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Chronic Pancreatitis Correlates With Increased Risk of Cerebrovascular Disease

A Retrospective Population-Based Cohort Study in Taiwan

Tuck-Siu Wong, MD, Kuan-Fu Liao, MD, MS, Chi-Ming Lin, MD, Cheng-Li Lin, MS, Wen-Chi Chen, MD, PhD, and Shih-Wei Lai, MD

Abstract: The aim of this study is to explore whether there is a relationship between chronic pancreatitis and cerebrovascular disease in Taiwan.

Using the claims data of the Taiwan National Health Insurance Program, we identified 16,672 subjects aged 20 to 84 years with a new diagnosis of chronic pancreatitis from 2000 to 2010 as the chronic pancreatitis group. We randomly selected 65,877 subjects aged 20 to 84 years without chronic pancreatitis as the nonchronic pancreatitis group. Both groups were matched by sex, age, comorbidities, and the index year of diagnosing chronic pancreatitis. The incidence of cerebrovascular disease at the end of 2011 was measured. The multivariable Cox proportional hazards regression model was used to measure the hazard ratio (HR) and 95% confidence interval (CI) for cerebrovascular disease risk associated with chronic pancreatitis and other comorbidities.

The overall incidence of cerebrovascular disease was 1.24-fold greater in the chronic pancreatitis group than that in the nonchronic pancreatitis group (14.2 vs. 11.5 per 1000 person-years, 95% CI = 1.19–1.30). After controlling for confounding factors, the adjusted HR of cerebrovascular

disease was 1.27 (95% CI = 1.19–1.36) for the chronic pancreatitis group as compared with the nonchronic pancreatitis group. Woman (adjusted HR = 1.41, 95% CI = 1.31–1.51), age (every 1 year, HR = 1.04, 95% CI = 1.04–1.05), atrial fibrillation (adjusted HR = 1.23, 95% CI = 1.02–1.48), chronic kidney disease (adjusted HR = 1.48, 95% CI = 1.31–1.67), chronic obstructive pulmonary disease (adjusted HR = 1.27, 95% CI = 1.16–1.40), diabetes mellitus (adjusted HR = 1.82, 95% CI = 1.72–1.92), hypertension (adjusted HR = 1.66, 95% CI = 1.56–1.76), and peripheral atherosclerosis (adjusted HR = 1.26, 95% CI = 1.06–1.51) were other factors significantly associated with cerebrovascular disease.

Chronic pancreatitis is associated with increased hazard of subsequent cerebrovascular disease.

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Abbreviation: ICD-9 code = International Classification of Diseases, 9th Revision, Clinical Modification.

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From the Department of Internal Medicine, Taichung Tzu Chi General Hospital, Taichung (T-SW, K-FL, C-ML); College of Medicine, Tzu Chi University, Hualien (K-FL); Graduate Institute of Integrated Medicine (K-FL, W-CC); College of Medicine, China Medical University (C-LL, S-WL); Management Office for Health Data (C-LL); Department of Urology (W-CC); and Department of Family Medicine, China Medical University Hospital (S-WL), Taichung, Taiwan.

Correspondence: Shih-Wei Lai, Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan (e-mail: wei@mail.cmuh.org.tw).

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INTRODUCTION

Chronic pancreatitis can be a serious disease with severe morbidity and mortality. In the French study of Levy et al, the prevalence of chronic pancreatitis is ~265/1,000,000 with a crude annual incidence of 7.7/100,000.¹ The incidence varies worldwide depending on the populations studied, but there is an increased incidence in the past decades.² Apart from the progressive inflammation and fibrotic destruction of the pancreatic secretory parenchyma that would cause complications and mortality, chronic pancreatitis has also been reported to be highly associated with pancreatic malignancies.³ Other studies have shown that patients with chronic pancreatitis would also possess a higher risk of developing diabetes mellitus.⁴ Because pancreas serves both endocrine and exocrine function, chronic pancreatitis would cause both endocrine and exocrine pancreatic insufficiency.⁵ The consequences of chronic pancreatitis may not only be localized to the pancreas or restricted to the gastrointestinal tract but would also be systemic. However, its correlations with cerebrovascular disease has not yet been mentioned.

