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Association between gastroesophageal reflux disease and coronary heart disease

A nationwide population-based analysis

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Abstract

In this study, we aimed to determine the association between gastroesophageal reflux disease (GERD) and subsequent coronary heart disease (CHD) development, if any, and to evaluate whether longer use of proton pump inhibitors (PPIs) increases the risk of CHD.

Patients diagnosed with GERD between 2000 and 2011 were identified as the study cohort (n = 12,960). Patients without GERD were randomly selected from the general population, frequency-matched with the study group according to age, sex, and index year, and evaluated as the comparison cohort (n = 51,840). Both cohorts were followed up until the end of 2011 to determine the incidence of CHD. The risk of CHD was evaluated in both groups by using Cox proportional hazards regression models.

The GERD patients had a greater probability of CHD than the cohort without GERD did (log-rank test, $P < 0.001$ and 11.8 vs 6.5 per 1000 person-years). The GERD cohort had a higher risk of CHD than the comparison cohort did after adjustment for age, sex, hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, chronic obstructive pulmonary disease, asthma, biliary stone, anxiety, depression, chronic kidney disease, and cirrhosis (adjusted hazard ratio [aHR]: 1.49, 95% confidence interval [CI]: 1.34–1.66). The risk of CHD was greater for the patients treated with PPIs for more than 1 year (aHR = 1.67, 95% CI = 1.34–2.08) than for those treated with PPIs for <1 year (aHR = 1.56, 95% CI = 1.39–1.74).

Our population-based cohort study results indicate that GERD was associated with an increased risk of developing CHD, and that PPI use for more than 1 year might increase the risk of CHD.

Abbreviations: ACS = acute coronary syndrome, aHR = adjusted hazard ratio, CHD = coronary heart disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, GERD = gastroesophageal reflux disease, LHID 2000 = Longitudinal Health Insurance Database 2000, NERD = nonerosive reflux disease, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, PPI = proton pump inhibitor.

Keywords: cohort, comorbidity, coronary heart disease, gastroesophageal reflux disease

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1. Introduction

Gastroesophageal reflux disease (GERD) is characterized by symptoms and complications such as esophagitis, esophageal stricture, Barrett esophagus, and esophageal adenocarcinoma, and is caused by the reflux of gastric contents.[1] Previous studies have reported the prevalence of GERD (as defined by experiencing heartburn or acid regurgitation at least once per week) was 14% to 24% in adults in Western countries, and 3% to 10.5% in Asian populations.[2,3] The manifestations of GERD include esophageal syndromes, such as erosive esophagitis and nonerosive reflux disease (NERD), and extra-esophageal syndromes such as reflux-associated cough, asthma, laryngitis, and dental erosion.[4]

The features of GERD-induced chest pain are similar to those of cardiac pain, and thus the 2 types of pain can be confused. In addition, GERD and coronary heart disease (CHD) can interact with each other to produce chest pain. Studies have shown that esophageal stimulation can cause cardiac pain by inducing cardiac dysrhythmia or coronary spasm to compromise coronary blood flow.[2,5,6] Studies have also shown that myocardial ischemia can worsen GERD by causing esophageal dysmotility or relaxation of the lower esophageal sphincter.[5,7,8]

A coexisting relationship between GERD and CHD has been widely accepted, though the mechanism underlying the relationship is complex. GERD and CHD share several components of metabolic disorders as common risk factors.[9] Previous studies have shown that male sex, obesity, diabetes, hypertension, smoking, and alcohol drinking are associated with GERD,[10–12] and that metabolic risk factors can influence the severity of symptoms or esophageal erosion in GERD patients.[13] Hyperlipidemia, hypertension, diabetes, alcoholism, and smoking are well-known risk factors for CHD.[14,15] However, the existence of an association between GERD and subsequent development of CHD remains under debate.[9] Moreover, it has been reported that proton pump inhibitors (PPIs) can reduce cardiac contractility and raise the risk of atherosclerosis by increasing the serum levels of homocysteine.[16,17]

We hypothesized that GERD might be related to an increased risk of the subsequent CHD development. In this nationwide population-based cohort study, we analyzed the data from the National Health Insurance Research Database (NHIRD) to evaluate the relationship between GERD and subsequent CHD development and to determine whether the risk of CHD increases after longer use of PPIs.

