Original research

Inflammatory bowel disease is associated with higher dementia risk: a nationwide longitudinal study

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ABSTRACT

Objective Increasing evidence supports reciprocal communication between the enteric and the central nervous system in disease, termed the 'gut–brain axis'. Recent findings suggest a connection between IBD and development of Parkinson's disease. The role of IBD in dementia, another insidious neurodegenerative disorder, has not been explored.

Design Using the Taiwanese National Health Insurance Research Database, we performed comparative analysis of 1742 patients with IBD ≥45 years old against 17 420 controls to assess dementia risk following IBD diagnosis. Controls were matched on bases of sex, access to healthcare, income and dementia-related comorbidities. All individuals were followed for dementia diagnosis for up to 16 years. Subanalyses included the relationship between sex, ulcerative colitis (UC) and Crohn's disease (CD), and dementia risk.

Results Overall incidence of dementia among patients with IBD was significantly elevated (5.5% vs 1.4% among controls). Patients with IBD were diagnosed with dementia at 76.24 years old on average, compared with 83.45 among controls. The HR of developing dementia among patients with IBD was 2.54 (95% CI 1.91 to 3.37). Among dementia types, the risk of developing Alzheimer's dementia demonstrated the greatest increase. Dementia risk did not differ between sex differences nor UC versus CD.

Conclusion This population-based cohort study demonstrates significant association between IBD and subsequent development of dementia. Dementia was diagnosed at an earlier age among patients with IBD, and disease risk appeared to increase with IBD chronicity. These findings highlight the need for future research to elucidate the relationship between IBD and dementia.

Significance of this study

What is already known on this subject?
- Chronic systemic inflammation is associated with neurocognitive decline.
- Communication between the gut and the central nervous system is implicated in health and disease via the 'gut–brain axis'.

What are the new findings?
- In this population-based longitudinal study, we found a significant increase in dementia risk among patients with IBD compared with matched controls.
- This suggests the roles of gut–brain axis and chronic inflammation in progressive neurocognitive degeneration.

How might it impact on clinical practice in the foreseeable future?
- The findings elucidate the need for further investigation into the relationship between intestinal inflammation and neurocognitive decline.
- Vigilance and education for dementia among elderly patients with IBD may improve early intervention to slow cognitive decline and improve quality of life.

INTRODUCTION

IBD, consisting mainly of ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory condition characterised by recurrent periods of disease activity and quiescence. Presence of inflammation can trigger symptoms including abdominal pain, diarrhoea, urgency and bloody stools, and is confirmed by endoscopy with biopsy or radiographic imaging. However, the lack of symptoms (clinical remission) does not always correlate with the absence of intestinal inflammation. Even the achievement of deep remission, defined by most gastroenterologists as clinical remission with mucosal healing, does not represent complete elimination of inflammation, as histological evidence of disease activity persists in many patients.[1 2]

The aetiology of IBD is not well defined, but is postulated to originate from dysregulated immune response to changes in the gut microbiome in a genetically susceptible individual. Intestinal homeostasis has been implicated in many psychiatric and neurological syndromes via the gut–brain axis, which describes the signalling between the gut, its microbiome and the central nervous system (CNS).[3] This bidirectionality of the gut–brain axis is evident yet complex.[4] Psychiatric disorders such as anxiety and depression are prevalent in 20%–30% patients with IBD[5 6]; psychological symptoms are independently associated with elevated risk of disease flare and worse outcomes.[7–9] Depression also correlates with an increased risk of developing IBD,[10] while treatment with specific antidepressants in patients with depression protects against CD and UC.[11] IBD may play a role in the development of Parkinson's disease through chronic systemic

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inflammation, disruption of intestinal and blood–brain barriers, and perturbations of the gut microbiome in addition to overlapping genetic predispositions.[12–14]

