given during hospitalisation recorded in the DNPR since 1999 (Table S6). Second, we examined records of total colectomy and any colorectal or small bowel surgery (ever vs. never) in the DNPR (Table S7). Third, we investigated IBD severity defined according to previously defined methodology,[16] categorising patients according to days of IBD activity and number of IBD flares (Table S8). Finally, we assessed the extent of healthcare system contact, calculating both the number of general practitioner contacts with physical attendance and all-cause hospital admissions in the period from four to 1 year prior to the date of dementia diagnosis/matching using the Danish National Health Service Register and the DNPR. We considered the same covariates as in the cohort analysis, but discharge diagnoses recorded in the DNPR used to define these covariates were collected until the date of dementia/matching.

2.4 | Statistical analysis

In the cohort study, IBD patients and matched general population comparators were followed from the index date until the first occurrence of dementia, death, emigration or study end (31 December 2018), whichever came first. Accounting for the insidious nature of dementia, we also introduced a 2-year induction period between the date of index and dementia in this analysis.

We calculated absolute risks of all-cause dementia and AD for IBD patients and comparisons as cumulative incidence proportions (CIPs), treating death as a competing risk.

Using conditional Cox proportional-hazards regression analysis, we computed unadjusted and adjusted hazard ratios (HRs) of dementia, comparing IBD patients with general population comparators. Adjusting factors were diabetes (type 1 or 2), atrial fibrillation or flutter, hypertension, obesity, chronic obstructive pulmonary disease, depression, hearing impairment and head trauma. The HRs for all-cause dementia and AD were stratified by sex, age and calendar year of IBD diagnosis. We also stratified for the modified CCI-score, but we dissolved matching in this analysis. Disparities between the CIP and HRs may be explained by competing risk of death, disrupting the one-to-one relationship between the hazard and cumulative incidence function.[38]

We conducted seven sensitivity analyses to assess the robustness of our cohort analysis. First, to address misclassification bias, we only included IBD patients who received a diagnosis of IBD on at least two separate occasions. The second record defined both the subgroup of IBD (UC or CD) and the index date. Second, we only considered dementia diagnoses when registered in the DCPRR or when given in a psychiatric, geriatric or neurologic inpatient or outpatient setting, defined according to hospital and department codes of the DNPR (Table S9). Third, we altered the induction period to 0, 5, 10 and 20 years. Fourth, we excluded patients with diagnoses that might represent early clinical manifestations of dementia (mild cognitive impairment or amnestic syndrome) recorded in the DNPR or DPCRR prior to the index (Table S10). Fifth, we regarded two prescriptions of dementia-specific medications recorded in the NPR as an outcome equivalent to a dementia diagnosis. This approach incorporated patients treated for dementia but never seen in an inpatient or outpatient hospital setting and therefore not registered in the DNPR or DCPRR (Table S11). As the NPR only contains data since 1995, this analysis was restricted to 1995 onwards. Sixth, we followed IBD patients and matched comparisons from the date of their 50-year birthday. In this analysis, we calculated the number of hospital admissions between IBD diagnosis and the age of 50 as a surrogate for healthcare system contact and adjusted for this in our multivariate model. In the fifth and sixth sensitivity analyses, we only regarded all-cause dementia and AD due to lack of cases for the other dementia subtypes. Seventh, we conducted a bias analysis by means of E-value estimation[39] of the HR of all-cause dementia in the UC- and CD-cohort, to assess potential unmeasured confounding including smoking associated with both increased risk of CD[40] and

dementia,[41] and educational level associated with both dementia[42] and potentially IBD.[43]

In the case–control study, we used conditional logistic regression to compute unadjusted and adjusted odds ratios (ORs) as an estimate of the incidence rate ratio reflecting the association between dementia and exposures.

All statistical analyses were conducted using Stata statistical software version 14.0 (Statacorp, Texas, USA). The study was reported to the Danish Data Protection Agency by Aarhus University; record number 2016-051-000001/736.

3 | RESULTS

3.1 | Cohort study

3.1.1 | Characteristics

We included 88,985 patients with incident IBD matched with 884,108 general population comparators, with a total follow-up time of 13,179,173 years (Figure 1). The majority were enrolled between

2005 and 2018 (Table 1). The median age at index was higher for UC patients than CD patients. In general, IBD patients had a higher prevalence of comorbidity than comparisons. During follow-up, 2076 IBD patients (1621 UC patients) and 23,011 comparisons (17,631 UC comparisons) received a diagnosis of all-cause dementia. In total, 173,538 individuals died, 12,541 emigrated and 394 had their civil registration number inactivated during follow-up.

3.1.2 | Risk of dementia

The 40-year CIP of all-cause dementia was 7.2% (95% confidence interval [CI]: 6.7;7.7) for UC patients and 5.8% (95% CI: 5.0–6.7) for CD patients, which was similar to the comparisons (Figure 2). Correspondingly, for AD it was 3.0% (95% CI: 2.6–3.3) and 1.8% (95% CI: 1.3–2.2) for UC and CD patients respectively (Figure S1).