Cerebrovascular disease is a worldwide public health problem associated with severe morbidity and mortality. In fact, cerebrovascular disease is the second most common cause of mortality and the third most common cause of disability worldwide.⁶ In recent decades, the overall rate of cerebrovascular disease-related mortality has decreased, but the absolute number of people with stroke, stroke survivors, cerebrovascular disease-related deaths, and the global burden of cerebrovascular disease-related disability is increasing.⁷ Previous studies have identified some nonmodifiable and modifiable risk factors of cerebrovascular disease. Diabetes mellitus is one of these.⁸ Atherosclerosis is one of the known direct causes of cerebrovascular disease.⁹

Previous studies have documented that chronic inflammation of the pancreas would cause irreversible parenchymal damage and functional impairment by destruction of the islet alpha, beta, and gamma cells combined with pre-existing risk factors for type 2 diabetes mellitus. This forms over 85% of pancreatogenic diabetes or type 3c diabetes, which often presents as a significantly larger swing in blood glucose that is more difficult to control.¹⁰ Sugar consumption is a controllable risk factor for both diabetes and cerebrovascular disease. Besides, there were previous studies which proposed that chronic inflammation is associated with accelerated atherosclerosis.¹¹ Thus, we hypothesize that chronic pancreatitis can be linked to subsequent cerebrovascular disease based on the above-mentioned epidemiological evidence, sugar control, and chronic inflammation theory. If chronic pancreatitis substantially correlated with an increased risk of developing cerebrovascular disease, interventions could be performed to reduce the risk of cerebrovascular disease for patients with chronic pancreatitis including more intense sugar control, controlling intensity of inflammation, and treating other related comorbidities. Knowledge of the association between chronic pancreatitis and subsequent cerebrovascular disease would be helpful in developing more comprehensive ways to treat patients with chronic pancreatitis. Therefore, we conducted a retrospective cohort study to explore whether patients with chronic pancreatitis have an increased risk of developing subsequent cerebrovascular disease and whether the risk associated with chronic pancreatitis is enhanced by other comorbidities.

MATERIALS AND METHODS

Data Sources

This retrospective nationwide cohort study analyzed the reimbursement claim data of the Taiwan National Health Insurance Program. This program was implemented in Taiwan in March 1995 and represents almost 99% of the 23 million Taiwan residents.¹² The details of the program can be found in previous high-quality studies.^{13–19} The study was approved by the Institutional Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2–115).

Study Participants

Using the inpatient claim dataset of the Taiwan National Health Insurance Program, we selected all of the hospitalized subjects aged 20 to 84 years with new discharge diagnosis of chronic pancreatitis (ICD-9 code 577.1) from 2000 to 2010 as the chronic pancreatitis group, based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 code). The date of diagnosing chronic pancreatitis was defined as the index date. We randomly selected subjects aged 20 to 84 years without chronic pancreatitis from the same dataset as the nonchronic pancreatitis group. Both groups were matched by sex, age (every 5-year span), comorbidities, and the index year of diagnosing chronic pancreatitis. In both groups, subjects who had the diagnosis of cerebrovascular disease (ICD-9 codes 430–438) or pancreatic cancer (ICD-9 code 157) at baseline were excluded.

Main Outcome Measurement

All of the study subjects were followed from the index date to the date of discharge diagnosis with cerebrovascular disease or to the end of 2011. Cerebrovascular disease was divided into

three categories, including ischemic type, hemorrhagic type, and other types.