Less explored is the relationship between IBD and dementia, another insidious neurodegenerative disorder with onset in later adulthood and chronic irreversible functional deterioration. Previous evidence suggests chronic inflammation as a driver of cognitive decline.[15–17] Systematic inflammation may drive neuroinflammatory changes and chronic activation of microglia, leading to oxidative stress and deposition of misfolded proteins in Alzheimer's dementia.[18 19] These destructive changes may be protected by chronic use of anti-inflammatory medications.[19] Chronic inflammation also increases the risk of thromboembolic events and ischaemic stroke, contributing to the development of vascular dementia, which leads to stepwise instead of gradual neurocognitive decline.[20 21] Finally, the linkage between dementia and disruption of the gut microbiome elucidates mechanisms of pathogenesis stemming from bacterial metabolism and immune activation, possibly from microbial metabolites and pathological inflammation.[18 22–25]

Early recognition and timely intervention for dementia will slow cognitive deterioration and improve the quality of life for both the patient and their caretakers.[26] However, diagnosis for this insidious syndrome requires vigilance and awareness. Characteristics of IBD include disrupted intestinal epithelial barrier, gut dysbiosis and chronic inflammatory burden, all of which likely contribute to the development of dementia. Therefore, it is plausible that compared with the general population, patients with IBD are predisposed to neurocognitive impairment and dementia. To investigate this hypothesis, we performed a population-based cohort study with a large sample size to assess the impact of IBD as a potential risk factor for subsequent development of dementia.

METHODS

Data source

The Taiwan National Health Insurance (NHI) programme is a universal single-payer system providing compulsory health insurance to all residents of Taiwan and was initiated in 1995. At the end of 2010, approximately 99.6% of the 23 million Taiwanese residents received medical coverage through this programme. Established for research purposes and audited by the Department of Health and the Bureau of the NHI programme, the Taiwan National Health Insurance Research Database (NHIRD) contains comprehensive information about the insured patients, such as demographics (birthdate, sex, residential location, income status) and clinical visits (dates and diagnoses) for the 23 million Taiwanese residents receiving medical coverage through the NHI. To protect privacy, each patient is assigned a unique and anonymous identifier on enrolment by the NHI, which allows researchers to follow their diseases and outcomes. Diagnoses were captured using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively for epidemiological studies.[27–30]

Inclusion criteria for patients with IBD and matched controls

Adults≥45 years old with a diagnosis of UC (ICD-9-CM code: 556) or CD (ICD-9-CM code: 555) by board-certified gastroenterologists or colorectal surgeons at least twice between 1 January 1998 and 31 December 2011 and who had no history of dementia before their IBD diagnoses were included in the IBD cohort. The first time of IBD diagnosis was defined as the time of enrolment into the NHI between these two dates; patients with history of IBD diagnosed prior to 1 January 1998 were entered as having been diagnosed on their enrolment on 1 January 1998. The type of IBD was defined by their latest ICD-9-CM diagnosis. Exact matching was used to match this cohort in a 1:10 fashion to controls without diagnoses of neither dementia nor IBD prior to the enrolment for other medical causes on the bases of age (±1 year), sex, enrolment time, dementia-related medical comorbidities, income level (levels 1–3 per month: ≤15 840 New Taiwanese Dollars (NTD) or US$528, 15 841–25 000 NTD or US$528–833, and ≥25 000 NTD or ≥US$833), and urbanisation level of residence (levels 1–5, most to least urbanised), a proxy for healthcare availability in Taiwan.[31] Additionally, Charlson Comorbidity Index (CCI), all-cause clinical visits and all-cause mortality were provided for the IBD and the matched-control cohorts. CCI consisting of 22 physical conditions was also assessed to determine the systemic health conditions of all enrolled subjects.[32]