The adjusted HR of all-cause dementia was slightly increased in both UC patients and CD patients (Table 2). We also observed a slightly increased HR for AD in UC patients but not in CD patients. Of note, the HR of PDD/DLB in UC patients was slightly increased, and CD patients had a high HR of frontotemporal dementia

FIGURE 1 Flowchart.
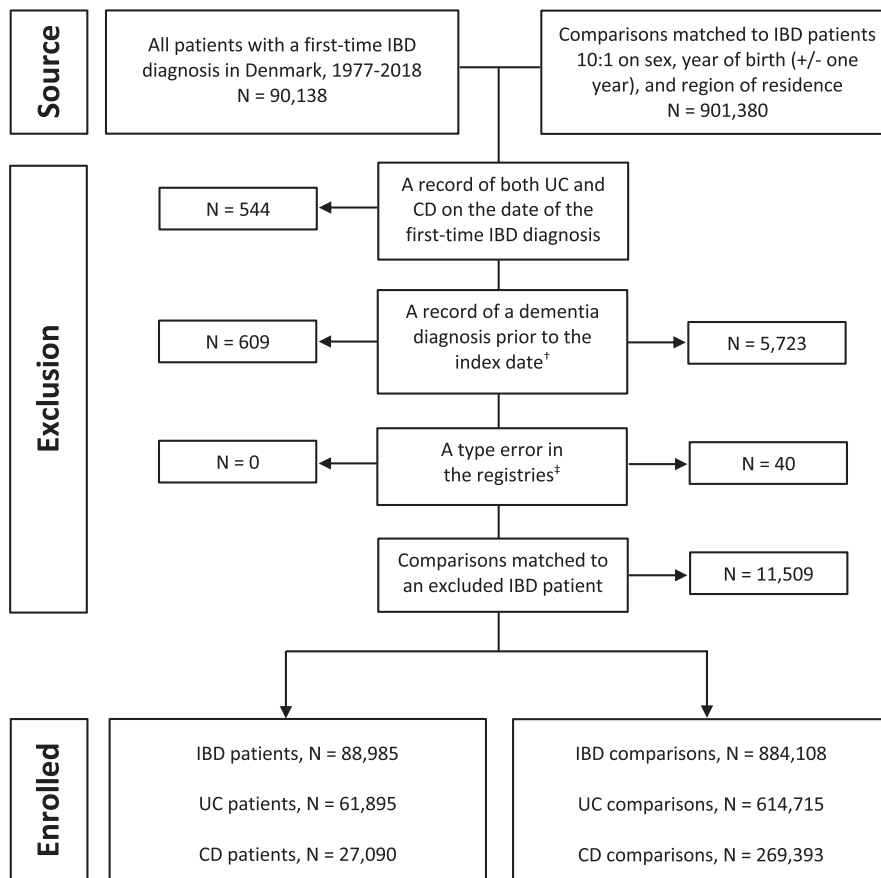Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.
[†]The index date was defined as the first-time admission date of an IBD diagnosis between 1 January 1977 and 31 December 2018 for IBD patients, which also served as the index date for the matched comparisons.
[‡]Type errors include death or emigration prior to the first-time IBD diagnosis.

TABLE 1 Characteristics of patients with inflammatory bowel disease and matched general population comparators, Denmark, 1977–2018

	UC patients	UC comparisons	CD patients	CD comparisons
Total	61,895 (100)	614,715 (100)	27,090 (100)	269,393 (100)
Sex, n (%)				
Female	32,795 (53.0)	325,457 (52.9)	15,321 (56.6)	152,290 (56.5)
Male	29,100 (47.0)	289,258 (47.1)	11,769 (43.4)	117,103 (43.5)
Age at index[a], n (%)				
0–29 years	16,665 (26.9)	166,644 (27.1)	10,786 (39.8)	107,778 (40.0)
30–49 years	19,946 (32.2)	199,398 (32.4)	7671 (28.3)	76,810 (28.5)
≥50 years	25,284 (40.9)	248,673 (40.9)	8633 (31.9)	84,805 (31.5)
Median age at index, years (IQR)	44 (30–62)	43 (29–62)	36 (23–56)	36 (23–56)
Calendar year of index, n (%)				
1977–1990	12,117 (19.6)	120,628 (19.6)	4016 (14.8)	40,031 (14.9)
1991–2004	20,835 (33.7)	207,120 (33.7)	8504 (31.4)	84,639 (31.4)
2005–2018	28,943 (46.8)	286,967 (46.7)	14,570 (53.8)	144,723 (53.7)
Hospital admission-type at IBD diagnosis, n (%)				
Inpatient	29,048 (47.0)	-	14,196 (52.4)	-
Outpatient clinic	32,619 (52.7)	-	12,738 (47.0)	-
Emergency room	228 (0.4)	-	156 (0.6)	-
Risk factors for dementia, n (%)				
Diabetes (type 1 or 2)	1992 (3.2)	14,072 (2.3)	811 (3.0)	5193 (1.9)
Atrial fibrillation or flutter	1546 (2.5)	10,457 (1.7)	594 (2.2)	3786 (1.4)
Hypertension	4356 (7,0)	29,638 (4.8)	1801 (6.7)	11,145 (4.1)
Obesity	1728 (2.8)	14,019 (2.3)	979 (3.6)	6243 (2.3)
Chronic obstructive pulmonary disease	1853 (3.0)	9484 (1.5)	772 (2.9)	3348 (1.2)
Depression	791 (1.3)	4400 (0.7)	389 (1.4)	1725 (0.6)
Hearing Impairment	2472 (4.0)	20,829 (3.4)	1019 (3.8)	7826 (2.9)
Head trauma	10,585 (17.1)	98,802 (16.1)	5682 (21.0)	50,588 (18.8)
CCI score[b], n (%)				
Low	44,935 (77.5)	525,411 (85.5)	20,762 (76.6)	234,185 (85.5)
Medium	11,056 (17.9)	75,414 (12.3)	5098 (18.8)	30,156 (12.1)
High	2904 (4.7)	13,890 (2.3)	1230 (4.5)	5052 (2.4)
CCI conditions, n (%)				
Myocardial infarction	1749 (2.8)	10,782 (1.8)	586 (2.2)	3450 (1.3)
Congestive heart failure	1342 (2.2)	6996 (1.1)	592 (2.2)	2317 (0.9)
Peripheral vascular disease	1643 (2.7)	8574 (1.4)	666 (2.5)	3137 (1.2)
Cerebrovascular disease	2573 (4.2)	16,750 (2.7)	952 (3.5)	5966 (2.2)
Chronic pulmonary disease[*]	3045 (4.9)	19,106 (3.1)	1683 (6.2)	9569 (3.6)
Connective tissue disease	1815 (2.9)	9363 (1.5)	952 (3.5)	3806 (1.4)