Comorbidities Potentially Related to Cerebrovascular Disease

Some risk factors of cerebrovascular disease, such as alcohol consumption, tobacco use, and obesity, were not recorded in this database owing to the inherent limitation. We included alcohol-related disease instead of alcohol consumption, tobacco use-related disease such as chronic obstructive pulmonary disease instead of tobacco use, and obesity-related diseases such as hypertension, diabetes mellitus, and peripheral atherosclerosis instead of obesity. These points have been addressed in previous studies.^{20,21} Comorbidities before the index date which could be potentially related to cerebrovascular disease were included as follows: alcohol-related disease (ICD-9 codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0–571.3, 790.3 and V11.3), atrial fibrillation (ICD-9 code 427.31), cancer (ICD-9 codes 140–208), chronic kidney disease (ICD-9 codes 585–586 and 588.8–588.9), chronic obstructive pulmonary disease (ICD-9 codes 491, 492, 493, and 496), coronary artery disease (ICD-9 codes 410–414), diabetes mellitus (ICD-9 code 250), heart failure (ICD-9 code 428), hyperlipidemia (ICD-9 codes 272.0, 272.1, 272.2, 272.3, and 272.4), hypertension (ICD-9 codes 401–405), and peripheral atherosclerosis (ICD-9 codes 440–448).

Statistical Analysis

The distributions of sex, age, and comorbidities were compared between the chronic pancreatitis group and nonchronic pancreatitis group using the chi-square test for categorized variables and the *t*-test for continuous variables. The incidence of cerebrovascular disease was measured as the number of cerebrovascular disease events identified during the follow-up period divided by the total follow-up person-years for each group. The sex-, age-, and follow-up period-specific incidence rates of cerebrovascular disease were measured. The incidence rates stratified by subtypes of cerebrovascular disease were also measured. Initially, we included all variables in the univariable Cox proportional hazards regression model. Those found to be significant in the univariable model were further included in the multivariable Cox proportional hazards regression model to estimate the hazard ratio (HR) and 95% confidence interval (CI) of cerebrovascular disease risk associated with chronic pancreatitis and other comorbidities. The statistical significance level was defined at a two-sided probability value <0.05. All analyses were performed with SAS software version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics of the Study Population

Table 1 discloses the distributions of sex, age, and comorbidities between the chronic pancreatitis group and nonchronic pancreatitis group. There were 16,672 subjects in the chronic pancreatitis group, and 65,877 subjects in the nonchronic pancreatitis group. Both groups had similar distributions of sex and age. The mean ages (standard deviation) of the study subjects were 47.5 ± 14.5 years for the chronic pancreatitis group and nonchronic pancreatitis group. The chronic pancreatitis group had a higher proportion of atrial fibrillation, chronic kidney disease, heart failure, and peripheral atherosclerosis than the nonchronic pancreatitis group (chi-square test, *P* < 0.05 for all).

TABLE 1. Baseline Information Between Chronic Pancreatitis Group and Nonchronic Pancreatitis Group

Variable	Chronic Pancreatitis, N = 16,672		Nonchronic Pancreatitis, N = 65,877		P Value*
	n	(%)	n	(%)	
Sex					0.85
Woman	2726	(16.3)	10,732	(16.3)	
Man	13,946	(83.7)	55,145	(83.7)	
Age group (year)					0.94
20–39	5878	(35.3)	23,134	(35.1)	
40–64	8403	(50.4)	33,281	(50.5)	
65–84	2391	(14.3)	9462	(14.4)	
Age (year), mean (standard deviation) [†]	47.5	(14.5)	47.5	(14.5)	0.93
Baseline comorbidities					
Alcohol-related disease	9330	(56.0)	36,676	(55.7)	0.50
Atrial fibrillation	197	(1.18)	630	(0.96)	0.01
Cancer**	497	(2.98)	1838	(2.79)	0.18
Chronic kidney disease	520	(3.12)	1779	(2.70)	0.003
Chronic obstructive pulmonary disease	856	(5.13)	3152	(4.78)	0.06
Coronary artery disease	1363	(8.18)	5143	(7.81)	0.11
Diabetes mellitus	5300	(31.8)	20,643	(31.3)	0.26
Heart failure	428	(2.57)	1500	(2.28)	0.03
Hyperlipidemia	4086	(24.5)	15,856	(24.1)	0.24
Hypertension	3915	(23.5)	15,218	(23.1)	0.30
Peripheral atherosclerosis	1731	(10.4)	6365	(9.66)	0.005

Data are presented as the number of subjects in each group with percentages given in parentheses or the means with standard deviation given in parentheses.