Diagnosis of dementia (ICD-9-CM codes: 290.0, 290.1, 290.2, 290.3, 290.4, 294.1, 294.2, 331.0, 331.1, 331.2, 331.82) was documented at least twice by board-certified psychiatrists or neurologists during the follow-up period (from enrolment to 31 December 2013 or death). The first date of dementia diagnosis was defined as the time of outcome. Given the chronic insidious nature of dementia, a minimum of 2 years between the diagnoses of IBD and subsequent dementia was introduced to minimise surveillance bias. Dementia-related comorbidities included history of cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidaemia, diabetes mellitus and smoking. Alzheimer's disease was defined either by the specific ICD-9-CM code of 331.0, or identified by ICD-9-CM codes of dementia (ICD-9-CM codes: 290.0, 290.1, 290.2, 290.3, 290.4, 294.1, 294.2) while also receiving medications for dementia. Based on the NHI regulations, reimbursable therapies for dementia (ie, cholinesterase inhibitors) were only approved after comprehensive laboratory and imaging examinations to exclude cognitive decline from other causes including thyroid dysfunction, vitamin B_{12} deficiency, or cerebrovascular events; medications were not approved for Alzheimer's disease with any evidence of cerebrovascular lesions.

Vascular dementia was defined by the specific ICD-9-CM code of 290.4.Other types of dementia, especially diagnosis of Alzheimer's disease with evidence of any cerebrovascular lesion, were defined as unspecified dementia in our study because the definite dementia pathology cannot be clearly defined based on the ICD-9-CM codes of 290.0, 290.1, 290.2, 290.3, 290.4, 294.1, 294.2 alone without concurrent medication prescription for Alzheimer's disease, reflecting the clinical practice in Taiwan. For this reason, Alzheimer's disease with cerebrovascular lesions were defined as unspecified dementia, and the diagnostic validity of Alzheimer's disease as the sole reason for neurocognitive degeneration is high.

To address the possibility of certain IBD medications (eg, anti-tumour necrosis factor α (anti-TNFα)) as a confounder for increased dementia risk, the severity of IBD was categorised based on medication history in accordance with the current clinical guidelines.[33 34] Specifically, patients who only received treatment with aminosalicylates, sulfasalazine and/or topical steroids without history of systemic steroids were classified as having mild disease. Patients with a history of systemic corticosteroids, immunomodulators and/or biologics therapy were deemed to have moderate–severe disease. Taiwanese surgical codes were used to identify patients with surgical history related to their IBD

diagnosis, including colectomy (73 011B, 73 012B, 73 013B, 73 014B, 73 015B), small bowel resection (73 008B, 73 010B), exploratory laparotomy (75 805B), ileostomy and enterostomy (73 016B, 73 017B, 73 022B), bowel anastomosis (73 031B, 73 032B, 73 038B) and repair of intestinal perforation (73 033B).[35]

Statistical analysis

For between-group comparisons, the F-test was used for continuous variables and Pearson's χ^2 test for nominal variables. Stratified Cox-regression analysis on each matched pair (the patient and their 10 matched controls in a 1:10 fashion) with adjustments for age, CCI scores and all-cause clinical visits was applied to investigate the dementia risk between the IBD and the control groups. Analysis using stratified competing risk-regression model was also performed with death as a competing risk. In both models, the numbers of clinical visits per year for the IBD cohort and the matched-controls cohort were included as a variable to account for potential detection bias. Subanalyses stratified by IBD type (UC or CD), sex, IBD severity, history of IBD-related surgery and dementia types were performed.

Given the insidious onset of dementia, two types of sensitivity analyses were performed to validate the results by minimising underdiagnosis of occult dementia at the time of IBD diagnosis. In the 'exclusion of observation period' model, the first 3 or 5 years of observation after the diagnosis of IBD were excluded, eliminating all cases of dementia diagnosed within these first years following IBD diagnosis. In the 'exclusion of enrolment period' model, only patients diagnosed with IBD after the dates 1 January 2000, or 1 January 2005, were included in the analysis; patients with IBD diagnosed prior to these time points were selectively excluded.

All relevant subject information was provided by the NHIRD without any missing data. Subject death was captured by the NHI and incorporated as competing risk in the stratified competing risk-regression model. Loss to follow-up from emigration was not known; however, the rate of emigration was <0.2% per year during the study period.[36] Statistical significance was set at two-tailed $p \leq 0.05$. Data processing and statistical analyses were performed with SAS (V.9.1, SAS Institute).

Patient involvement

No patients were involved for any part of the study, including concept and study design, data collection, analysis and interpretation, drafting of the manuscript and critical revision. The public was involved indirectly through the collection of their medical records by the Taiwan NHIRD.