(Continues)

TABLE 1 (Continued)

	UC patients	UC comparisons	CD patients	CD comparisons
Peptic ulcer disease	2075 (3.4)	10,273 (1.7)	1144 (4.2)	3544 (1.3)
Mild liver disease	642 (1.0)	2896 (0.5)	341 (1.3)	1127 (0.4)
Hemiplegia	152 (0.3)	968 (0.2)	70 (0.3)	426 (0.2)
Moderate to severe renal disease	926 (1.5)	4350 (0.7)	459 (1.7)	1786 (0.7)
Cancer without metastases	3360 (5.4)	23,300 (3.8)	1277 (4.7)	8434 (3.1)
Leukaemia	99 (0.2)	660 (0.1)	43 (0.2)	288 (0.1)
Lymphoma	171 (0.3)	1325 (0.2)	98 (0.4)	526 (0.2)
Moderate to severe liver disease	173 (0.3)	667 (0.1)	79 (0.3)	245 (0.1)
Metastatic solid tumour	347 (0.6)	2076 (0.3)	166 (0.6)	782 (0.3)
Acquired immunodeficiency syndrome	91 (0.2)	325 (0.1)	33 (0.1)	116 (0.04)
End of follow-up[c]				
Median follow-up time, years (IQR)	12.7 (6.9–21.0)	12.9 (7.2–21.2)	11.5 (6.0–20.0)	12.1 (6.3–20.7)
Median age at death, years (IQR)	77 (67–85)	79 (69–87)	74 (61–83)	78 (68–86)
Median age at dementia, years (IQR)	81 (75–86)	82 (76–87)	78 (72–85)	82 (76–87)

Abbreviations: CCI, Charlson Comorbidity Index; CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; UC, ulcerative colitis.

[a]The index date was defined as the first-time admission date of an IBD diagnosis between 1 January 1977 and 31 December 2018 for IBD patients, which also served as the index date for the matched comparisons.

[b]According to Charlson Comorbidity Index sore (low = 0, medium = 1–2, high ≥3). We excluded any dementia, diabetes (type 1 or 2) and diabetes (type 1 or 2) with end-organ damage from the index conditions and omitted chronic obstructive pulmonary disease from *chronic pulmonary disease*.

[c]Defined as the first-time date of a dementia diagnosis, or the date of death, emigration or study end (31 December 2018).

(Figure 3). Only 179 patients were classified with more than one dementia subtype.

3.1.3 | Sensitivity analyses

Restricting dementia diagnoses to those given only in a psychiatric, geriatric or neurologic inpatient or outpatient setting caused an attenuation of the adjusted HR of all-cause dementia in the CD-cohort and an increased HR of frontotemporal dementia (Table S12). Including only IBD patients who had attained the age of 50 years, yielded a slightly attenuated HR of all-cause dementia when we adjusted for the total number of hospital admissions before the age of 50, but it remained elevated (Table S13). E-value estimation of the HR of all-cause dementia in the CD-cohort resulted in an E-value of 1.57 for the point estimate and 1.28 for the lower 95% CI interval, and the corresponding values for the UC-cohort were 1.34 and 1.11 respectively (Figure S2). No other sensitivity analysis substantially changed of the main results (Table S14–S17).

3.2 | Nested case–control analysis

We included 1067 cases of demented IBD patients matched to 4004 dementia-free IBD controls. We excluded 69 cases (2.85%

of all available cases between 1977 and 2018) because no controls qualified according to the matching criteria. The OR of receiving ≥5 prescriptions of a systemic steroid was 0.83 (95% CI: 0.68–1.01) (Table 3). Among CD patients, dementia was associated with an increased OR for history of total colectomy although risk estimates were imprecise. We observed no clear association between IBD severity and dementia. Finally, we observed incrementally rising ORs with accumulating numbers of hospital admissions and general practitioner in both demented UC and CD patients.

