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Irritable bowel syndrome correlates with increased risk of Parkinson's disease in Taiwan

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Abstract This study investigated whether an association exists between irritable bowel syndrome (IBS) and the risk of Parkinson's disease. This is a retrospective cohort study using the dataset of the Taiwan National Health Insurance Program from 2000 to 2010. We identified 23,875 patients (aged 20 years or older) with newly diagnosed IBS as the IBS group and 95,500 subjects without IBS as the non-IBS group for comparison. The main outcome was incident Parkinson's disease compared between both groups by the end of 2010. We measured the hazard ratio (HR) to evaluate the association between IBS and Parkinson's disease. The overall incidence of Parkinson's disease in the IBS group was 1.76-fold higher than that in the non-IBS group (16.4 vs. 9.33 per 10,000 person-years). The multivariable Cox proportional hazards regression analysis revealed that the adjusted HR of Parkinson's disease associated with IBS was 1.48 (95 % CI 1.27, 1.72), compared with the non-IBS group. Age, women, hypertension, dementia, cerebrovascular disease and depression were also significantly associated with Parkinson's disease. Patients with irritable bowel syndrome are at an increased risk of developing Parkinson's disease. Further studies are required to explore the pathophysiological connection between these disorders.

Keywords Irritable bowel syndrome · Non-motor · Parkinson's disease

Introduction

Irritable bowel syndrome (IBS) is a frustrating disorder common in adults. A systematic review by Lovell et al. [1] has demonstrated that the prevalence of IBS varies from approximately 1.1 to 45.0 % worldwide according to different criteria defining the disease. According to the Rome III criteria [2, 3], the cardinal symptoms include recurrent abdominal pain or discomfort associated with the onset of either diarrhea predominant, constipation predominant, or mixed types. Although the real pathophysiology of IBS remains unclear, studies have proposed the novel pathogenesis mediated by the

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bidirectional dysregulation of brain–gut axis [4–6]. Various psychosocial, environmental, or/and genetic factors can influence the brain, which releases numerous neurotransmitters to alter the gastro-intestinal tract motility [4–6].

Aside from traditional motor disorders, such as resting tremor, cogwheel rigidity and bradykinesia, non-motor symptoms of Parkinson's disease have drawn little attention because they are frequently unrecognized and/or underdiagnosed [7, 8]. Among the non-motor symptoms of Parkinson's disease, gastrointestinal symptoms such as constipation, and sensory symptoms such as abdominal pain are the most common. The prevalence of constipation is about 46.7–52.5 %, and the prevalence of abdominal pain is about 28 % [9, 10]. Although the real pathophysiology of non-motor symptoms are not well recognized in clinical practice, studies on the neurodegeneration of the brain–gut axis have shown the existing Lewy bodies and alpha-synuclein in neurons and neuritis in patients with Parkinson's disease [11–13]. Different potential mechanisms converge in the degenerative process of the central nervous system and enteric nervous system mediated by the Lewy bodies, Lewy neurites, and other neurological alterations.

Here we proposed the hypothesis to investigate whether a relationship exists between IBS and Parkinson's disease because the brain–gut axis is potentially involved in these two conditions. If a relationship does exist, more attention can be focused on these two conditions simultaneously in clinical practice. Therefore, we conducted a cohort study to investigate whether patients with IBS are at a higher risk of subsequent Parkinson's disease in Taiwan.

Materials and methods

Data sources

We designed a retrospective cohort study using the dataset from the Taiwan National Health Insurance. Previous studies have documented the details of the insurance program [14–16]. Insurance reimbursement claims data in this study were available from the National Health Research Institutes for public use. Patient identification numbers were scrambled to maintain patient confidentiality. An approval of institutional review board was not necessary for data capturing. We used the International Classification of Diseases (ICD) 9th Revision to identify diseases from the claims data files.

Criteria and definition

This cohort study included two groups of study subjects. The IBS group consisted of 23,875 patients with newly diagnosed IBS (ICD-9 codes 564.1) who had received medical care for IBS at least three times, including outpatient visits and/or hospitalizations (aged 20 years and older) in 2000–2010. For each IBS patient, 4 reference individuals were selected from people without diagnosis of IBS as the non-IBS group, frequency matched by gender, age (within 5 years), and index year of diagnosing IBS. We selected a large comparison group to increase the statistical power and control the potential confounding. Both groups were followed up to determine the incidence of Parkinson's disease (based on ICD-9 codes 332.0) until being diagnosed with Parkinson's disease, withdraw or loss to follow-up from the insurance coverage, or until December 31, 2010. Similarly, only those who had received medical care for Parkinson's disease at least three times, including outpatient visits and/or hospitalizations, were considered.