*Chi-square test.

**Pancreatic cancer was excluded.

[†]t-test comparing subjects with and without chronic pancreatitis.

Incidence of Cerebrovascular Disease of the Study Population

The follow-up results disclosed that the overall incidence of cerebrovascular disease was 1.24-fold greater in the chronic pancreatitis group than that in the nonchronic pancreatitis group (14.2 vs. 11.5 per 1000 person-years, 95% CI = 1.19–1.30). The incidence rates of cerebrovascular disease as stratified by sexuality, age, and follow-up period were all higher in the chronic pancreatitis than in the nonchronic pancreatitis group. The chronic pancreatitis group aged 65 to 84 had the highest incidence of cerebrovascular disease (34.7 per 1000 person-years). The analysis stratified by follow-up period disclosed that the risk of cerebrovascular disease persisted over time even after 1 year from diagnosis with chronic pancreatitis. However, the incidence rate ratio was much higher during the first 1 year of follow-up (Table 2).

Cerebrovascular Disease Potentially Associated With Chronic Pancreatitis and Other Comorbidities

After controlling for potentially confounding factors, the multivariable Cox proportional hazard regression model disclosed that the adjusted HR of cerebrovascular disease was 1.27 (95% CI = 1.19–1.36) for the chronic pancreatitis group versus the nonchronic pancreatitis group. Woman (adjusted HR = 1.41, 95% CI = 1.31–1.51), age (every 1 year, adjusted HR = 1.04, 95% CI = 1.04–1.05), atrial fibrillation

(adjusted HR = 1.23, 95% CI = 1.02–1.48), chronic kidney disease (adjusted HR = 1.48, 95% CI = 1.31–1.67), chronic obstructive pulmonary disease (adjusted HR = 1.27, 95% CI = 1.16–1.40), diabetes mellitus (adjusted HR = 1.82, 95% CI = 1.72–1.92), hypertension (adjusted HR = 1.66, 95% CI = 1.56–1.76), and peripheral atherosclerosis (adjusted HR = 1.26, 95% CI = 1.06–1.51) were other factors significantly associated with cerebrovascular disease (Table 3).

Incidence Density and Hazard Ratio of Ischemic, Hemorrhagic, and Other Types of Cerebrovascular Disease Potentially Associated With Chronic Pancreatitis

In further analysis, the incidence rates of ischemic, hemorrhagic, and other types of cerebrovascular disease were all higher in the chronic pancreatitis than those in the nonchronic pancreatitis group (Table 4). After controlling for potentially confounding factors, the adjusted HRs were 1.20 (95% CI = 1.08–1.33) for ischemic cerebrovascular disease, 1.33 (95% CI = 1.15–1.52) for hemorrhagic cerebrovascular disease, and 1.32 (95% CI = 1.19–1.47) for other types of cerebrovascular disease, when comparing the chronic pancreatitis group with the nonchronic pancreatitis group.

Figure 1A–D disclose that the chronic pancreatitis group had a significantly higher cumulative incidences of overall cerebrovascular disease ($P < 0.001$) (Figure 1A), ischemic ($P = 0.006$) (Figure 1B), hemorrhagic ($P < 0.001$)

TABLE 2. Incidence of Cerebrovascular Disease Stratified by Sex, Age and Follow-Up Period Between Chronic Pancreatitis Group and Nonchronic Pancreatitis Group