4 | DISCUSSION

4.1 | Key results

In this large population-based study, we showed that the risk of dementia up to 40 years after an IBD diagnosis was 7.2% in UC patients and 5.8% in CD patients, similar to that of the general population. However, we observed a slightly increased HR for all-cause dementia in both UC (HR = 1.07 [95% CI: 1.01–1.12]) and CD patients (HR = 1.15 [95% CI: 1.05–1.27]). UC patients had a slightly increased HR of AD and PDD/DLB, and CD patients had an increased HR of frontotemporal dementia. Finally, dementia was associated with increased healthcare system contact in demented IBD patients.
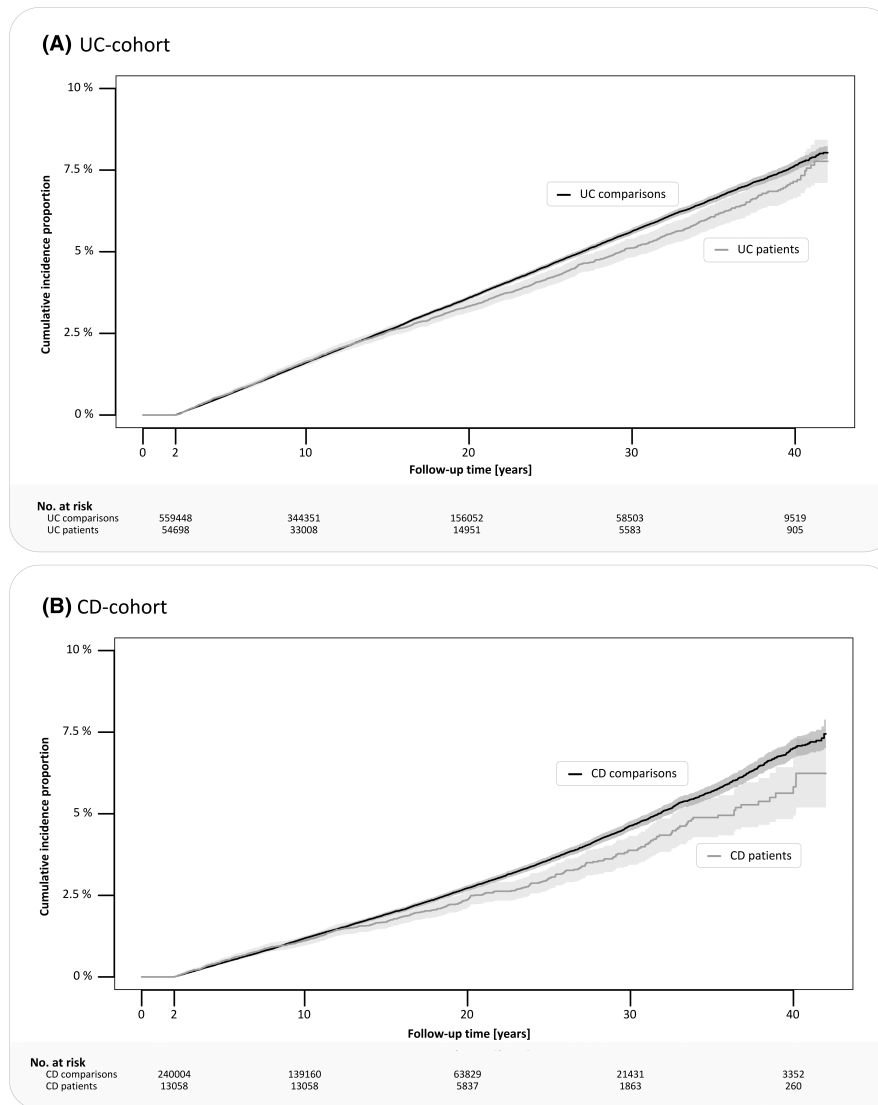
FIGURE 2 Cumulative incidence functions of all-cause dementia in patients with inflammatory bowel disease and matched general population comparators.
Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; CI, confidence interval.

4.2 | Interpretation

To our knowledge, this study is the largest to investigate dementia risk in IBD patients, and it provides the longest follow-up. Our results question those of a Taiwanese study, reporting much higher HRs of all-cause dementia of 2.69 (95% CI: 1.89–3.85) in UC patients and 2.29 (95% CI: 1.42–3.69) in CD patients, and also AD in both UC (HR = 6.77 [95% CI: 2.82–16.22]) and CD patients (HR = 7.53 [95% CI: 2.67–21.28]).[22] The incidence of both IBD and dementia in Taiwan, although rising, is lower than that observed in Europe.[44,45] Moreover, intestinal diseases other than IBD have been shown to influence the risk of especially Parkinson's disease but also AD differently in Europe and Asia.[46] Consequently, underlying differences in diet, lifestyle factors and potentially genetical differences may in part explain the discrepancy. However, our study results are supported by a

recent German study of IBD patients followed by general practitioners finding slightly increased all-cause dementia risk in both UC (HR = 1.25 [95% CI: 1.07–1.46]) and CD patients (HR = 1.17 [95% CI: 0.93–1.47]).[23] Although a Swiss cross-sectional study reported a prevalence OR of all-cause dementia in IBD patients of 0.82 (95% CI: 0.63–1.05),[24] lower dementia prevalence could be explained by a higher mortality among demented IBD patients,[47] combined with a generally higher mortality among IBD patients compared to the general population.[48] Finally, a recent study from the United Kingdom concluded that there was no association between IBD and dementia,[26] supported by a Canadian study investigating general comorbidity in IBD patients.[25] Of note, results of the United Kingdom study found an all-cause dementia risk in UC (1.20 [95% CI: 0.94–1.39]) and CD patients (1.12 [95% CI: 0.89–1.42]) similar to our study results but estimated with lower precision.[26]

TABLE 2 Unadjusted and adjusted hazard ratios of all-cause dementia and Alzheimer's disease in patients with inflammatory bowel disease relative to matched general population comparators

