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Alcohol Use Disorder Increases the Risk of Irritable Bowel Disease

A Nationwide Retrospective Cohort Study

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Abstract: Alcohol use disorder (AUD) is considered a possible risk factor for irritable bowel syndrome (IBS); however, previous studies investigating the association between AUD and IBS have yielded inconsistent results. The study investigated whether AUD increases the risk of IBS by using a population-based database in Taiwan.

This retrospective matched-cohort study included the health insurance claims data of 56,355 AUD inpatients and 225,420 randomly selected controls by frequency-matched for sex, age, and index year. Cox proportional hazards regression analysis was performed to measure the risk of IBS among AUD patients compared with non-AUD patients.

During the follow-up period, the incidence rate ratio (IRR) of IBS had 12.3-fold (95% CI: 11.9–12.7) in the AUD patients than non-AUD patients and the adjusted hazard ratio (aHR) for IBS in the AUD patients was 5.51 (95% CI: 4.36–6.96). For several comorbidities, the risk of IBS was significantly higher in the AUD patients than in non-AUD patients, with aHRs of 2.14 (95% confidence interval [CI]: 1.19–3.84), 2.05 (95% CI: 1.06–3.96), and 2.91 (95% CI: 1.26–6.72) for sleep disorders, acute pancreatitis, and hepatitis B, respectively. When we stratified the severity of AUD according to the length of hospital stay, the aHRs exhibited a significant correlation ($P < 0.001$) with severity, yielding aHRs of 3.24 (95% CI: 2.49–4.22), 11.9 (95% CI: 8.96–15.9), and 26.1 (95% CI: 19.4–35.2) for mild, moderate, and severe AUD, respectively.

The risk of IBS was higher among AUD patients, and increased with the length of hospital stay.

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Abbreviations: aHR = adjusted hazard ratio, AUD = alcohol use disorder, CI = confidence interval, GI = gastrointestinal, IBS = irritable bowel syndrome, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, NHIRD = National Health Insurance Research Database, SD = standard deviation.

INTRODUCTION

Irritable bowel syndrome (IBS) is a worldwide public health problem. Although IBS is not life-threatening, it is one of the most diagnosed gastrointestinal (GI) disorders, with prevalence rates between 7% and 21% in the general population.[1] Annually, IBS is estimated to cost the United States an average of US$1.35 billion in direct medical expenses, and US$205 million more in indirect costs.[2] No consensus regarding the pathophysiology of IBS exists, because numerous factors, such as visceral hypersensitivity,[3] psychological disorders,[4] infections,[5] and food allergies,[6] are considered possible causes.

Alcohol use disorder (AUD) is also a severe public health problem. Approximately 3.8% of all global deaths and 4.6% of global disability-adjusted life-years are attributed to alcohol.[7] According to recent reports, AUD has a lifetime prevalence of about 30%[8] and increasing rates according to the new diagnostic criteria.[9] Alcohol causes a substantial number of physical and psychiatric disorders. In the digestive system, alcohol causes adverse effects such as gastritis, hepatitis, cirrhosis, and pancreatitis.[10] However, the association between AUD and IBS remains unclear. Previous studies examining AUD and IBS have yielded conflicting results; some reported that alcohol consumption is more prevalent in patients with IBS, whereas others observed no such association.[11–16]

Elucidating the possible association between AUD and IBS would aid in preventing and treating IBS. Therefore, we conducted a retrospective matched-cohort study to determine whether patients with AUD are at an increased risk of developing IBS and whether other comorbidities increase this risk.

MATERIALS AND METHODS

Study Design

By using the health insurance claims data from the National Health Insurance Research Database (NHIRD) of Taiwan, we conducted a nationwide retrospective matched-cohort study. This database was established in 1995 upon the launch of the National Health Insurance program. The National Health Insurance covers approximately 99.9% of Taiwan's population. The National Health Research Institutes manages various insurance databases, including the registration files of insurees and claims data for reimbursement. Our data source was NHIRD inpatient claims data from 1996 to 2011. Diseases were diagnosed according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Before release for research, the personal identification numbers in the database are encrypted to protect patient privacy. The Institutional Review Board of China Medical University approved this study (CMU-REC-101-012).