2. Methods

2.1. Data source

The Taiwan Government has operated the National Health Insurance (NHI) since 1995. Furthermore, this compulsory single-payer healthcare system covers more than 99% of the 23 million Taiwan residents and has contracts with >97% of medical care facilities nationwide (http://www.nhi.gov.tw/english/index.aspx).[18] The government conducts a peer review system by appointing several medical specialists to audit the accuracy of all insurance claims. The National Health Research Institutes (NHRI) (http://nhird.nhri.org.tw) is in charge of maintaining the data security obtained from the NHIRD (http://w3.nhri.org.tw/nhird//date_01.html) and all data were deposited in a public repository. Each encrypted patient's unique personal identification number was crossly linked in the datasets of NHIRD to obtain each patient's longitudinal medical history, and the researchers can access the database after approval for research purpose. All the data relevant to ambulatory care, inpatient care, prescriptions, and medications of 1,000,000 patients randomly sampled from the 2000 Registry of Beneficiaries in the NHIRD are included in the Longitudinal Health Insurance Database 2000 (LHID 2000), which has been widely used for research in Taiwan. Furthermore, the NHRI has validated that the LHID 2000 is representative of the general Taiwan population. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used for coding the diagnosis in the NHIRD database. We conducted this study under approval by the Research Ethics Committee of China Medical University (CMUH-104-REC2-115).

2.2. Sampled patients

Patients age ≥20 years who were newly diagnosed with GERD (ICD-9-CM codes 530.11 and 530.81) between 2000 and 2011 were identified from the LHID 2000. To increase the validity of GERD diagnoses, we only included patients diagnosed using endoscopy or 24-h pH monitoring who subsequently received PPI treatment. The date of GERD diagnosis was set as the index date. Patients with CHD (ICD-9-CM codes 410–414) before the index date and those without complete information in the LHID 2000 were excluded. Furthermore, the patients with CHD were classified into subgroups, namely those with acute coronary syndrome (ACS; ICD-9-CM codes 410, 411.1, and 411.8), old myocardial infarction (ICD-9-CM code 412), angina pectoris (ICD-9-CM code 413), and chronic ischemic heart disease (ICD-9-CM code 414). Patients without a history of GERD or CHD were randomly selected from the same database as the comparison cohort. The comparison cohort was frequency-matched with the study cohort by sex, age (every 5 years), and index year of GERD diagnosis from 2000 to 2011 at a ratio of 4:1. All the patients were followed up from the index date until the date of CHD diagnosis. The patients were censored at death, loss to follow-up, withdrawal from the insurance program, or the end of 2011, whichever came first.

2.3. Comorbidities

The baseline comorbidity history was determined for each patient, including hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), alcohol-related illness (ICD-9-CM codes 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), stroke (ICD-9-CM codes 430–438), obesity (ICD-9-CM code 278), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, and 496), asthma (ICD-9-CM code 493), biliary stone (ICD-9-CM code 574), anxiety (ICD-9-CM code 300), depression (ICD-9-CM codes 296.2–296.3, 300.4, and 311), thyroid disease (ICD-9-CM codes 240–242 and 244–246), chronic kidney disease (ICD-9-CM codes 580–589), and cirrhosis (ICD-9-CM code 571).

2.4. Statistical analysis

The demographic characteristics, including age, sex, and comorbidities, of the GERD cohort were compared with those of the comparison cohort by using a chi-squared test for categorical variables and Student *t* tests for continuous variables. To estimate the probability of CHD-free events in the GERD and comparison cohorts, a survival analysis was performed using the Kaplan–Meier method, with significance based on the log-rank test. The incidence densities of CHD (per 1000 person-years) were calculated for both cohorts. Univariable and multivariable Cox proportion hazards regression models were used to determine the relative risk of CHD in the study cohort compared

Table 1

Demographic characteristics and comorbidity in patient with and without GERD.