	All-cause dementia			Alzheimer's disease		
	Cases observed IBD patients/ comparisons	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Cases observed IBD patients/ comparisons	Unadjusted R (95% CI)[a]	Adjusted HR (95% CI)[b]
UC-cohort						
Total	1621/17,631	1.10 (1.04–1.16)	1.07 (1.01–1.12)	626/6792	1.10 (1.02–1.20)	1.10 (1.01–1.19)
Sex						
Female	1001/10,356	1.17 (1.10–1.25)	1.14 (1.07–1.22)	397/4267	1.12 (1.01–1.24)	1.12 (1.01–1.24)
Male	620/7275	1.00 (0.92–1.08)	0.96 (0.89–1.01)	229/2525	1.08 (0.94–1.23)	1.07 (0.93–1.22)
Calendar year of index[c]						
1977–1994	730/8452	1.04 (0.96–1.12)	1.02 (0.94–1.10)	284/3102	1.10 (0.97–1.24)	1.10 (0.97–1.24)
1995–2018	891/9179	1.15 (1.07–1.23)	1.11 (1.04–1.19)	342/3690	1.10 (0.99–1.23)	1.10 (0.98–1.23)
Age at index						
0–29 years	19/193	1.02 (0.64–1.63)	1.01 (0.63–1.62)	–[d]/44	1.18 (0.47–2.98)	1.19 (0.47–3.01)
30–49 years	194/1784	1.16 (1.00–1.34)	1.13 (0.98–1.32)	–/591	1.27 (0.99–1.63)	1.28 (1.00–1.64)
≥50 years	1408/15,654	1.09 (1.03–1.15)	1.06 (1.00–1.12)	591/ 6157	1.08 (0.99–1.18)	1.07 (0.98–1.17)
CCI score[e]						
Low	1102/13,974	1.05 (0.99–1.12)	1.04 (0.98–1.11)	470/5490	1.15 (1.05–1.26)	1.15 (1.04–1.26)
Medium	431/3154	1.13 (1.03–1.26)	1.12 (1.01–1.24)	–/1151	0.96 (0.80–1.15)	0.95 (0.80–1.14)
High	88/503	1.08 (0.86–1.35)	1.06 (0.84–1.33)	–/151	0.99 (0.65–1.53)	0.98 (0.64–1.51)
CD-cohort						
Total	455/5380	1.19 (1.08–1.31)	1.15 (1.05–1.27)	131/2021	0.91 (0.76–1.09)	0.91 (0.76–1.09)
Sex						
Female	287/3468	1.17 (1.03–1.32)	1.14 (1.01–1.29)	84/1388	0.85 (0.68–1.05)	0.85 (0.68–1.06)
Male	168/1912	1.24 (1.06–1.45)	1.18 (1.00–1.38)	47/633	1.07 (0.79–1.44)	1.05 (0.78–1.42)
Calendar year of index[c]						
1977–1994	209/2634	1.18 (1.02–1.36)	1.15 (1.00–1.33)	63/946	0.99 (0.77–1.28)	0.99 (0.77–1.28)
v1995–2018	246/2746	1.21 (1.06–1.38)	1.15 (1.01–1.32)	68/1075	0.85 (0.66–1.09)	0.84 (0.66–1.08)
Age at index						
0–29 years	9/81	1.15 (0.58–2.29)	1.13 (0.57–2.27)	–/24	0.44 (0.60–3.26)	0.48 (0.06–3.53)
30–49 years	69/602	1.44 (1.12–1.84)	1.37 (1.07–1.76)	–/214	0.80 (0.45–1.39)	0.79 (0.45–1.38)
≥50 years	377/4697	1.16 (1.04–1.29)	1.11 (1.00–1.24)	117/1783	0.93 (0.77–1.13)	0.93 (0.77–1.12)
CCI score[e]						
Low	307/4287	1.16 (1.04–1.31)	1.15 (1.02–1.29)	100/1642	1.05 (0.86–1.28)	1.00 (0.82–1.22)
Medium	113/949	1.05 (0.86–1.28)	1.04 (0.86–1.27)	–/326	0.63 (0.42–0.94)	0.70 (0.46–1.05)
High	35/144	1.44 (0.99–2.08)	1.39 (0.96–2.01)	–/53	0.52 (0.23–1.20)	0.45 (0.16–1.25)

Abbreviations: CCI, Charlson Comorbidity Index; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; UC, ulcerative colitis.

[a]Controlled for sex, year of birth (±1 year), calendar year and region of residence.

[b]Adjusted for modified Charlson Comorbidity Index score, diabetes (type 1 or 2), atrial fibrillation or flutter, hypertension, obesity, chronic obstructive pulmonary disease, depression, hearing impairment and head trauma.

[c]The index date was defined as the first-time admission date of an IBD diagnosis between 1 January 1977 and 31 December 2018 for IBD patients, which also served as the index date for the matched comparisons.

[d]Dashes (–) marks cells where observations are not presented as they would expose microdata (<5 cases).