Data Availability Statement

All data and related metadata were deposited in an appropriate public repository. The data on the study population that were obtained from the NHIRD (http://w3.nhri.org.tw/nhird//date_01.html) are maintained in the NHIRD (http://nhird.nhri.org.tw/). The NHRI is a nonprofit foundation established by the government.

Study Population

Investigating the association between AUD and IBS was the study objective. A cohort of patients newly diagnosed with AUD (ICD-9-CM: 303, 3050, and V113) from 2000 to 2009 (N = 56,355) was established and compared with a cohort of non-AUD patients. The index date was defined as the date of AUD diagnosis. For selecting controls, inpatient claims data and a 1:4 ratio of AUD-to-comparison patients were used, and 225,420 non-AUD patients were selected and frequency-matched by sex, age, and index year. The main outcome was IBS (ICD-9-CM: 5641). Patients with IBS diagnosis before the index date or missing sex or age information were excluded. Follow-up was terminated after an IBS event or on December 31, 2011 (the end of the evaluation period). During the study period, the data of patients with comorbidities before the end date were estimated after adjustment for hypertension (ICD-9-CM: 401-405), hyperlipidemia (ICD-9-CM: 272), diabetes (ICD-9-CM: 250), depression (ICD-9-CM: 2962, 2963, 29682, 3004, and 311), anxiety (ICD-9-CM: 30000), fibromyalgia (ICD-9-CM: 7291), sleep disorder (ICD-9-CM: 3074 and 7805), acute pancreatitis (ICD-9-CM: 5770), cirrhosis (ICD-9-CM: 5712, 5715, and 5716), hepatitis B (ICD-9-CM: V0261, 07020, 07022, 07030, and 07032), and hepatitis C (ICD-9-CM: V0262, 07041, 07044, 07051, and 07054).

Statistical Analysis

For comparing differences in the distributions of demographic variables and comorbidities between the AUD and non-AUD patient groups, Chi-square and Student *t*-tests were used for the categorical and continuous variables, respectively. The IBS incidence rate was calculated for both groups. The Kaplan–Meier method was then used for estimating the event survival functions for IBS between the AUD and non-AUD patient groups during the follow-up period, and the log-rank test was used for assessing the differences between both curves. The incidence rate ratios and 95% confidence intervals (CIs) of IBS between the AUD and non-AUD patient groups were calculated using the Poisson regression model. The Cox proportional hazards regression model was used for measuring the risk of IBS in the AUD patients compared with the non-AUD patients and presented using adjusted hazard ratios (aHRs) and 95% CIs. We presented the aHR of IBS between AUD and non-AUD groups stratified by sex (women/men), age, and different comorbidity types (yes/no) by Cox proportional hazards regression model too. The mean of age was chosen as an age stratified analysis cut-point and then presented the relative risk of IBS between both groups in <45 years old and >45 years old. We further examined the association between the severity of AUD and IBS according to severity, which was defined as the total length of hospital stay caused by AUD in the follow-up period to the length of follow-up period. The AUD severity was classified by the tertile method, including mild (the 1st tertile in the AUD severity, T1), moderate (the 2nd tertile in the AUD severity, T2), and severe (the 3rd tertile in the AUD severity, T3).

All statistical analyses were performed using the SAS statistical package, version 9.4 (SAS Institute Inc., NC). A 2-tailed *P* value of <0.05 was considered significant. Survival curves were graphed using R program (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Table 1 presents the demographic and comorbidity data of the AUD and non-AUD patient groups. Age and sex did not differ significantly between the groups. Most of the patients were aged 35 to 65 years (69.9%) and were male (90.1%). After the frequency-matched, the mean of age was similar in AUD (44.5; standard deviation [SD]: 12.5) and non-AUD (44.4; SD: 12.6) group (Student's *t*-test *P*-value = 0.49). The proportion of patients with comorbidities was higher in the AUD patient group than in the non-AUD patient group (*P* < 0.0001, Chi-square test). The mean of follow-up were presented 5.53 and 6.84 in AUD (SD: 3.26) and non-AUD (SD: 2.98) groups, respectively. Toward the end of the follow-up period, the cumulative incidence of IBS was higher in the AUD patient group than in the non-AUD patient group (log-rank test *P* < 0.0001; Fig. 1).