RESULTS

Three million subjects were available for patient selection (figure 1). Among these, we identified 3744 patients with two diagnoses of IBD, from which 62 had dementia prior to IBD and 1856 were <45 years of age and were excluded. From the remaining 1888 patients aged ≥45 years diagnosed with IBD between 1998 and 2011 and without prior dementia, 146 could not be matched due to lack of adequate controls from the over 2.6 million potential control candidates and were therefore excluded. After applying exact matching based on medical history and demographics information described in the Methods section, 1742 patients with IBD and 17 420 matched controls were included in the study (table 1). CCI scores were higher among patients with IBD (average 3.48, SD 2.55) than matched controls (average 2.59, SD 2.35). On average, all individuals received at least one clinical visit per month.

Overall incidence of dementia was significantly increased among patients with IBD compared with non-IBD controls (5.5% vs 1.4%, p<0.001) during the follow-up period. This elevated risk spanned across Alzheimer's disease (1.9% vs 0.2%, p<0.001), vascular dementia (0.7% vs 0.2%, p=0.001) and unspecified dementia (2.9% vs 1.9%, p<0.001). Furthermore, patients with IBD were diagnosed with dementia at an average age of 76.24 (±8.22 years), over 7 years younger than the average age among the matched controls (83.45±6.32 years; table 1).

Using stratified Cox-regression model, the HR of developing dementia among patients with IBD was 2.54 (95% CI 1.91 to 3.37) compared with matched controls after adjustment for age, CCI score and all-cause clinical visits (table 2). After the introduction of death as a competing risk in the stratified competing risk regression model, the HR remained relatively unchanged (2.55, 95% CI 1.92 to 3.39). The presence of IBD had the greatest impact on the subsequent development of Alzheimer's disease (HR 6.19, 95% CI 3.31 to 11.57), although increased risks were also demonstrated for vascular and unspecified dementia. There were no significant sex differences nor differences between UC and CD for dementia.

There has been evidence to suggest the involvement of IBD medications in neurodegeneration. Particularly, anti-TNFs have been associated with central and peripheral

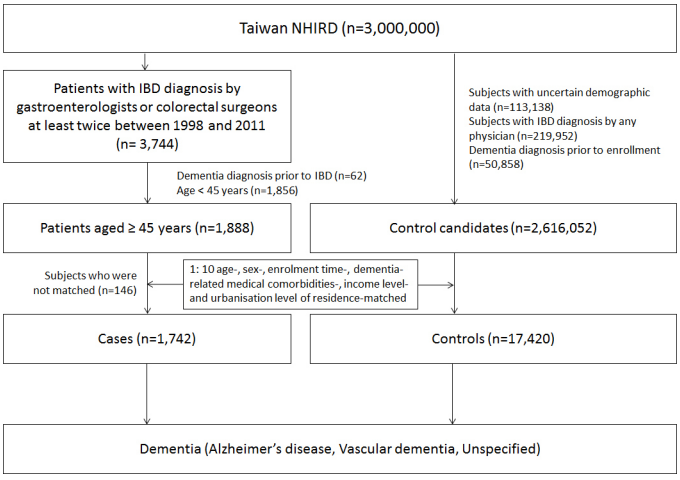

Figure 1 Study flow chart. NHIRD, National Health Insurance Research Database.

Table 1 Demographic data and incidence of dementia among patients with IBD and control group