In order to reduce bias, subjects who had a diagnosis of Parkinson's disease before the baseline date were excluded from the study. Similarly, subjects who had a diagnosis of secondary Parkinsonism, major psychiatric diseases, mental retardation, cancer, colorectal adenomas, inflammatory bowel diseases, or Celiac disease before the baseline date and during the follow-up period were also excluded from the study. All disorders were identified with ICD-9 codes (Supplemental Table). Therefore, all the IBS patients had their IBS diagnosis before the diagnosis of Parkinson's disease.

Socio-demographic information, such as age, gender, as well as co-morbidities potentially associated with Parkinson's disease including head injury, hypertension, diabetes mellitus, hyperlipidemia, dementia, cerebrovascular disease, depression, and chronic kidney disease were analyzed. All co-morbidities were determined before the date of diagnosing IBS.

Statistical analysis

Chi square test and t test were used to compare the differences between the IBS and non-IBS groups regarding the baseline demographic status and comorbidities. The incidence of Parkinson's disease was calculated as the number of Parkinson's disease patients identified during the follow-up divided by the total person-years of follow-up for each group. Moreover, multivariable Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95 % confidence interval (CI) to evaluate the association between IBS and risk of Parkinson's disease [17]. All analyses were performed using the SAS software version 9.1 (SAS Institute Inc., Cary, NC), and the statistical significance level was set at two-sided $P < 0.05$.

Results

Baseline characteristics of the study population

Table 1 shows that the study population consisted of approximately 20 % being the elderly and there were more females than males. Head injury, hypertension, diabetes mellitus, hyperlipidemia, dementia, cerebrovascular disease, depression, and chronic kidney disease were more prevalent in the IBS group than in the non-IBS group. The number of outpatient visits and number of hospitalizations per person were also significantly higher in the IBS group than in the non-IBS group.

Incidence of Parkinson's disease stratified by gender, age and follow-up year

Table 2 shows that the overall incidence rate of Parkinson's disease was 1.76-fold higher in the IBS group than in the non-IBS group (16.4 vs. 9.33 per 10,000 person-years), with an adjusted HR of 1.48 (95 % CI 1.27, 1.72). The incidence rates of Parkinson's disease, as stratified by gender, age and follow-up year, were all higher in subjects with IBS than those without IBS. The incidence of Parkinson's disease increased with age in both groups, much greater for the elderly than the younger groups. The risk of developing Parkinson's disease appeared somewhat prompter during the early 2 years of follow-up, with an incidence rate ratio of 2.19 (95 % CI 2.09, 2.29).

Figure 1a shows the overall cumulative incidence of Parkinson's disease was 0.54 % higher in the IBS group than in the non-IBS group ($P < 0.0001$) at the end of 11-year follow-up. The age-specific incidence showed again that the difference between the 2 groups increased sharply with age. The incidence difference was 1.55 % for the elderly ($P < 0.0001$) (Fig. 1d).

Association between Parkinson's disease, IBS, and other comorbidities

The multivariable Cox proportional hazards regression analysis further evaluated the role of age, gender and comorbidity in the association with developing Parkinson's disease for IBS group, compared with the non-IBS group (Table 3). The adjusted hazard had a 10 % increment as the function of age. Female gender, hypertension, dementia, cerebrovascular disease and depression were also significantly associated with Parkinson's disease. The Cox model was also used to evaluate whether the comorbidity interacted with IBS. There was no strong interaction found (data not shown).

Table 1 Baseline data between irritable bowel syndrome group and non-irritable bowel syndrome group