Variable	Chronic pancreatitis				Nonchronic pancreatitis				IRR* (95% CI)
	N	Event	Person-years	Rate [†]	N	Event	Person-years	Rate [†]	
All	16,672	1139	80,207	14.2	65,877	4186	365,209	11.5	1.24 (1.19–1.30)
Sex									
Woman	2726	202	13,148	15.4	10,732	831	60,042	13.8	1.11 (0.99–1.24)
Man	13,946	937	67,059	14.0	55,145	3355	305,167	11.0	1.27 (1.21–1.33)
Age group (year)									
20–39	5878	240	31,794	7.55	23,134	600	140,746	4.26	1.77 (1.64–1.91)
40–64	8403	592	39,565	15.0	33,281	2156	180,933	11.9	1.26 (1.18–1.34)
65–84	2391	307	8848	34.7	9462	1430	43,530	32.9	1.06 (0.95–1.18)
Follow-up period									
≤6 months	16,672	130	8063	16.1	65,877	375	32,537	11.5	1.40 (1.32–1.48)
6–12 months	15,652	129	7618	16.9	64,305	377	31,792	11.9	1.43 (1.35–1.51)
>1 year	14,841	880	64,526	13.6	62,873	3434	300,880	11.4	1.19 (1.14–1.25)

CI = confidence interval, IRR = incidence rate ratio.

*IRR (incidence rate ratio): chronic pancreatitis vs. nonchronic pancreatitis (95% CI).

[†]Incidence rate: per 1000 person-years.

(Figure 1C), and other types of cerebrovascular disease ($P < 0.001$) (Figure 1D), when compared with the nonchronic pancreatitis group.

DISCUSSION

This is the first population-based cohort study to study the risk of subsequent cerebrovascular disease in patients with chronic pancreatitis and the effects associated with comorbidities in Taiwan. No other study has reported this association. We used a well-preserved database in Taiwan that has been

analyzed to explore numerous epidemiological problems with an excellent established role in the literature. The accuracy and reliability of the diagnosis codes in the present study have been well examined in previous high-quality journals.^{22–26}

We found that the incidence of cerebrovascular disease in the chronic pancreatitis group was ~1.24-fold greater than that in the nonchronic pancreatitis group. We noted that the risk of cerebrovascular disease persisted over time even after 1 year from diagnosis with chronic pancreatitis (Table 2). The multivariable regression analysis disclosed that the adjusted HR of cerebrovascular disease was 1.27 (95% CI = 1.19–1.36) for the

TABLE 3. Hazard Ratio and 95% Confidence Interval of Cerebrovascular Disease Associated With Chronic Pancreatitis and Other Comorbidities

Variable	Crude		Adjusted [†]	
	HR	(95% CI)	HR	(95% CI)
Sex (woman vs. man)	1.22	(1.14–1.31)	1.41	(1.31–1.51)
Age (per 1 year)	1.05	(1.04–1.05)	1.04	(1.04–1.05)
Chronic pancreatitis	1.24	(1.16–1.32)	1.27	(1.19–1.36)
Baseline comorbidities (yes vs. no)				
Alcohol-related disease	0.95	(0.90–1.01)	–	–
Atrial fibrillation	3.42	(2.86–4.08)	1.23	(1.02–1.48)
Cancer*	1.41	(1.19–1.66)	0.86	(0.73–1.02)
Chronic kidney disease	2.59	(2.29–2.91)	1.48	(1.31–1.67)
Chronic obstructive pulmonary disease	2.65	(2.42–2.90)	1.27	(1.16–1.40)
Coronary artery disease	2.61	(2.43–2.81)	0.94	(0.79–1.12)
Diabetes mellitus	2.03	(1.92–2.14)	1.82	(1.72–1.92)
Heart Failure	3.63	(3.22–4.09)	1.12	(0.96–1.31)
Hyperlipidemia	1.05	(0.99–1.12)	–	–
Hypertension	2.86	(2.71–3.02)	1.66	(1.56–1.76)
Peripheral atherosclerosis	2.68	(2.50–2.87)	1.26	(1.06–1.51)

CI = confidence interval, HR = hazard ratio.

*Pancreatic cancer was excluded.

[†]Adjusting for sex, age, atrial fibrillation, cancers, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, heart failure, hypertension, and peripheral atherosclerosis.