	Patients with IBD (n=1742)	Controls (n=17 420)	Patients with CD (n=584)	Controls (n=5840)	Patients with UC (n=1158)	Controls (n=11 580)
Age at enrolment (years, SD)	60.64 (10.75)	60.63 (10.76)	61.41 (11.04)	61.40 (11.05)	60.26 (10.58)	60.24 (10.59)
Sex (n, %)						
Male	894 (51.3)	8940 (51.3)	301 (51.5)	3010 (51.5)	593 (51.2)	5930 (51.2)
Female	848 (48.7)	8480 (48.7)	283 (48.5)	2830 (48.5)	565 (48.8)	5650 (48.8)
IBD diagnosis (n, %)						
CD	584 (33.5)					
UC	1158 (66.5)					
Disease severity (n, %)						
Mild	1323 (75.9)		482 (82.5)		841 (72.6)	
Moderate–severe	288 (16.5)		64 (11.0)		224 (19.3)	
Surgery	131 (7.5)		38 (6.5)		93 (8.0)	
Dementia-related comorbidities (n, %)						
Cerebrovascular diseases	310 (17.8)	3100 (17.8)	110 (18.8)	1100 (18.8)	200 (17.3)	2000 (17.3)
Traumatic brain injury	46 (2.6)	460 (2.6)	12 (2.1)	120 (2.1)	34 (2.9)	340 (2.9)
Hypertension	919 (52.8)	9190 (52.8)	319 (54.6)	3190 (54.6)	600 (51.8)	6000 (51.8)
Dyslipidaemia	562 (32.3)	5620 (32.3)	209 (35.8)	2090 (35.8)	353 (30.5)	3530 (30.5)
Diabetes mellitus	425 (24.4)	4250 (24.4)	150 (25.7)	1500 (25.7)	275 (23.7)	2750 (23.7)
Smoking	31 (1.8)	310 (1.8)	5 (0.9)	50 (0.9)	26 (2.2)	260 (2.2)
CCI score (SD)	3.48 (2.55)	2.59 (2.35)	3.60 (2.48)	2.64 (2.35)	3.42 (2.58)	2.56 (2.35)
Level of urbanisation (n, %)						
1 (most urbanised)	207 (11.9)	2070 (11.9)	76 (13.0)	760 (13.0)	131 (11.3)	1310 (11.3)
2	337 (19.3)	3370 (19.3)	93 (15.9)	930 (15.9)	244 (21.1)	2440 (21.1)
3	189 (10.8)	1890 (10.8)	69 (11.8)	690 (11.8)	120 (10.4)	1200 (10.4)
4	149 (8.6)	1490 (8.6)	39 (6.7)	390 (6.7)	110 (9.5)	1100 (9.5)
5 (most rural)	860 (49.4)	8600 (49.4)	307 (52.6)	3070 (52.6)	553 (47.8)	5530 (47.8)
Income-related insured amount						
≤15 840 NTD/month	741 (42.5)	7410 (42.5)	252 (43.2)	2520 (43.2)	489 (42.2)	4890 (42.2)
15 841–25 000 NTD/month	636 (36.5)	6360 (36.5)	209 (35.8)	2090 (35.8)	427 (36.9)	4270 (36.9)
≥25 001 NTD/month	365 (21.0)	3650 (21.0)	123 (21.0)	1230 (21.0)	242 (20.9)	2420 (20.9)
Incidence of any dementia (n, %)	95 (5.5)	250 (1.4)	30 (5.1)	93 (1.6)	65 (5.6)	157 (1.4)
Age at diagnosis of any dementia (years, SD)	76.24 (8.22)	83.45 (6.32)	75.94 (7.84)	83.07 (7.11)	76.37 (8.45)	83.69 (58.2)
Duration between enrolment and dementia (years, SD)	5.93 (3.57)	7.32 (4.45)	5.49 (3.16)	6.34 (4.41)	6.13 (3.75)	7.90 (4.39)
Dementia type (n, %)						
Alzheimer's disease	33 (1.9)	32 (0.2)	11 (1.9)	14 (0.2)	22 (1.9)	18 (0.2)
Vascular dementia	12 (0.7)	40 (0.2)	3 (0.5)	16 (0.3)	9 (0.8)	24 (0.2)
Unspecified	50 (2.9)	178 (1.9)	16 (2.8)	63 (1.1)	34 (2.9)	115 (1.0)
All-cause clinical visits (times per year, SD)	25.17 (25.59)	15.01 (15.04)	24.45 (21.38)	15.65 (16.15)	25.54 (27.47)	14.68 (14.44)
All-cause mortality (n, %)	22 (1.3)	126 (0.7)	7 (1.2)	37 (0.6)	15 (1.3)	89 (0.8)