Variables	GERD		P
	No (N = 51,840), n (%)	Yes (N = 12,960), n (%)	
Gender			0.99
Female	25,524 (49.2)	6381 (49.2)	
Male	26,316 (50.8)	6579 (50.8)	
Stratify age			0.99
≤34	9412 (36.9)	2353 (18.2)	
35–49	19,124 (36.9)	4781 (36.9)	
50–64	15,940 (30.8)	3985 (30.8)	
65+	7364 (14.2)	1841 (14.2)	
Age, mean (SD)*	48.6 (14.7)	48.8 (14.5)	0.11
Comorbidity			
Hypertension	10,449 (20.2)	3331 (25.7)	<0.001
Diabetes	3359 (6.48)	1041 (8.03)	<0.001
Hyperlipidemia	7318 (14.1)	3098 (23.9)	<0.001
Alcohol-related illness	1940 (3.74)	1060 (8.18)	<0.001
Stroke	1114 (2.15)	384 (2.96)	<0.001
Obesity	681 (1.31)	286 (2.21)	<0.001
COPD	3200 (6.17)	1714 (13.2)	<0.001
Asthma	2422 (4.67)	1220 (9.41)	<0.001
Biliary stone	935 (1.80)	903 (6.97)	<0.001
Anxiety	6105 (11.8)	4206 (32.5)	<0.001
Depression	1936 (3.73)	1321 (10.2)	<0.001
Thyroid disease	1924 (3.71)	903 (6.97)	<0.001
Chronic kidney disease	2070 (3.99)	965 (7.45)	<0.001
Cirrhosis	7393 (14.3)	4116 (31.8)	<0.001

Chi-squared test.

COPD = chronic obstructive pulmonary disease, GERD = gastroesophageal reflux disease, SD = standard deviation.

* Two sample *T* test.

with the comparison cohort, shown as a hazard ratio (HR) and 95% confidence interval (CI). When the patients were stratified according to sex, age, and comorbidities, the relative risk of CHD in the GERD cohort compared with the comparison cohort was also analyzed by using Cox models. The proportionality assumption was violated since there was a significant relationship between Schoenfeld residuals for GERD and follow-up time (P value = 0.002). Therefore, the follow-up duration was then stratified to address the violation of the proportional hazard assumption. The multivariable Cox models included age, sex, and comorbidities of GERD, hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, COPD, asthma, biliary stone, anxiety, depression, chronic kidney disease, and cirrhosis. Among the comorbidities, only GERD, hypertension, hyperlipidemia, and anxiety exhibited a significant association with the development of CHD in the multivariable Cox models. Further data analysis was performed to evaluate the joint effect of GERD with comorbidities of hypertension, hyperlipidemia, and anxiety. On the basis of propensity score matching, a Cox proportional hazards model was used to estimate the HR and 95% CI of the risk of CHD associated with GERD. All statistical analyses were performed using the SAS package (Version 9.3 for Windows; SAS Institute, Inc, Cary, NC). Two-tailed $P < 0.05$ was considered statistically significant.

3. Results

Table 1 shows the demographic characteristics and comorbidities of the GERD and comparison cohorts. In both cohorts, most of the patients were men (50.8%) and the mean age was 49 years. The GERD cohort was significantly more likely than the comparison cohort to have comorbidities of hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, obesity, COPD, asthma, biliary stone, anxiety, depression, chronic kidney disease, and cirrhosis (all $P < 0.001$).

Table 2 shows the incidences and HRs of CHD stratified by sex, age, comorbidities, and duration of GERD follow-up in the

Table 2

Comparison of incidence and hazard ratio of coronary heart disease stratified by sex, age, comorbidity, and follow-up years between those subjects with and without GERD.