The incidence of IBS in the AUD patient group was 11.5 per 10,000 person-years, which was nearly 12.3-fold (95% CI: 11.9–12.7) higher than that in the non-AUD patient group (0.93 per 10,000 person-years; Table 2). After adjustment for potential risk factors, the AUD patient group exhibited a 5.51-fold (95% CI: 4.36–6.96) higher risk of developing IBS than the non-AUD patient group did.

The incidence rates and aHRs of IBS were stratified according to sex, age (<45 and ≥45 years), and comorbidity (no or yes). The risk of IBS was higher in the AUD patients than in the non-AUD patients, regardless of sex (females, aHR: 4.32, 95% CI: 1.97–9.50; males, aHR: 5.52, 95% CI: 4.31–7.06). After adjustment for sex and each comorbidity, the AUD patients aged <45 years exhibited a 12.5-fold (95% CI: 8.74–17.8) higher risk of developing IBS than the non-AUD patients did. The incidence of IBS was increased in subjects with comorbidities. The aHR of IBS in the AUD patient group was 2.75-fold (95% CI: 2.10–3.61) higher than that in the non-AUD patient group.

Table 3 presents the risk of IBS of both groups stratified according to comorbidities. For several comorbidities, the AUD

TABLE 1. Comparison of Demographics and History of Comorbidity Between AUD and Non-AUD Groups

| | AUD | | | | |
| | No (N = 225,420) | | Yes (N = 56,355) | | |
	N	%	N	%	*P*-Value
Sex					0.99
Women	22,212	9.85	5553	9.85	
Men	203,208	90.1	50,802	90.1	
Age, year					0.99
<35	52,036	23.1	13,009	23.1	
35–65	157,676	69.9	39,419	69.9	
≥65	15,708	6.97	3927	6.97	
Mean (SD)*	44.4 (12.6)		44.5 (12.5)		0.49
Comorbidity					
Hypertension	3255	1.44	1236	2.19	<0.0001
Hyperlipidemia	3066	1.36	986	1.75	<0.0001
Diabetes	1987	0.88	941	1.67	<0.0001
Depression	1672	0.74	10,102	17.9	<0.0001
Anxiety	752	0.33	1783	3.16	<0.0001
Fibromyalgia	722	0.32	1501	2.66	<0.0001
Sleep disorder	2547	1.13	6246	11.1	<0.0001
Acute pancreatitis	2038	0.90	13,073	23.2	<0.0001
Cirrhosis	3610	1.60	17,057	30.3	<0.0001
Hepatitis B	4195	1.86	6286	11.2	<0.0001
Hepatitis C	2128	0.94	4288	7.61	<0.0001
Mean of follow-up years (SD)	6.84 (2.98)		5.53 (3.26)		<0.0001

AUD = alcohol use disorder, SD = standard deviation, Chi-square test.

* Student's *t*-test.
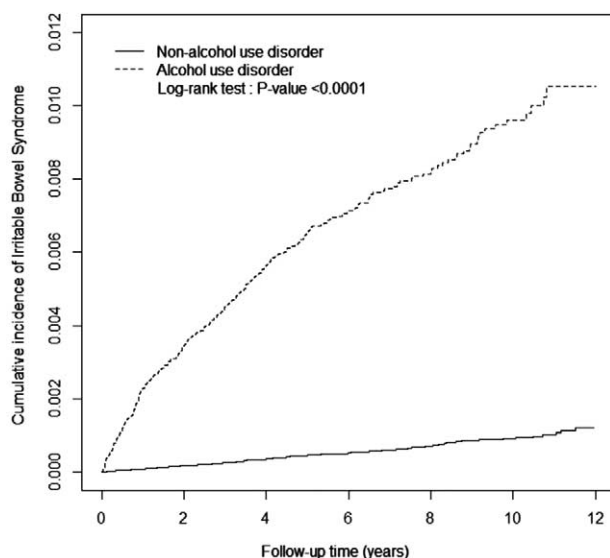
FIGURE 1. Cumulative incidence of irritable bowel syndrome between the alcohol use disorder (dashed line) and comparison (solid line) patient groups.

patients had a significantly higher risk of IBS than the non-AUD patients did, specifically for sleep disorder (aHR: 2.14, 95% CI: 1.19–3.84), acute pancreatitis (aHR: 2.05, 95% CI: 1.06–3.96), and hepatitis B (aHR: 2.91, 95% CI: 1.26–6.72).