[e]According to Charlson Comorbidity Index sore (low = 0, medium = 1–2, high ≥3). The score was modified, excluding any dementia, diabetes (type 1 or 2) and diabetes (type 1 or 2) with end-organ damage from the index conditions and omitted chronic obstructive pulmonary disease from *chronic pulmonary disease*.
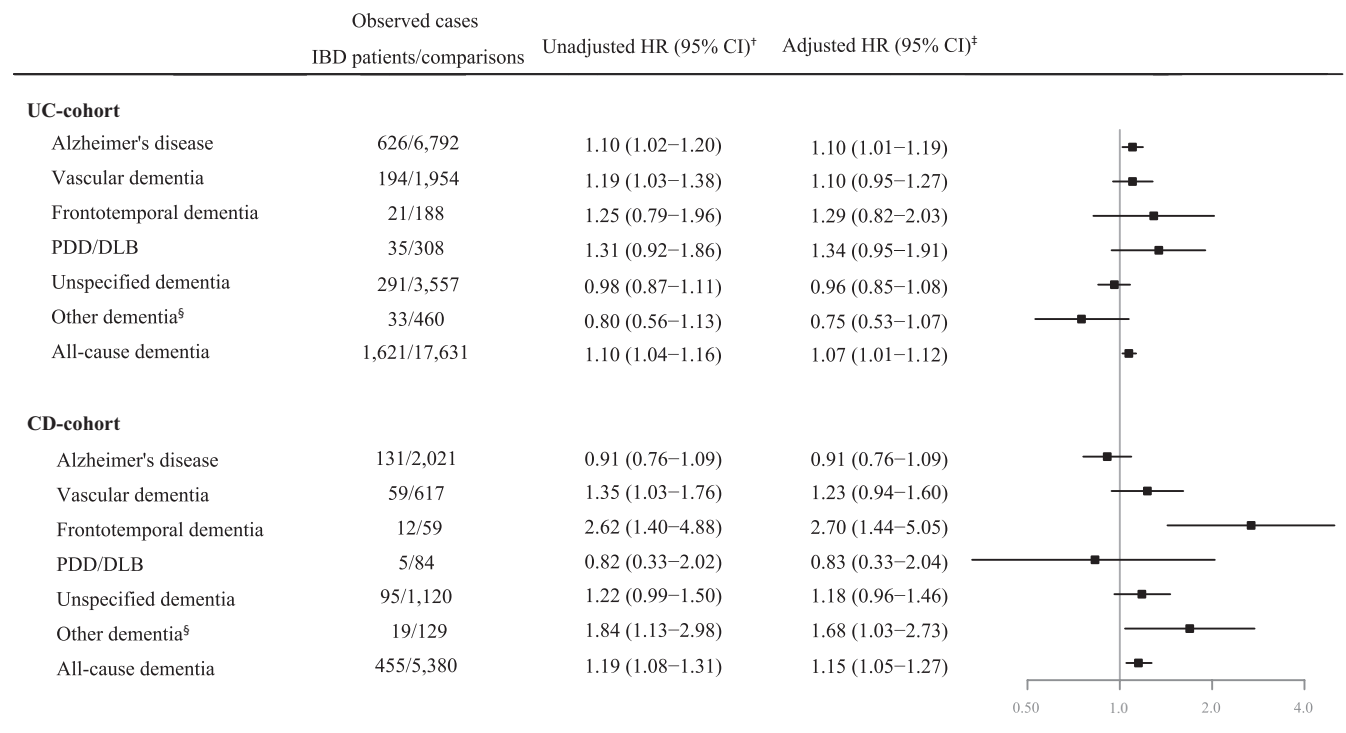
	Observed cases IBD patients/comparisons	Unadjusted HR (95% CI)[†]	Adjusted HR (95% CI)[‡]	
UC-cohort				
Alzheimer's disease	626/6,792	1.10 (1.02−1.20)	1.10 (1.01−1.19)	
Vascular dementia	194/1,954	1.19 (1.03−1.38)	1.10 (0.95−1.27)	
Frontotemporal dementia	21/188	1.25 (0.79−1.96)	1.29 (0.82−2.03)	
PDD/DLB	35/308	1.31 (0.92−1.86)	1.34 (0.95−1.91)	
Unspecified dementia	291/3,557	0.98 (0.87−1.11)	0.96 (0.85−1.08)	
Other dementia[§]	33/460	0.80 (0.56−1.13)	0.75 (0.53−1.07)	
All-cause dementia	1,621/17,631	1.10 (1.04−1.16)	1.07 (1.01−1.12)	
CD-cohort				
Alzheimer's disease	131/2,021	0.91 (0.76−1.09)	0.91 (0.76−1.09)	
Vascular dementia	59/617	1.35 (1.03−1.76)	1.23 (0.94−1.60)	
Frontotemporal dementia	12/59	2.62 (1.40−4.88)	2.70 (1.44−5.05)	
PDD/DLB	5/84	0.82 (0.33−2.02)	0.83 (0.33−2.04)	
Unspecified dementia	95/1,120	1.22 (0.99−1.50)	1.18 (0.96−1.46)	
Other dementia[§]	19/129	1.84 (1.13−2.98)	1.68 (1.03−2.73)	
All-cause dementia	455/5,380	1.19 (1.08−1.31)	1.15 (1.05−1.27)	

FIGURE 3 Unadjusted and adjusted hazard ratios of dementia subtypes in patients with inflammatory bowel disease compared to matched general population comparators.
Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; HR, hazard ratio; CI, confidence interval; PDD/DLB, Parkinson's disease dementia and dementia with Lewy bodies.
[†]Controlled for sex, birthyear (±1 year) and region of residence.
[‡]Adjusted for modified Charlson Comorbidity Index score, diabetes (type 1 or 2), atrial fibrillation or flutter, hypertension, obesity, chronic obstructive pulmonary disease, depression, hearing impairment and head trauma.
[§]Other dementia represented any other dementia than the subtypes shown in the table.

Regarding IBD severity, the Taiwanese study reported a HR of 2.70 (95% CI: 1.94–3.76) in IBD patients with mild disease and 2.07 (95% CI: 1.04–4.11) in patients with moderate–severe disease.[22] The analysis might be subject to immortal-time bias, however, as the data used for defining IBD severity were collected during the follow-up period.[49] Our results question the impact of IBD severity and, hence, the influence of the microbiota–gut–brain axis on all-cause dementia risk in IBD patients, as the degree of intestinal inflammation is related to microbiota alterations in IBD[8].