Variables	GERD							
	No			Yes				
	Event	PY	Rate†	Event	PY	Rate†	Crude HR‡ (95% CI)	Adjusted HR§ (95% CI)
All	1229	188,994	6.50	553	46,691	11.8	1.82 (1.65, 2.01)***	1.49 (1.34, 1.66)***
ACS	113		0.60	50		1.07	1.79 (1.28, 2.50)***	1.62 (1.13, 2.32)**
Old myocardial infarction	7		0.04	3		0.06	1.74 (0.45, 6.74)	1.29 (0.31, 5.46)
Angina pectoris	325		1.72	159		3.41	1.98 (1.64, 2.39)***	1.49 (1.22, 1.83)***
Chronic ischemic heart disease	784		4.15	341		7.30	1.77 (1.55, 2.00)***	1.47 (1.28, 1.68)***
Gender								
Female	541	91,154	5.94	227	22,734	9.98	1.68 (1.44, 1.96)***	1.33 (1.13, 1.57)***
Male	688	97,841	7.03	326	23,957	13.6	1.94 (1.70, 2.21)***	1.62 (1.41, 1.87)***
Stratify age								
≤34	27	34,712	0.78	20	8741	2.29	2.94 (1.65, 5.25)***	1.52 (0.79, 2.94)
35–49	248	72,061	3.44	157	17,962	8.74	2.54 (2.08, 3.10)***	1.75 (1.41, 2.19)***
50–64	528	57,250	9.22	250	13,894	18.0	1.95 (1.68, 2.27)***	1.55 (1.32, 1.82)***
65+	426	24,970	17.1	126	6094	20.7	1.21 (0.99, 1.48)	1.13 (0.91, 1.39)
Comorbidity‖								
No	257	104,526	2.46	61	12,373	4.93	2.02 (1.53, 2.67)***	2.39 (1.81, 3.16)***
Yes	972	84,468	11.5	492	34,319	14.3	1.25 (1.12, 1.39)***	1.39 (1.24, 1.55)***
Follow time, y								
≤2	625	95,431	6.55	335	23,704	14.1	2.16 (1.89, 2.46)***	1.69 (1.47, 1.95)***
3–5	496	76,114	6.52	184	18,786	9.79	1.50 (1.27, 1.78)***	1.28 (1.07, 1.54)**
>5	108	17,449	6.19	34	4201	8.09	1.31 (0.89, 1.93)	1.31 (0.86, 1.98)

ACS = acute coronary syndrome, CI = confidence interval, COPD = chronic obstructive pulmonary disease, GERD = gastroesophageal reflux disease, HR = hazard ratio, PY = person-years.

† Incidence rate, per 1000 person-years.

‡ Relative hazard ratio.

§ Multivariable analysis including age sex, and comorbidities of hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, COPD, asthma, biliary stone, anxiety, depression, chronic kidney disease, and cirrhosis.

‖ Only to have 1 of comorbidities (including hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, obesity, COPD, asthma, biliary stone, anxiety, depression, thyroid disease, chronic kidney disease, and cirrhosis) classified as the comorbidity group.

** $P < 0.01$.

*** $P < 0.001$.

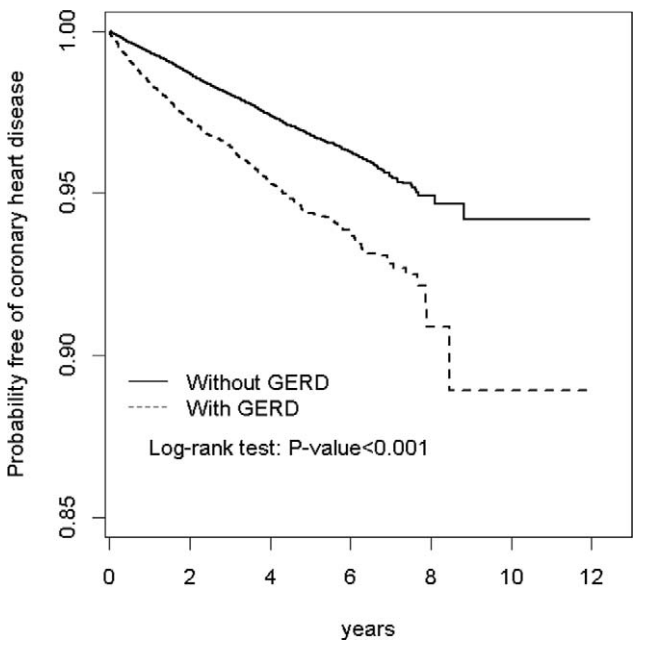

Figure 1. Probability of coronary heart disease for patients with and without GERD. GERD = gastroesophageal reflux disease.