	Irritable bowel syndrome				*P* value
	No		Yes		
	N = 95,500		N = 23,875		
	n	(%)	n	(%)	
Age group (year)					
20–39	28,693	30.05	7,173	30.04	0.99
40–64	47,271	49.50	11,818	49.50	
65–84	19,536	20.46	4,884	20.46	
Mean (SD) (year)[a]	49.27	16.12	49.76	15.92	<0.0001
Gender					
Women	51,372	53.79	12,843	53.79	0.99
Men	44,128	46.21	11,032	46.21	
Follow-up year, mean (SD)[a]	6.22	3.15	6.32	3.12	<0.0001
Mean outpatient visits (SD)[a]	16.4	15.3	30.3	21.2	<0.0001
Mean hospitalizations (SD)[a]	0.18	0.83	0.24	0.76	<0.0001
Baseline comorbidities					
Head injury	3,069	3.21	964	4.04	<0.0001
Hypertension	23,449	24.55	7,631	31.96	<0.0001
Diabetes mellitus	10,201	10.68	3,536	14.81	<0.0001
Hyperlipidemia	10,224	10.71	4,214	17.65	<0.0001
Dementia	397	0.42	152	0.64	<0.0001
Cerebrovascular disease	6,653	6.97	2,533	10.61	<0.0001
Depression	2,189	2.29	1,678	7.03	<0.0001
Chronic kidney disease	1,216	1.27	459	1.92	<0.0001

Chi square test, and [a]*t* test comparing subjects with irritable bowel syndrome and non-irritable bowel syndrome

Discussion

Our data suggest that patients with IBS have 48 % higher hazard of Parkinson's disease than population who are free of IBS. This research is the first study of its kind, with no relevant studies having addressed this association. We demonstrated that the subjects diagnosed with IBS preceded the clinical diagnosis of Parkinson's disease. But, the follow-up duration between the diagnosis of IBS and the onset of Parkinson's disease is less than 10 years. We cannot rule out that IBS actually belongs to early signs of gastrointestinal involvement of Parkinson's disease. It is also possible this is a unique event that coincides with Parkinson's disease. More studies on the temporal relationship are needed.

Previous studies have shown that colonoscopy biopsies can demonstrate the Lewy pathology in the submucosal plexus of the colon in patients with Parkinson's disease

Table 2 Incidence of Parkinson's disease for irritable bowel syndrome group and non-irritable bowel syndrome group

Variables	Irritable bowel syndrome				Incidence rate ratio (95 % CI)	Adjusted HR[a] (95 % CI)
	No		Yes			
	Event	Incidence	Event	Incidence		
All	554	9.33	247	16.4	1.76 (1.68, 1.83)	1.48 (1.27, 1.72)
Gender						
Women	277	8.51	122	14.8	1.74 (1.64, 1.84)	1.45 (1.17, 1.80)
Men	277	10.3	125	18.3	1.77 (1.67, 1.88)	1.51 (1.22, 1.87)
Age group (year)						
20–39	5	0.27	2	0.42	1.56 (1.42, 1.72)	1.14 (0.21, 6.30)
40–64	126	4.21	60	7.94	1.89 (1.78, 2.01)	1.46 (1.06, 2.00)
65–84	423	38.7	185	66.0	1.71 (1.57, 1.85)	1.49 (1.25, 1.78)
Follow-up year						
≤2	136	7.58	75	16.6	2.19 (2.09, 2.29)	1.77 (1.33, 2.36)
>2	418	10.1	172	16.3	1.61 (1.54, 1.69)	1.38 (1.16, 1.66)

Incidence: per 10,000 person-years

Incidence rate ratio: irritable bowel syndrome to non-irritable bowel syndrome (95 % CI)

[a] Cox model adjusted hazard ratio: adjusted for age, gender, head injury, hypertension diabetes mellitus, hyperlipidemia, dementia, cerebrovascular disease, depression, and chronic kidney disease

[18, 19]. This finding partially explains the pathophysiology of gastrointestinal symptoms even prior to the development of motor symptoms of Parkinson's disease. It also provides a valuable evidence that Lewy pathology of the colon can be partially used as a diagnostic clue of Parkinson's disease [20]. Though, to date, no definite biomarker is available to validate Parkinson's disease. Based on the Rome III criteria [2], only after the exclusion of inflammatory, metabolic, anatomic or neoplastic cause, IBS can be diagnosed by clinical features. Furthermore, routine colonoscopy biopsies should be considered for patients with clinically suspected IBS to determine whether Lewy pathology or other lesions can be detected. It has been well-documented that patients with IBS are more likely to suffer from stress and anxiety, this type of examination would improve the quality of life in these patients. Supposing Lewy pathology or other lesions can be detected by colonoscopy biopsies, these patients are not likely misdiagnosed and early treatment efforts can be applied to patients with Parkinson's disease.