CCI, Charlson Comorbidity Index; CD, Crohn's disease; IBD, inflammatory bowel disease; SD, standard deviation; UC, ulcerative colitis.

neurodegeneration.[37 38] To address this, patients were stratified as mild or moderate–severe IBD based on their medication history. Of the 1742 patients with IBD, 1323 (75.9%) had mild disease and 288 (16.5%) had moderate–severe disease; 131 patients had a history of IBD-related surgery (table 1). Analyses using stratified Cox-regression model revealed adjusted HR of 2.70 (95% CI 1.94 to 3.76) for patients with mild disease, and 2.07 (95% CI 1.04 to 4.11) for patients with moderate–severe disease (table 3), which were confirmed with stratified competing risk regression model. Due to inadequate power, analyses did not reveal elevated risk for dementia among patients with IBD with history of disease-related surgeries, of which only eight were diagnosed with dementia during follow-up. We further examined the cumulative effect of IBD chronicity on dementia risk over time. Kaplan-Meier survival curve with log-rank test indicated that patients with IBD had significantly higher risk of developing dementia ($p<0.001$) than the matched controls (figure 2) during the follow-up duration. Interestingly, dementia risk appeared to accelerate over time correlating with the chronicity of IBD diagnosis.

Sensitivity analysis

Given the insidious onset of dementia, we performed two types of sensitivity analyses using stratified Cox-regression model and stratified competing risk regression model to validate the findings. In exclusion of observation period sensitivity analysis, selective exclusion of patients with IBD and matched controls who were enrolled in our study and subsequently developed dementia within 3 or 5 years after the diagnosis of IBD yielded consistent findings that lifetime dementia risk was significantly higher among patients with IBD than controls (table 4; online supplementary figure 1,2). The results were confirmed with exclusion of enrolment period sensitivity analysis, in which patients and controls enrolled prior to the years 2000 or 2005 were selectively excluded (table 4; online supplementary figure 3,4).

Table 2 Risk of developing dementia among patients with IBD and controls*

	Alzheimer's disease	Vascular dementia	Unspecified dementia	Total
Stratified Cox-regression model (HR (95% CI))				
IBD (presence vs absence)	**6.19 (3.31 to 11.57)**	**2.60 (1.18 to 5.70)**	**2.88 (2.11 to 3.93)**	**2.54 (1.91 to 3.37)**
Stratified by disease				
UC	**6.77 (2.82 to 16.22)**	**4.39 (1.64 to 11.80)**	**3.10 (2.12 to 4.51)**	**2.69 (1.89 to 3.85)**
CD	**7.53 (2.67 to 21.28)**	1.10 (0.24 to 5.15)	**2.46 (1.42 to 4.28)**	**2.29 (1.42 to 3.69)**
Stratified by sex				
Male IBD	**4.87 (1.80 to 13.16)**	**6.67 (2.44 to 18.25)**	**3.10 (2.02 to 4.77)**	**2.79 (1.87 to 4.18)**
Female IBD	**7.67 (3.36 to 17.49)**	0.57 (0.15 to 2.25)	**2.80 (1.79 to 4.40)**	**2.43 (1.63 to 3.64)**
Stratified competing risk regression model (HR (95% CI))				
IBD (presence vs absence)	**7.06 (3.88 to 12.83)**	1.93 (0.90 to 4.14)	**2.25 (1.56 to 3.24)**	**2.55 (1.92 to 3.39)**
Stratified by disease				
UC	**7.95 (3.56 to 17.75)**	2.47 (0.96 to 6.43)	**2.39 (1.52 to 3.76)**	**2.69 (1.88 to 3.85)**
CD	**7.86 (2.81 to 21.99)**	1.09 (0.25 to 4.75)	**2.01 (1.07 to 3.76)**	**2.32 (1.43 to 3.75)**
Stratified by sex				
Male IBD	**5.34 (2.10 to 13.57)**	**4.67 (1.78 to 12.24)**	**2.39 (1.41 to 4.07)**	**2.88 (1.91 to 4.32)**
Female IBD	**8.75 (3.96 to 19.35)**	0.72 (0.16 to 3.18)	**2.21 (1.32 to 3.68)**	**2.41 (1.61 to 3.60)**

Bold type indicates the statistical significance.
*Adjusted by age, Charlson Comorbidity Index score and all-cause clinical visits.
CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; UC, ulcerative colitis.