patients with and without GERD. The mean duration of follow-up was 3.60 ± 1.95 years in the GERD cohort and 3.65 ± 1.95 years in the comparison cohort. The overall incidence of CHD was 82% higher in the GERD cohort than in the comparison cohort (11.8 vs 6.50 per 1000 person-years), with an adjusted HR (aHR) of 1.49 (95% CI = 1.34–1.66). The risks of ACS, angina pectoris, and chronic ischemic heart disease were higher in the GERD cohort than in the comparison cohort. The age-specific relative risk of CHD in the GERD cohort was lowest in the ≥65 years age group than in the comparison cohort. Compared with the non-GERD cohort, the GERD cohort had a greater risk of CHD among women and men (aHR = 1.33, 95% CI = 1.13–1.57 for women; aHR = 1.62, 95% CI = 1.41–1.87 for men), patients age 35 to 49 and 50 to 64 years (aHR = 1.75, 95% CI = 1.41–2.19 for patients age 35–49 years; aHR = 1.55, 95% CI = 1.32–1.82 for patients age 50–64 years), and patients with or without comorbidity (aHR = 2.39, 95% CI = 1.81–3.16 for patients without comorbidity; aHR = 1.39, 95% CI = 1.24–1.55 for patients with comorbidity). The relative risk of CHD contributed by GERD was greater in the patients without comorbidity than in those with comorbidity. As shown in Fig. 1, the probability of CHD was significantly higher in the GERD cohort than in the comparison cohort (log-rank test, $P < 0.001$). However, the incidence of CHD was not correlated with the total duration of GERD (Table 2) and a significant relationship existed between Schoenfeld residuals for GERD and follow-up time (P value = 0.002). The aHR was greatest during the first 2 years follow-up after GERD diagnosis, even though the risk of CHD remained correlated with GERD within the first 5 years after GERD diagnosis.

Table 3 shows the HRs of CHD associated with age, sex, and comorbidities in univariable and multivariable Cox regression models. The aHR of CHD development increased with every 1-year increment in age (aHR = 1.03, 95% CI = 1.03–1.04), and was higher among men than women (aHR = 1.30, 95% CI = 1.18–1.43). The risk of developing CHD was higher in patients with comorbidities of hypertension (aHR = 2.30, 95% CI = 2.06–2.58), hyperlipidemia (aHR = 1.39, 95% CI = 1.25–1.56), and anxiety (aHR = 1.44, 95% CI = 1.28–1.62) than in those without the comorbidities. Furthermore, the GERD cohort was associated with a higher risk of CHD than was the comparison

Table 3

Hazard ratios of coronary heart disease in association with age, sex, and comorbidities in univariable and multivariable Cox regression models.

	Crude†		Adjusted‡	
Variables	**HR**	**(95% CI)**	**HR**	**(95% CI)**
Age, y	1.05	(1.04, 1.05)***	1.03	(1.03, 1.04)***
Sex (male vs female)	1.24	(1.13, 1.36)***	1.30	(1.18, 1.43)***
Baseline comorbidities (yes vs no)				
GERD	1.82	(1.65, 2.01)***	1.49	(1.34, 1.66)***
Hypertension	4.49	(4.09, 4.93)***	2.30	(2.06, 2.58)***
Diabetes	2.63	(2.31, 3.00)***	1.07	(0.93, 1.23)
Hyperlipidemia	2.91	(2.64, 3.20)***	1.39	(1.25, 1.56)***
Alcohol-related illness	1.50	(1.23, 1.82)***	1.18	(0.97, 1.45)
Stroke	1.94	(1.52, 2.48)***	0.84	(0.66, 1.08)
Obesity	1.26	(0.88, 1.80)	–	–
COPD	2.50	(2.21, 2.83)***	1.05	(0.91, 1.21)
Asthma	1.96	(1.68, 2.29)***	1.08	(0.92, 1.28)
Biliary stone	1.86	(1.50, 2.30)***	1.01	(0.81, 1.26)
Anxiety	2.08	(1.88, 2.31)***	1.44	(1.28, 1.62)***
Depression	1.50	(1.25, 1.80)***	0.85	(0.70, 1.04)
Thyroid disease	1.19	(0.96, 1.47)	–	–
Chronic kidney disease	2.37	(2.03, 2.76)***	1.09	(0.93, 1.28)
Cirrhosis	1.77	(1.59, 1.96)***	1.08	(0.97, 1.21)

CI = confidence interval, COPD = chronic obstructive pulmonary disease, GERD = gastroesophageal reflux disease, HR = hazard ratio.