We have noted that the association between IBS and the risk of Parkinson's disease is significant and the risk increased with age. There is an excess incidence of 71 % for the elderly IBS cases compared with the elderly without IBS. For the elderly with these GI symptoms, it is necessary to pay attention to the potential of developing Parkinson's disease among them. We performed further data analysis and found 98.95 % of IBS cases had been diagnosed from the outpatient care, with an incidence of 16.0 per 10,000 person-years for Parkinson's disease. On the other hand, the incidence of Parkinson's disease was 48.8 per 10,000 person-years in IBS cases diagnosed from inpatients. Inpatients could be more serious and at higher risk of Parkinson's disease.

Some limitations exist in this database. First, IBS diagnosis requires multiple criteria and involves ruling out diseases or IBS-like symptoms. A screening colonoscopy is recommended. Among patients with IBS, only 6,536 (27.38 %) of cases had undergone colonoscopy in this study. We could not obtain the information on colonoscopic findings in patients with suspected IBS from the insurance claims data if they have not undergone colonoscopy. Therefore, it could lead to misclassification of IBS with other gastro-intestinal symptoms including but not limited to constipation, gastroparesis, and other non-syndromic symptoms. We rely on physicians' ability to make a correct IBS diagnosis. The IBS diagnosis based on ICD-9 codes has been validated in a previous study on the risk erectile dysfunction in men with IBS using the same database [21]. The misclassification could also happen for Parkinson's disease to a lesser extent due to the same limitation. Second, other non-motor symptoms of Parkinson's disease might not be clearly documented in this database. Therefore, we were unable to clarify the temporal association between the occurrence of IBS and the onset of other non-motor symptoms. Third, the information on body mass index, alcohol drinking and cigarette smoking were not available from the insurance claims data. Although we tried to define obesity, alcoholism and tobacco use by ICD-9 codes, the sizes of subjects were too small to determine