TABLE 4. Incidence Density and Hazard Ratio of Ischemic, Hemorrhagic, and Other Types of Cerebrovascular Disease Between Chronic Pancreatitis Group and Nonchronic Pancreatitis Group

Variable	Chronic Pancreatitis				Nonchronic Pancreatitis				IRR* (95% CI)	Adjusted HR‡ (95% CI)
	N	Event	Person-Years	Rate†	N	Event	Person-Years	Rate†		
Overall	16,672	1139	80,207	14.2	65,877	4186	365,209	11.5	1.24 (1.19, 1.30)	1.27 (1.19, 1.36)
Ischemic type		449		5.60		1779		4.87	1.15 (1.09, 1.21)	1.20 (1.08, 1.33)
Hemorrhagic type		255		3.18		878		2.40	1.32 (1.26, 1.39)	1.33 (1.15, 1.52)
Other types		435		5.42		1529		4.19	1.30 (1.23, 1.36)	1.32 (1.19, 1.47)

CI = confidence interval, HR = hazard ratio, IRR = incidence rate ratio.

*IRR (incidence rate ratio): chronic pancreatitis vs. nonchronic pancreatitis (95% CI).

†Incidence rate: per 1000 person-years.

‡Adjusting for atrial fibrillation, cancer, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, heart failure, hypertension, and peripheral atherosclerosis.

chronic pancreatitis group when compared with the nonchronic pancreatitis group (Table 3). In further analysis, we found the adjusted HRs were 1.20 for ischemic cerebrovascular disease, 1.33 for hemorrhagic cerebrovascular disease, and 1.32 for other types of cerebrovascular disease when comparing the chronic pancreatitis group with the nonchronic pancreatitis group (Table 4). These findings indicate that chronic pancreatitis is associated with increased hazard of cerebrovascular disease, no matter ischemic, hemorrhagic, or other types.

Although the cause of the association between chronic pancreatitis and cerebrovascular disease cannot be clarified in this observational study, we reviewed some relevant studies to explain the mechanism between chronic pancreatitis and the risk of cerebrovascular disease. First, chronic pancreatic inflammation because of chronic pancreatitis causes irreversible parenchymal damage and functional impairment of the pancreatic islets that contribute to the development of 85% of pancreatogenic diabetes. This accounts for 5% to 10% of all diabetes mellitus.¹⁰ Diabetes mellitus is a known risk factor for cerebrovascular disease, although most of the previous studies about diabetes related to cerebrovascular disease are type 2 diabetes mellitus. After diabetes developed—regardless of the diabetes type—they shared at least a common pathway in diabetes-related macrovascular diseases, causing cerebrovascular disease. Second, chronic inflammation of the pancreas aggregate macrophage, neutrophils, and injured acinar cell, releasing cytokines such as interleukin-1 β , interleukin-6, tumor necrosis factor- α , transforming growth factor- β , platelet-derived growth factor, and reactive oxygen species.^{27,28} Reactive oxygen species were shown to be increased significantly in patient with chronic pancreatitis.²⁹ There are multiple animal models pointing that excessive level of reactive oxygen species is related to cerebrovascular disease, including both ischemic and hemorrhagic cerebrovascular disease.³⁰ Some researchers even proposed nicotinamide adenine dinucleotide phosphate oxidase as a therapeutic target for neuroprotection against ischemic stroke, based on animal studies.³¹

We found that women had a rather large HR besides the comorbidities listed above which carried HR >1. Traditionally, men were known to have a higher incidence of cerebrovascular disease before the incidence reversed—women were found to have higher incidence when aged >75 years.³² This was probably because of the differences in the production of reactive

oxygen species, and the antioxidant capacity between the two sexes.³³

Endothelial dysfunction was often noted in chronic inflammation and was associated with atherosclerosis, hypertension, and diabetes mellitus.¹¹ There were complicated interactions among inflammation, reactive oxygen species, hyperglycemia, hypertension, atherosclerosis, and thromboembolism. Each may aggravate the others, and the definite mechanism cannot be clarified here.³⁴ However, since appropriate treatment of modifiable risk factor would reduce the incidence of cerebrovascular disease, we think that by treating chronic pancreatitis intensively—especially when the extent of the blood sugar swing can be lessened—cerebrovascular disease may be avoided in some individuals, whereas usefulness of antioxidant therapy to treat chronic pancreatitis, diabetic complications, or to prevent cerebrovascular disease is yet to be concluded.