† Relative hazard ratio.

‡ Multivariable analysis including age sex, and comorbidities of hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, COPD, asthma, biliary stone, anxiety, depression, chronic kidney disease, and cirrhosis.

*** $P < 0.001$.

Table 4

Cox proportional hazard regression analysis for the risk of GERD with joint effect of GERD and comorbidity.

Variables		N	Event, n	Adjusted HR† (95% CI)
GERD	Hypertension			
No	No	41,391	564	1 (reference)
No	Yes	10,449	665	2.60 (2.28, 2.96)***
Yes	No	9629	268	1.83 (1.57, 2.13)***
Yes	Yes	3331	285	3.26 (2.77, 3.84)***
GERD	Hyperlipidemia			
No	No	44,522	835	1 (reference)
No	Yes	7318	394	1.46 (1.28, 1.67)***
Yes	No	9862	326	1.57 (1.37, 1.79)***
Yes	Yes	3098	227	2.01 (1.71, 2.36)***
GERD	Anxiety			
No	No	45,735	957	1 (reference)
No	Yes	6105	272	1.61 (1.39, 1.86)***
Yes	No	8754	330	1.64 (1.45, 1.87)***
Yes	Yes	4206	223	1.98 (1.69, 2.33)***

CI = confidence interval, GERD = gastroesophageal reflux disease, HR = hazard ratio.

† Adjusted for age, sex, and other comorbidities.

*** $P < 0.001$.

cohort (aHR = 1.49, 95% CI = 1.34–1.66) after adjustment for age, sex, hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, COPD, asthma, biliary stone, anxiety, depression, chronic kidney disease, and cirrhosis.

Table 4 shows the results of a Cox proportional hazard regression analysis of the combined effects of GERD and comorbidities on the risk of CHD. Compared with the patients without GERD or hypertension, those with GERD and hypertension exhibited an increased risk of CHD (aHR = 3.26; 95% CI = 2.77–3.84). Compared with the patients without GERD or hyperlipidemia, those with GERD and hyperlipidemia had an increased risk of CHD (aHR = 2.01; 95% CI = 1.71–2.36). Similarly, compared with the patients without GERD and anxiety, those with GERD and anxiety displayed an increased risk of CHD (aHR = 1.98, 95% CI = 1.69–2.33).

The effects of PPI treatment on CHD risk are shown in Table 5. The risk of CHD was higher among the GERD cohort patients who were treated with PPIs for <1 year (aHR = 1.56, 95% CI = 1.39–1.74) and more than 1 year (aHR = 1.67, 95% CI = 1.34–2.08) than among the control cohort patients. Moreover, the relative risk of CHD contributed by PPI use was greater for more than 1 year of treatment than for <1 year of treatment.

The second set of cohorts revealed a higher incidence of CHD among the patients with GERD than among the propensity score-matched controls (11.6 and 8.00 per 1000 person-years, respectively) (Table 6). The GERD patients had a HR of 1.46 (95% CI = 1.28–1.67) for developing CHD relative to patients without GERD.

4. Discussion

Consistent with the results from previous studies, our study results show that GERD is more common in men than in women (50.8% vs 49.2%). We identified 12,960 GERD patients, diagnosed through endoscopy or 24-h pH monitoring, from a population of 1,000,000, indicating a prevalence of approximately 1.3%. In previous population-based studies on GERD in Chinese ethnic populations, the prevalence of GERD, diagnosed through direct interviews, was highly variable, with 0.8% identified in Singapore, 2.5% in Hong Kong, and 6.2% in South China.[19–21] The reason for higher incidence of GERD in men than in women has yet to be fully elucidated, though the relatively low parietal cell mass in women, relatively poor lower esophageal function in men, and higher body mass index or number of GERD-related comorbidities in men might contribute to the trend.[22,23] Our study results indicate that the age-specific relative risk of CHD in the GERD cohort decreased with increasing age, but no difference was observed in the risk of CHD between patients age ≥65 years with and without GERD. It is possible that increased prevalence of other CHD-associated risk factors in patients age ≥ 65 years could have reduced the relative influence of GERD on CHD risk. Moreover, it has been reported

Table 5

Development of coronary heart disease in patients with GERD according to PPI usage.