DISCUSSION

In this population-based cohort study, we found that patients with IBD are predisposed to the subsequent development of dementia, and with a younger average age onset than the general population. Dementia risk may correlate with the chronicity of IBD diagnosis—cumulative dementia risk suggests an accelerated rate in those diagnosed with IBD for a longer duration. No significant differences in dementia risk were detected between sex nor UC vs CD.

Several plausible mechanisms may contribute to increased dementia risk among patients with IBD. Alzheimer's disease is the most common diagnosis of dementia, and is characteristically accompanied by neuroinflammation, neuronal loss, neurotransmitter abnormalities and brain atrophy concurrent with accumulation of neurofibrillary tangles and amyloid plaques.[39] Recent studies have suggested cumulative detrimental effect of chronic inflammation on these neurocognitive changes and the accompanying functional decline.[15 17] IBD is a chronic inflammatory disease with intestinal and extraintestinal involvement; despite achieving the therapeutic target of deep remission in IBD, histological activity and extraintestinal symptoms may continue to manifest, contributing to systemic inflammatory burden.[33 34 40] Furthermore, studies have demonstrated the capacity of intestinal flora to synthesise and release neurotransmitters and neuromodulators such as short-chain fatty acids, dopamine, serotonin and gamma aminobutyric acid.[25] Gut–brain communication is through the autonomous nervous system via the vagus nerve and the blood–brain barrier, both allow the passage of signalling molecules.[41 42] The disruption of the intestinal epithelial barrier and microbiome dysbiosis associated with IBD may facilitate passage of gut microbial-derived neurotoxic metabolites into the CNS.[43–45]

Global disease burden of IBD and prevalence of dementia continue to rise alongside the world population's average life expectancy.[46–49] The identification of increased dementia risk and earlier onset among patients with IBD suggest that this population may benefit from education and increased clinical vigilance through a multidisciplinary approach. Early recognition and intervention will slow cognitive decline, improve life quality and allow opportunity for life and future care planning while mental capacity of the patient is still maintained.[26] Future research directions include investigating the mechanistic relationship between IBD and dementia, the impact of better IBD management on dementia with novel therapeutics and development of potential novel treatments through gut microbial manipulation leveraging the gut–brain axis.

To our knowledge, this is the first study to thoroughly explore IBD as a potential inciting factor for dementia. We applied a rigorous selection process of including patients at least 45 years of age at enrolment and with two IBD diagnoses to a population

Table 3 Risk of developing dementia among patients with IBD and controls, based on disease severity from medication and surgical history

		Stratified Cox-regression model		Stratified competing risk regression model	
	Dementia case (n, %)	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*
Control group	250 (1.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
IBD group					
Mild	69 (5.2)	**4.54 (3.41 to 6.05)**	**2.70 (1.94 to 3.76)**	**4.62 (3.47 to 6.17)**	**2.73 (1.95 to 3.80)**
Moderate–severe	18 (6.3)	**4.58 (2.62 to 8.03)**	**2.07 (1.04 to 4.11)**	**4.56 (2.60 to 7.99)**	**2.06 (1.04 to 4.10)**
Surgery	8 (6.1)	**2.82 (1.28 to 6.22)**	2.33 (0.96 to 5.66)	**2.85 (1.29 to 6.30)**	2.31 (0.95 to 5.63)

Bold type indicates the statistical significance.
*Adjusted by age, Charlson Comorbidity Index score and all-cause clinical visits.
CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; Mild, aminosalicylates, sulfasalazine and/or topical steroids; Moderate–severe, systemic corticosteroids, immunomodulators, and/or biologics therapy.