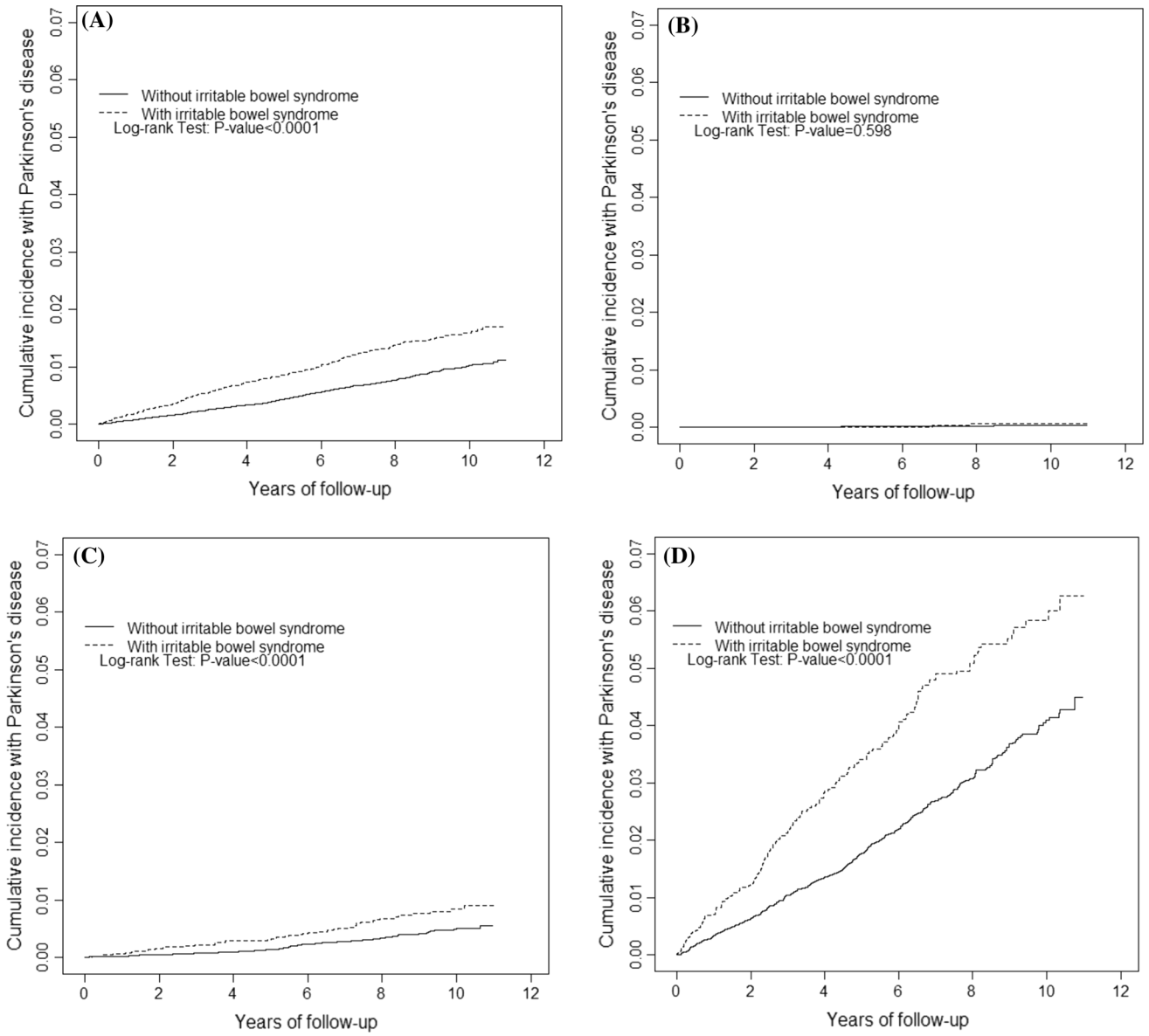

Fig. 1 Cummulative incidence of Parkinson's disease by age group for subjects with and without irritable bowel syndrome. **a** Overall, **b** 20–39 years, **c** 40–64 years and **d** 65–84 years

a clinical significance (data not shown). Last, the number of outpatient visits and number of hospitalizations per person were higher in the IBS group than in the non-IBS group, with statistic significance. Thus, medical surveillance bias should be considered. That is, IBS patients might tend to notice their body changes and could have higher probability to get a diagnosis with Parkinson's disease in the clinical practice. Despite the mutual mechanism between IBS and Parkinson's disease is still unknown and it is not easy to draw any causal link so far, therefore, one has to be careful when interpreting the results.

However, the strength of the present study is using a large number of population and it is dealing with an important issue of general concern for medicine and public health. In order to reduce bias, subjects with a diagnosis of Parkinson's disease before the date of diagnosing IBS were excluded from the study. Therefore, all the IBS patients were diagnosed before the diagnosis of Parkinson's disease. To increase the diagnosing accuracy, only those who had received medical care for IBS and Parkinson's disease for at least three times, including outpatient visits and/or hospitalizations, were included in this study. Hence, the statistical analysis is relevant and strengthens the study.

This present study suggests that patients with irritable bowel syndrome are at an increased risk of developing Parkinson's disease in Taiwan. Further studies are required

Table 3 Cox model measured hazard ratio and 95 % confidence intervals of Parkinson's disease associated with irritable bowel syndrome and comorbidities

Variable	Crude HR (95 % CI)	Adjusted[a] HR (95 % CI)
Irritable bowel syndrome	1.75 (1.51, 2.04)	1.48 (1.27, 1.72)
Age (per 1 year)	1.11 (1.11, 1.12)	1.10 (1.09, 1.10)
Gender (women vs. men)	1.23 (1.07, 1.41)	1.17 (1.02, 1.35)
Baseline comorbidities (yes vs. no)		
Head injury	1.95 (1.42, 2.67)	1.12 (0.81, 1.53)
Hypertension	7.09 (6.10, 8.23)	1.49 (1.26, 1.78)
Diabetes mellitus	3.34 (2.86, 3.90)	1.11 (0.94, 1.31)
Hyperlipidemia	2.70 (2.29, 3.18)	1.11 (0.93, 1.33)
Dementia	16.0 (11.3, 22.7)	2.24 (1.56, 3.22)
Cerebrovascular disease	7.95 (6.88, 9.18)	1.93 (1.64, 2.26)
Depression	2.95 (2.27, 3.83)	1.43 (1.10, 1.88)
Chronic kidney disease	2.86 (1.89, 4.32)	0.81 (0.53, 1.22)

[a] Adjusted hazard ratio: adjusted for age, gender, head injury, hypertension, diabetes mellitus, hyperlipidemia, dementia, cerebrovascular disease, depression and chronic kidney disease

to explore the pathophysiological connection between these disorders and to investigate whether an early intervention to irritable bowel syndrome could alter the natural course of Parkinson's disease.

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Conflict of interest The authors disclose no conflicts of interest.

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