GERD	N	Event	Rate†	Crude HR‡ (95% CI)	Adjusted HR§ (95% CI)
No	51,840	1229	6.50	1 (reference)	1 (reference)
GERD with PPIs treatment < 1 y	11,758	463	11.2	1.72 (1.54, 1.91)***	1.56 (1.39, 1.74)***
GERD with PPIs treatment ≥ 1 y	1202	90	17.0	2.64 (2.13, 3.27)***	1.67 (1.34, 2.08)***

CI = confidence interval, COPD = chronic obstructive pulmonary disease, GERD = gastroesophageal reflux disease, HR = hazard ratio, PPI = proton pump inhibitor.

† Incidence rate, per 1000 person-years

‡ Relative hazard ratio.

§ Multivariable analysis including age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, COPD, asthma, biliary stone, anxiety, depression, chronic kidney disease, and cirrhosis.

*** $P < 0.001$.

Table 6

Incidence (per 1000 person-years) and hazard ratio of coronary heart disease in propensity score-matched between those subjects with and without GERD.

	Propensity score matched GERD	
	No (N = 12,586)	Yes (N = 12,586)
Person-years	45,153	45,274
Coronary heart disease		
Overall		
Event, n	361	525
Incidence rate	8.00	11.6
HR (95% CI)	1 (reference)	1.46 (1.28, 1.67)***

CI = confidence interval, GERD = gastroesophageal reflux disease, HR = hazard ratio.
*** $P < 0.001$.

that older patients tend to be insensitive to acid reflux and might become asymptomatic.[24]

Our study results indicate that GERD patients have a greater number of comorbidities than do non-GERD patients, and indicate that GERD is associated with hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, obesity, COPD, asthma, biliary stone, anxiety, depression, chronic kidney disease, and cirrhosis. According to our analyses, risk of CHD is increased in GERD patients who are older, male, or have hypertension, hyperlipidemia, or anxiety. Our results indicate that GERD is associated with subsequent CHD development after adjustment for age, sex, hypertension, diabetes, hyperlipidemia, alcohol-related illness, stroke, COPD, asthma, biliary stones, anxiety, depression, chronic kidney disease, and cirrhosis. However, further investigation is required to determine whether GERD is a risk factor or epiphenomenon for CHD development.[9–15]

Previous studies have suggested that shared pathophysiological mechanisms might underlie the association between GERD and CHD. First, in linked angina, exposure of the esophageal mucosa to acid and reduced lower esophageal sphincter pressure might compromise myocardial perfusion resulting from coronary spasm and cause arrhythmia through sympathetic activation.[5,6,25–27] In addition, myocardial ischemia can induce esophageal dysmotility or relaxation of the lower esophageal sphincter.[5,7,8] Second, many visceral pain receptors are polymodal and sensitive to acid, mechanical distension, and changes in temperature. Cardiac and esophageal afferent sensory innervations entering the spinal cord can overlap, and thus stimulation of the esophagus or heart might be perceived and summed up over the dermatomes corresponding to either organ.[28,29] Third, the relationship between GERD and sleep disturbances is bidirectional and interactive,[30] and it is well established that sleep apnea increases the risk of a cardiovascular event. Finally, PPI use can reduce the cardioprotective effects of certain therapies by reducing the metabolism of antiplatelet agents to their active form.[31–33] PPIs might also reduce the contractility of myocardial tissue and increase homocysteine by impairing the absorption of vitamin B12.[16,17] Moreover, our results suggest that PPI use might have a detrimental effect on CHD, because the risk of CHD among the patients treated for more than 1 year was greater than that of patients treated for <1 year.