Table 4 Sensitivity analyses of developing any dementia among patients with IBD and controls*

	Total	Exclusion of observation period		Exclusion of enrolment period	
		>3 years	>5 years	Enrolment year≥2000	Enrolment year≥2005
Stratified Cox-regression model					
IBD					
Presence	**2.54 (1.91 to 3.37)**	**2.60 (1.91 to 3.55)**	**2.30 (1.61 to 3.28)**	**2.35 (1.72 to 3.20)**	**2.26 (1.41 to 3.63)**
Absence	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Stratified competing risk regression model					
IBD					
Presence	**2.55 (1.92 to 3.39)**	**3.14 (2.36 to 4.24)**	**2.53 (1.80 to 3.57)**	**2.35 (1.72 to 3.21)**	**2.26 (1.41 to 3.63)**
Absence	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

Bold type indicates the statistical significance.
*Adjusted by age, Charlson Comorbidity Index score and all-cause clinical visits.
CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease.

healthcare research database with large sample size and adequate follow-up period to capture the intended population of age-associated dementia. The validity of this healthcare database has been well established.[50 51] The ability to track patients using their anonymised identifiers provided the opportunity to establish temporal relationship between IBD and dementia. Affiliations between the types of IBD (UC vs CD), sex, Alzheimer's, vascular and unspecified dementia were independently inspected. Confounders including multiple dementia-related comorbidities and socioeconomic status were appropriately controlled for; two different types of statistical models were used to adjust for multiple variables potentially affecting the outcome, and several sensitivity analyses were performed to confirm the findings.

Study limitations reflect those shared by other registry-based analyses. Despite emphasising the strong unidirectional association between IBD and subsequent dementia development, a causal relationship cannot be inferred. Although anti-inflammatory therapeutics may preserve neurocognitive function, regional medication prescribing differences reflecting healthcare policies, drug availability and style of practice preclude the assessment of individual IBD medications on dementia.[14] The association between dementia and IBD-related surgeries also could not be adequately explored due to lack of power. Lifestyle confounders such as diet and exercise were not available in the database. Loss to follow-up from emigration could not be accounted for; however, the rate was low at <0.2% per year during the study period.[36] Misclassification of IBD and exclusion of mild IBD cases were possible[52]; however, diagnoses and coding are highly reliable as mandated by the Taiwanese government for medical reimbursement.[12] For this reason, the 'unspecified' dementia type in our analysis likely reflected patients who did not receive dementia medications. Patients with IBD prior to 1998 were entered as being diagnosed in 1998 when enrolled into the database; therefore, the temporal effect of IBD on dementia may be underestimated.

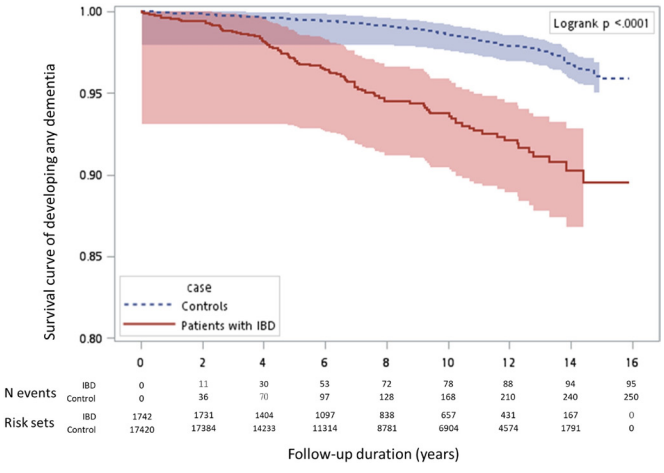

Figure 2 Kaplan-Meier survival curve of developing any dementia among patients with IBD and control group.

In conclusion, we found increased risk of dementia following the diagnosis of IBD, with the average age of onset 7 years younger compared with matched controls. Future research on the pathogenic mechanism and molecular underpinning between the two disease conditions may lead to the development of novel therapeutics. Clinical implications include vigilance of dementia among elderly patients with IBD, support and education for patients with IBD and their caregivers, and early detection and timely medical care through a multidisciplinary approach.

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