To our knowledge, our study is the first to investigate the risk of frontotemporal dementia and PDD/LBD in IBD patients. The slightly elevated HR of PDD/DLB in UC patients corresponds with a meta-analysis showing a relative risk of Parkinson's disease of 1.30 (95% CI: 1.15–1.47) in UC patients and 1.28 (95% CI: 1.08–1.52) in CD patients.[14] Unfortunately, we lacked statistical precision for proper risk assessment in CD patients. The high HR of FTD in CD patients is potentially noteworthy. Approximately 30–40% of FTD is inherited, commonly caused by mutation in the C9ORF72 gene. Interestingly, an experimental study of mice with a C9ORF72 mutation concluded that a pro-inflammatory gut microbiota may contribute to adverse outcomes in this disease model.[50] Hence, CD patients with a C9ORF72 mutation might be particularly vulnerable. Unfortunately, we were unable to examine genetic factors in our study population.

Increased healthcare system contact among demented IBD patients could, in part, explain the slightly increased HR of all-cause dementia. Frequent healthcare system contact among IBD patients potentially increases the detection level of dementia and could also indicate more severe disease or a higher comorbidity. However, disease severity neither appears to affect risk nor did analyses adjusted for aspects of comorbidity captured by the CCI. Hospitalisation and surgery may increase dementia risk independently of above-mentioned factors as well.[19,20] Correspondingly, CD patients with history of total colectomy had increased OR for a dementia diagnosis.

Finally, the HRs of all-cause dementia may be influenced by shared risk factors for IBD and dementia including smoking and educational level, which we were not able to adjust for. Active smoking reduces the risk of UC but increases the risk of CD[40] and is also associated with a slightly increased risk of all-cause dementia.[41] According to E-value estimation, active tobacco smoking could explain the association of CD and dementia if the relative risk association of both CD and dementia with smoking is at least as large as 1.28, assuming the absence of other unrecognised confounders. This is possible for CD[40] but unlikely for all-cause dementia.[41] Moreover, former smoking is not associated with dementia,[41] limiting potential confounding as smoking cessation is a key part of CD treatment in

TABLE 3 Odds ratios of steroid usage, colorectal or small bowel surgery, IBD severity and healthcare surveillance in cases with dementia and inflammatory bowel disease compared to non-demented inflammatory bowel disease controls, 1996–2018

	Ulcerative colitis			Crohn's disease		
	Observed Cases/ controls	Unadjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]	Observed Cases/ controls	Unadjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Steroid usage						
Prescriptions of systemic steroid						
0	336/1208	1.00 (Reference)	1.00 (Reference)	88/308	1.00 (Reference)	1.00 (Reference)
1–4	282/1094	0.93 (0.78–1.12)	0.95 (0.79–1.14)	75/280	0.94 (0.66–1.34)	0.93 (0.64–1.33)
≥5	229/986	0.84 (0.70–1.02)	0.83 (0.68–1.01)	57/197	1.02 (0.70–1.50)	1.00 (0.67–1.49)
Prescriptions of any steroid						
0	186/716	1.00 (Reference)	1.00 (Reference)	69/235	1.00 (Reference)	1.00 (Reference)
1–9	407/1542	1.02 (0.84–1.24)	1.06 (0.86–1.29)	99/363	0.95 (0.67–1.37)	0.98 (0.67–1.42)
≥10	254/1030	0.97 (0.78–1.20)	0.98 (0.79–1.22)	52/187	1.00 (0.66–1.51)	1.01 (0.65–1.56)
Colorectal or small bowel surgery						
Record of total colectomy						
No	804/3131	1.00 (Reference)	1.00 (Reference)	214/774	1.00 (Reference)	1.00 (Reference)
Yes	43/157	1.09 (0.77–1.54)	1.09 (0.77–1.56)	6/11	2.03 (0.73–5.65)	1.97 (0.67–5.80)
Record of any surgery						
No	639/2477	1.00 (Reference)	1.00 (Reference)	147/497	1.00 (Reference)	1.00 (Reference)
Yes	308/811	1.00 (0.84–1.19)	0.99 (0.82–1.18)	73/288	0.86 (0.62–1.19)	0.85 (0.61–1.19)
IBD severity						
Number of IBD flares						
0	347/1312	1.00 (Reference)	1.00 (Reference)	104/344	1.00 (Reference)	1.00 (Reference)
1	184/683	1.04 (0.85–1.27)	1.09 (0.88–1.33)	47/174	0.92 (0.62–1.37)	0.86 (0.57–1.29)
2	104/460	0.88 (0.69–1.12)	0.87 (0.68–1.12)	28/96	0.97 (0.60–1.57)	1.02 (0.62–1.68)
≥3	212/833	0.98 (0.80–1.19)	0.98 (0.80–1.21)	41/171	0.80 (0.52–1.23)	0.74 (0.47–1.15)
Days of IBD activity[c]						
0	347/1312	1.00 (Reference)	1.00 (Reference)	104/344	1.00 (Reference)	1.00 (Reference)
120–499	285/1085	1.01 (0.85–1.21)	1.04 (0.87–1.25)	70/264	0.89 (0.62–1.26)	0.84 (0.58–1.21)
≥500	215/891	0.93 (0.76–1.13)	0.93 (0.76–1.13)	46/177	0.89 (0.59–1.34)	0.86 (0.56–1.32)
Healthcare system contact[d]						
All-cause hospital admissions						
0–3	331/1521	1.00 (Reference)	1.00 (Reference)	87/370	1.00 (Reference)	1.00 (Reference)
4–9	384/1432	1.25 (1.06–1.48)	1.14 (0.96–1.36)	100/325	1.41 (1.00–1.98)	1.27 (0.89–1.82)
≥10	132/335	1.91 (1.50–2.43)	1.56 (1.21–2.02)	33/90	1.73 (1.08–2.77)	1.25 (0.75–2.08)
All-cause general practitioner contacts						
0–14	132/732	1.00 (Reference)	1.00 (Reference)	35/188	1.00 (Reference)	1.00 (Reference)
15–29	376/1497	1.42 (1.14–1.78)	1.27 (1.01–1.59)	87/353	1.44 (0.91–2.27)	1.32 (0.83–2.11)