The increased prevalence of other CHD-associated risk factors in older patients might attenuate the effects of GERD on CHD risk with increasing age. The risk of developing CHD was consistently increased after we have controlled the confounding risk factors as possible as we could, even though the association might be caused by their shared risk factors. However, we still could not ascertain whether there is a causal relationship between GERD and CHD or whether the duration of PPI use imposes the deteriorating defect on CHD development in a dose–response effect. Johansson et al[9] reported that the incidence of CHD significantly differed between patients with and without GERD within 1 month of GERD diagnosis, and the authors suggested that the misinterpretation of prodromal ischemic symptoms as reflux symptoms could have caused this finding. Similarly, our results suggest that the risk of CHD is greatest in the first 2 years after GERD diagnosis rather than increasing incrementally with follow-up duration after GERD diagnosis (Table 2). The possible reasons for the discordance between the incidence of CHD and the total duration of GERD follow-up may include the delayed diagnosis of GERD for the patients with GERD symptoms, the early compromise of myocardial perfusion after GERD diagnosis, and misinterpretation because of overlapping sensory innervation of the esophagus and the heart. However, our results consistently indicate a close association between GERD and CHD, and suggest that GERD with PPI treatment for more than 1 year might increase the risk of CHD development.

According to our research, our study is the largest population-based study to examine the association between GERD and subsequent development of CHD. The national database we used contains a representative cohort of 1,000,000 people covered by the Taiwan NHI program, and the 12-year observation period ensured the power of our statistical analyses. The evaluated patients were sampled from a stable population and represent approximately 99% of the residents of Taiwan. Our study also used a longitudinal rather than cross-sectional approach to evaluate the temporal and casual associations between GERD and CHD. This is the first population-based study to suggest that GERD is associated with an increased risk of CHD development, though some risk factors for GERD are associated with the development of CHD.

Our study has limitations. First, we may have overlooked some potential confounding factors because the NHIRD does not include detailed information on the CHD-related lifestyle factors, socioeconomic status, and family history of patients. However, we controlled for a number of potential CHD-associated comorbidities and GERD was consistently associated with CHD development. Second, we did not evaluate patients not covered by the NHI program. However, the program currently covers more than 99% of the Taiwan population. Third, the proportionality assumption was violated because a significant relationship existed between the Schoenfeld residuals for GERD and follow-up time. These residual confounding might raise concerns about overadjustment bias and collider stratification bias. Moreover, the association between GERD severity and CHD severity could not be assessed in our study. The casual relationship between GERD and CHD may remain debated, but our results support the association between GERD and CHD. Fourth, the pathophysiological mechanisms of ACS and others are quite different. ACS might be caused by plaque rupture and arterial thrombosis, whereas mechanisms of coronary artery disease might be related to the progression of atherosclerosis. The date of diagnosis for reimbursement was made by physicians. It might be difficult to validate the date of old myocardial infarction, the beginning of stable angina pectoris, and other forms of chronic ischemic heart disease. Nonetheless, GERD was consistently associated in our study with ACS and other forms of stable coronary artery disease, particularly angina pectoris and

chronic ischemic heart disease (Table 2). However, our study also has strengths such as its longitudinal population-based design and use of NHIRD records with a large sample size and low loss to follow-up. In addition, the reimbursement policy is universal and operated by a single payer, namely the Taiwan Government. All insurance claims are scrutinized by medical reimbursement specialists and peer reviewed according to standard diagnosed criteria.[34] Doctors or hospitals are heavily penalized if they make incorrect diagnoses or provide incorrect codes. Therefore, the CHD diagnoses based on ICD-9 codes in this study were highly reliable. In addition, related studies have used the same diagnosis method and criteria with ICD-9 coding.[35–37] Furthermore, patients with CHD diagnosed before the index date and those without complete information in the LHID 2000 were excluded in our study. The inclusion of all CHD diagnoses in our end-point data would have reduced the lost recruitment of patients with asymptomatic coronary artery disease because silent myocardial infarction is reported to account for 9% to 37% of all nonfatal myocardial infarction events.[38] In addition, the association between GERD and CHD, rather than the casual relationship, can still be supported by our study. Finally, the asymptomatic GERD patients might be included in the control patients; likewise, some patients with asymptomatic CHD might be misclassified. However, this misclassification would overestimate the risk of CHD in the comparison cohort rather than in the GERD cohort; therefore, the relative risk of CHD contributed by GERD night be greater than that in our study.

In conclusion, the results from our population-based cohort study indicate that GERD was associated with an increased risk of developing CHD, and PPI usage for more than 1 year might increase the risk of CHD.

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