Compared with the non-AUD patient group, an increased risk of IBS stratified according to AUD severity was observed, with aHRs of 3.24 (95% CI: 2.49–4.22), 11.9 (95% CI: 8.96–15.9), and 26.1 (95% CI: 19.4–35.2) for mild, moderate, and severe AUD, respectively (Table 4).

DISCUSSION

Previous studies investigating the association between IBS and AUD have yielded conflicting results. Masand et al[11] reported that IBS was more prevalent among patients with AUD than among controls in a general physician's clinic for other medical illnesses (41.9% vs 2.5%, respectively). However, this study had a small sample size (71 patients) and did not consider other possible risk factors that may influence AUD and IBS development.

A study in Japan analyzed 2717 completed self-report questionnaires and revealed that alcohol consumption was only associated with diarrhea-predominant IBS (adjusted odds ratio [OR]: 2.15, 95% CI: 1.40–3.31),[12] and another nationally representative study of 98,411 Japanese adolescents reported an association between AUD and IBS (adjusted OR: 1.21, 95% CI: 1.17–1.26).[13] Similarly, a study involving 340 Chinese nurses indicated that alcohol consumption is a risk factor for IBS (OR: 2.611, 95% CI: 1.25–5.43).[14]

By contrast, a questionnaire study of 3022 participants in the United States[15] and an unmatched case–control study involving 316 patients in Iran[16] both observed no association between AUD and IBS. The researchers ascribed their conflicting results to the study design, diagnostic criteria, cultural differences, environmental factors, and sample size of their and the previous studies.

Halder et al[17] reported that alcohol consumption (>7 drinks per week) was associated with increased odds of dyspepsia (OR: 2.3; 95% CI: 1.1–5.0) and frequent abdominal pain (OR: 1.5; 95% CI: 1.1–2.0) but not IBS. However, in females with a low somatic symptom checklist score, excessive alcohol consumption (≥7 drinks per week) increased the odds of IBS more than moderate alcohol consumption did. Reding et al[18] demonstrated that for IBS patients, the strongest related associations were between binge drinking and GI symptoms the following day. The authors suggested that different drinking patterns may partly explain the inconsistent findings between AUD and IBS symptoms. In summary, most of the aforementioned studies have agreed that people with AUD, particularly binge or heavy drinkers, have a higher risk of IBS than non-AUD people do, which is consistent with our results. In this study, the aHRs of IBS also increased with the severity of AUD. When the patients with AUD were stratified into tertiles as mild, moderate, or severe AUD according to their length of hospital stay, the incidence rates of IBS per 10,000 person-years were 5.12, 23.4, and 52.0, respectively, with aHRs of 3.24, 11.9, and 26.1, respectively (Table 4).

Compared with previous study results, our results showed a higher risk of IBS in the AUD patients than in the non-AUD patients. Unlike the questionnaire methods used in previous studies, we analyzed inpatient claims data from a national database and conducted a 10-year follow-up. Self-reports of alcohol consumption in questionnaire studies often have inaccuracies because patients frequently underestimate their alcohol

TABLE 2. Incidence and Adjusted Hazard Ratio of Irritable Bowel Syndrome Stratified by Sex, Age, and Comorbidity (Yes/No) Between 2 Groups

| | Alcohol Use Disorder (AUD) | | | | | | Compared to Non-AUD Group | |
| | No | | | Yes | | | | |
Variables	Event	PY	Rate	Event	PY	Rate	IRR (95% CI)	Adjusted HR[†](95% CI)
Overall	144	154,2097	0.93	357	311,439	11.5	12.3(11.9–12.7)***	5.51(4.36–6.96)***
Sex								
Women	14	150,491	0.93	40	33,125	12.1	13.0(11.7–14.4)***	4.32(1.97–9.50)***
Men	130	1,391,606	0.93	317	278,314	11.4	12.2(11.8–12.6)***	5.52(4.31–7.06)***
Age, year								
<45	46	882,410	0.52	257	185,219	13.9	26.6(25.3–28.0)***	12.5(8.74–17.8)***
≥45	98	659,686	1.49	100	126,220	7.92	5.33(5.11–5.57)***	2.23(1.57–3.19)***
Comorbidity								
No	78	1,422,935	0.55	42	121,786	3.45	6.29(6.07–6.52)***	6.10(4.19–8.89)***
Yes	66	119,162	5.54	315	189,652	16.6	3.00(2.77–3.24)***	2.75(2.10–3.61)***

***$P < 0.001$. AUD = alcohol use disorder, IRR = incidence rate ratio, PY = person-year, Rate = incidence rate (per 10,000 person-years).
† Multiple analysis including age, sex, and comorbidities.