We also found that although the increased risk of cerebrovascular disease persisted over long periods, the risk was particularly increased during the first 12 months (Table 2). This may indicate a golden period after chronic pancreatitis is diagnosed that certain intervention may be useful to effectively lower the risk of cerebrovascular disease. Before some further larger or prospective investigation can be done, we suggest that clinicians should be particularly cautious about cerebrovascular disease risk after diagnosing chronic pancreatitis and treating the sugar problems more intensively.

Limitations of this present study are as follow. First, this database does not record how chronic pancreatitis and cerebrovascular disease were diagnosed. Only discharge diagnosis based on ICD-9 codes were recorded in the hospitalization dataset. From a view of high quality of the Taiwan National Health Insurance Program, the accuracy of discharge diagnosis can be sure. Therefore, chronic pancreatitis, cerebrovascular disease, and other comorbidities were included based on ICD-9 codes. Second, there was no information concerning the severity of chronic pancreatitis, cerebrovascular disease, or the subsequent type of diabetes mellitus—this plays an important role in the development of cerebrovascular disease and the potentially most practical management in our hypothesis. Owing to the same reason, we were unable to detect the difference based on pancreatitis severity or whether the existence of chronic pancreatitis complications, such as pseudoaneurysms, biliary/duodenal obstruction, pseudocysts, or splenic