TABLE 3 (Continued)

	Ulcerative colitis			Crohn's disease		
	Observed Cases/controls	Unadjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]	Observed Cases/controls	Unadjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]
≥30	339/1059	1.84 (1.46–2.31)	1.49 (1.16–1.89)	98/244	2.43 (1.52–3.86)	2.05 (1.26–3.33)

Abbreviations: CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; UC, ulcerative colitis.

[a]Controlled for sex, year of birth (±1 year) and year of IBD diagnosis (±1 year).

[b]Adjusted for modified Charlson Comorbidity Index score, diabetes (type 1 or 2), atrial fibrillation or flutter, hypertension, obesity, chronic obstructive pulmonary disease, depression, hearing impairment and head trauma.

[c]According to the used algorithm for defining days of IBD activity, the lowest number of activity days was 120.

[d]Records of hospital admissions and general practitioner contacts were only regarded in the period from 4 to 1 year prior to the dementia diagnosis/matching date. GP contacts were calculated from the number of weekly service fees.

Denmark. Finally, adjustment for chronic obstructive pulmonary disease and CCI-score may, in part, indirectly have adjusted for tobacco smoking. Regarding education, the effect of low educational level on increased dementia risk could potentially account for our findings for both CD and UC[42], based on e-values of the lower CI intervals of all-cause dementia. However, low educational level has not been clearly associated with IBD[43]. Moreover, adjustment for educational level and socioeconomic status in the United Kingdom study only slightly attenuated their results, which were similar to our results, as mentioned previously.[26] Consequently, confounding by educational level on our results may be limited.

4.3 | Limitations

Validation of IBD diagnosis codes in the DNPR has reported a high completeness (94%) and a positive predictive value (PPV) of 90% and 98% for UC and CD, respectively,[51] yet lower in IBD patients aged above 50.[52] Potential misclassification would likely be non-differential with bias towards the null. However, considering only patients who received a diagnosis of inflammatory bowel disease on at least two separate occasions did not substantially alter our results except for FTD in CD patients, where the adjusted HR increased to 3.42 (95% CI: 1.63–7.18). The accuracy of dementia diagnosis codes is high for all-cause dementia (PPV = 86%) and AD (PPV = 81%) but low for VaD (PPV = 19%) and FTD (PPV = 33%) when the DNPR and DPCRR are combined, but it has not been validated for other dementia subtypes.[35] Of note, the PPV for FTD was estimated from only three cases and might therefore be inaccurate.[35] Our use of primary (not secondary) diagnoses to define all dementia subtypes except AD which may have increased the PPVs of the diagnostic codes, but we cannot rule out substantial misclassification. Misclassification of all-cause dementia would most likely be non-differential with bias towards the null. In a sensitivity analysis only regarding dementia diagnosed in psychiatric, geriatric or neurologic inpatient or outpatient setting, the risk of all-cause dementia in CD patients was slightly attenuated, but other estimates did not substantially change. This analysis suggests limited impact of misclassification bias. This

method has not been validated, however. Mild cases of dementia are likely underrepresented in the DNPR and DPCRR.[35] However, incorporating two prescriptions of dementia-specific medication as an outcome equivalent to a dementia diagnosis did not change the results with respect to all-cause dementia and AD.

As mentioned, a potential threat to the validity of our study was elevated healthcare system contact in IBD patients. However, adjustment for all-cause hospital admissions in the design setting with IBD patients aged 50 years only, caused a slight attenuation of the results; nonetheless, they remained slightly elevated. Finally, we did not have access to data on educational level, personal income level, employment status and lifestyle covariates including smoking, alcohol consumption and dietary habits, as these are not recorded in Danish registries.

In conclusion, UC and CD may be associated with a slightly increased risk of all-cause dementia. One main driver of this association may be less common dementia subtypes, especially FTD in CD patients. However, our results could also, in part, be explained by detection bias associated with increased healthcare system contacts of IBD patients.

AUTHOR CONTRIBUTIONS
Jakob Rønnow Sand: Conceptualization (equal); data curation (equal); formal analysis (lead); funding acquisition (supporting); investigation (lead); methodology (lead); project administration (lead); validation (equal); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Frederikke Schønfeldt Troelsen:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); supervision (lead); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Erzsébet Horváth-Puhó:** Conceptualization (equal); formal analysis (supporting); investigation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Victor Henderson:** Investigation (equal); methodology (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Henrik Toft Sørensen:** Conceptualization (lead); data curation (lead); funding acquisition (lead); investigation (equal);

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