TABLE 3. Incidence and Adjusted Hazard Ratio of Irritable Bowel Syndrome Stratified by Comorbidity Between AUD and Non-AUD Groups

| | Alcohol Use Disorder (AUD) | | | | | | Compared to Non-AUD Group | |
| | No | | | Yes | | | | |
Variables	Event	PY	Rate	Event	PY	Rate	IRR (95% CI)	Adjusted HR[†] (95% CI)
Hypertension								
No	141	1,518,770	0.93	351	304,173	11.5	12.4(12.1–12.8)***	5.59(4.41–7.07)***
Yes	3	23,327	1.29	6	7265	8.26	6.42(5.05–8.17)***	2.66(0.46–15.4)
Hyperlipidemia								
No	142	1,519,848	0.93	346	305,493	11.3	12.1(11.8–12.5)***	5.52(4.36–6.98)***
Yes	2	22,249	0.90	11	5946	18.5	20.6(15.4–27.6)***	5.45(0.84–35.3)
Diabetes								
No	142	1,527,899	0.93	351	306,035	11.5	12.3(12.0–12.7)***	5.54(4.38–7.00)***
Yes	2	14,197	1.41	6	5403	11.1	7.88(5.83–10.7)***	3.44(0.45–26.3)
Depression								
No	123	1,530,978	0.80	241	251,161	9.60	11.9(11.6–12.3)***	5.44(4.18–7.09)***
Yes	21	11,119	18.9	116	60,278	19.2	1.02(0.86–1.21)	0.89(0.54–1.48)
Anxiety								
No	133	1,537,006	0.87	306	300,502	10.2	11.8(11.4–12.1)***	5.54(4.33–7.08)***
Yes	11	5090	21.6	51	10,937	46.6	2.16(1.57–2.97)***	1.76(0.83–3.75)
Fibromyalgia								
No	141	1,537,097	0.92	338	301,854	11.2	12.2(11.8–12.6)***	5.51(4.34–6.98)***
Yes	3	5000	6.00	19	9585	19.8	3.30(2.21–4.94)***	2.13(0.55–8.33)
Sleep disorder								
No	128	1,524,738	0.84	248	274,416	9.04	10.8(10.5–11.1)***	5.11(3.94–6.63)***
Yes	16	17,358	9.22	109	37,023	29.4	3.19(2.60–3.92)***	2.14(1.19–3.84)**
Acute pancreatitis								
No	134	1,528,381	0.88	202	237,651	8.50	9.69(9.41–9.99)***	4.38(3.35–5.73)***
Yes	10	13,716	7.29	155	73,787	21.0	2.88(2.30–3.61)***	2.05(1.06–3.96)*
Cirrhosis								
No	127	1,520,778	0.84	220	232,029	9.48	11.4(11.0–11.7)***	4.60(3.51–6.03)***
Yes	17	21,318	7.97	137	79,410	17.3	2.16(1.86–2.52)***	1.39(0.81–2.37)
Hepatitis B								
No	136	1514,,710	0.90	309	280,114	11.0	12.3(11.9–12.7)***	5.40(4.23–6.90)***
Yes	8	27,387	2.92	48	31,324	15.3	5.25(4.34–6.34)***	2.91(1.26–6.72)*
Hepatitis C								
No	137	1,528,080	0.90	321	289,143	11.1	12.4(12.0–12.8)***	5.49(4.31–6.99)***
Yes	7	14,017	4.99	36	22,296	16.2	3.23(2.56–4.08)***	1.98(0.78–5.01)

*$P < 0.5$, **$P < 0.01$, ***$P < 0.001$. AUD = alcohol use disorder, IRR = incidence rate ratio, PY = person-year, rate = incidence rate (per 10,000 person-years).
† Multiple analysis including age, sex, and comorbidities.