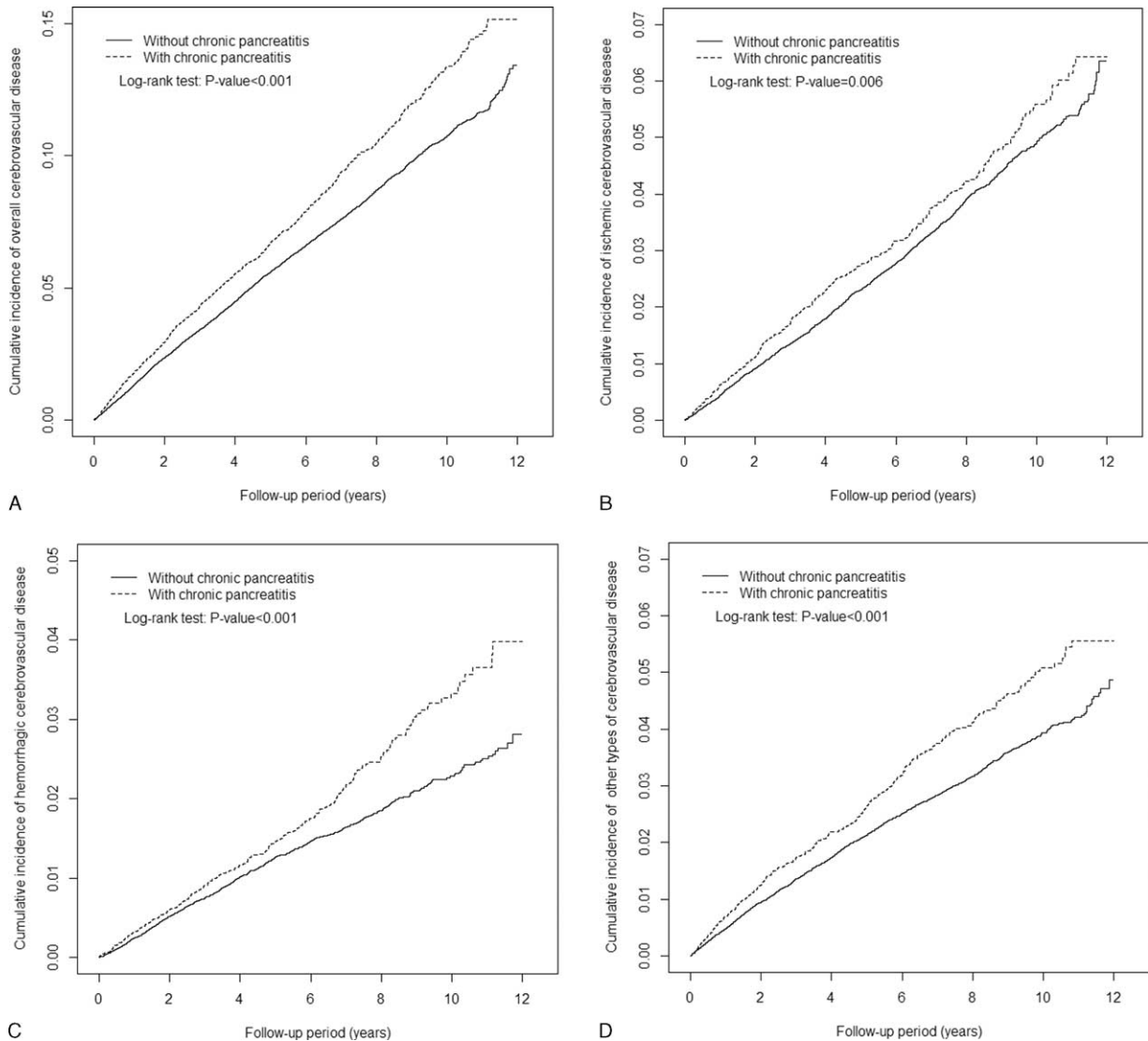


FIGURE 1. A–1D disclose that the chronic pancreatitis group had a significantly higher cumulative incidences of overall cerebrovascular disease ($P < 0.001$) (A); ischemic type ($P = 0.006$) (B); hemorrhagic type ($P < 0.001$) (C); and other types of cerebrovascular disease ($P < 0.001$) (D), when compared with the nonchronic pancreatitis group.

vein thrombosis, has different impacts on risk of cerebrovascular disease. Third, owing to the same limitations, the exact etiologies of chronic pancreatitis were not recorded. Alcohol abuse, which is an important cause of chronic pancreatitis, is also a known modifiable risk factor for cerebrovascular disease. Ideally, this should be analyzed independently—this might bring a more statistically and clinically useful result that may block the still unspecified pathway from chronic pancreatitis to cerebrovascular disease. Fourth, although our results showed that chronic pancreatitis is associated with increased risk of subsequent cerebrovascular disease, we still cannot precisely state how intense the treatment should be nor how to suggest treatment that prevents patients with chronic pancreatitis from getting cerebrovascular disease. Further prospective investigation such as randomized controlled trials should be done to determine the actual benefits of different levels of intensive treatment for chronic pancreatitis to prevent

the development of cerebrovascular disease. Although we proposed a hypothesis that poor sugar control may be one of the reasons underlying cerebrovascular disease, we could not definitively conclude that chronic pancreatitis is the reason behind cerebrovascular disease.

Some strengths of this study should be mentioned. This study provides a different interpretation of the association between chronic pancreatitis and cerebrovascular disease. We also suggest a likely probable biological mechanism that links the two diseases. Further investigation may be conducted to develop a risk of subsequent cerebrovascular disease assessment calculator for patients with chronic pancreatitis or other comorbidities. In addition, none of our investigators faced any of the subjects directly while collecting the data, yet the diagnostic codes are clear and reliable in the database. This makes the study free from selection bias and misclassification bias while also minimizing information bias.

We conclude that chronic pancreatitis is associated with increased hazard of subsequent cerebrovascular disease, no matter ischemic, hemorrhagic, or other types. Woman, age, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, and peripheral atherosclerosis are other factors significantly associated with cerebrovascular disease. Further studies are needed to clarify the actual biological mechanism by which chronic pancreatitis is associated with risk of developing cerebrovascular disease while exploring which specific groups may benefit the most from receiving intensive management of chronic pancreatitis in order to lower the risk of cerebrovascular disease.

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