TABLE 4. Incidence Rate and Hazard Ratio for Irritable Bowel Syndrome Stratified by Severity of AUD

Severity of AUD	Event	Rate	Adjusted HR[†] (95% CI)
Non-AUD group	144	0.93	1.00
AUD group			
Mild (T_1)	122	5.12	3.24(2.49–4.22)[***]
Moderate (T_2)	120	23.4	11.9(8.96–15.9)[***]
Severe (T_3)	115	52.0	26.1(19.4–35.2)[***]
P for trend			<0.0001

[***]$P < 0.001$. AUD = alcohol use disorder, CI = confidence interval, HR = hazard ratio, rate = incidence rate, per 10,000 person-years, T_1 = first tertile, T_2 = second tertile, T_3 = third tertile.

[†] Severity of alcoholism = (total length of hospital stay due to alcohol use disorder during the follow-up duration) (length of follow-up duration). Adjusted for age, sex, and comorbidities.

intake.[17] Moreover, previous studies have included participants with AUD mainly from outpatient clinics, community centers, and schools, whereas we included inpatient participants with AUD; therefore, our patient group experienced more severe IBS. This finding may explain our markedly higher HR results.

The association between AUD and IBS may be of psychiatric origin. Several psychiatric disorders, such as anxiety and sleep disorder, and related somatic symptoms are independent risk factors for IBS development.[19] Patients with AUD have a high risk to envelope mood disorders and anxiety disorders that are risk factors for IBS. And also anxious patients often use alcohol like therapy.[20] The role of stress and psychosocial dysfunction in IBS is associated with alterations in central corticotropin-releasing factor (CRF) signaling pathways.[21] Many studies have indicated that the CRF system is influenced by alcohol addiction, as is IBS.[22,23] Furthermore, in animal experiments, some CRF antagonists have exhibited therapeutic effects on both IBS and AUD.[24–26] Recently, in human studies, pexacerfont, a CRF antagonist, has been demonstrated to be effective for both IBS[27] and AUD.[28] This evidence indicated that IBS and AUD have the same central neuropsychiatric dysfunction.

Aside from the possible central cause of CRF pathway dysfunction, alcohol itself may also directly influence IBS development. The alcohol metabolism process affects the bloodstream, motility, and digestive functions of the GI tract.[29] In addition, alcohol exerts a toxic effect on autonomic nerves,[30] and a subgroup of IBS patients showed various autonomic abnormalities.[31] Thus, AUD may trigger or aggravate IBS.

It has been reported that incidence of IBS ranged between 2 per 1000 person-years and 67 per 1000 person-years with female predominance.[32] However, IBS incidence rates in our study is significantly lower (11.5 and 0.93 per 10,000 person years in the AUD and comparison groups, respectively). This may be because that our cohort is not the same with normal population in sex and age, even the comparison group is a 4-folds of AUD patients selected and frequency-matched by sex, age, and index year. AUD is a male predominant disorder as our data revealed (male 90.1%) and therefore the 2 groups both contained a majority of male subjects who are less susceptible to IBS in the follow-up period. Besides, 50% of patients with IBS report having first had symptoms before the age of 35 years,[33] and prevalence is 25% lower in those aged over 50 years than in

those who are younger,[34] while the mean age in our cohorts is older than normal population (44.5 and 44.4 years in AUD and comparison groups, respectively). The median age of general population in Taiwan in 2015 is 39.7 years).[35] These disparities of sex ratio and age may explain the lower incidence rates of IBS in our study.

This study had several limitations. First, the NHIRD does not include patients' personal histories, including smoking, diet, occupational exposure, and family disease information. Second, accurate diagnosis depends on ICD-9 coding by the treating physician in this study. However, NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single-buyer, the government in Taiwan. All insurance claims should be scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria in the study. If these doctors or hospitals make wrong diagnoses or coding, they will be punished with a lot of penalties. Therefore, the diagnoses of the diseases based on ICD-9 codes in this study were highly reliable. Finally, data on alcohol consumption frequency per week and IBS subtypes were not available.

In conclusion, by analyzing nationwide health insurance data, we demonstrated that AUD increased the risk of IBS. After adjustment for age, sex, and comorbidities, AUD was associated with a 5.51-fold increased risk of IBS. The risk increased with the length of hospital stay for AUD. CRF pathway dysfunction is likely the common pathophysiology in IBS and AUD, which itself may also trigger IBS by directly affecting the GI tract and autonomic nerves.

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