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The association between gastro-oesophageal reflux disease and subsequent rheumatoid arthritis occurrence: a nested case–control study from Taiwan

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ABSTRACT

Objective Gastro-oesophageal reflux disease (GORD) is a common comorbidity among patients with rheumatoid arthritis (RA). While GORD has been attributed to the antirheumatic medications, no studies of human cohorts have investigated a link between GORD and RA. This study investigates whether GORD is associated with a subsequent RA diagnosis over a 5-year follow-up using a population-based dataset.

Setting Taiwan

Participants We used data from the Taiwan Longitudinal Health Insurance Database. The study group consisted of 13 645 patients with an ambulatory claim showing a GORD diagnosis. We used propensity score matching to select 13 645 comparison patients (one per study patient with GORD).

Intervention We tracked each patient's claims over a 5-year period to identify those who subsequently received a diagnosis of RA. Cox proportional hazard (PH) regression modelling was used for analysis.

Results Over 5-year follow-up, RA incidence rate per 1000 person-years was 2.81 among patients with GORD and 0.84 among the comparison group. Cox PH modelling showed that GORD was independently associated with a 2.84-fold increased risk of RA (95% CI 2.09 to 3.85) over 5-year follow-up, after adjusting for the number of ambulatory care visits within the year following the index date (to mitigate surveillance bias).

Conclusions We observed that GORD might associate with subsequent RA occurrence. Because current treatment guidelines for RA emphasise early diagnosis and prompt treatment, the observed association between GORD and RA may help acquaint clinicians to patients with GORD with higher RA risk and facilitate early diagnosis and treatment.

Strengths and limitations of this study

► This study used a population-based dataset.
► The large sample size provided appropriate statistical power to detect real differences between the two groups.
► The dataset used lacks clinical information and therefore did not allow us to distinguish study patients according to the severity of their gastro-oesophageal reflux disease or rheumatoid arthritis.
► As no standardised criteria were used to define cases, some room for bias may have existed due to case misclassification.

manifestations.[1] RA affects about 0.5%–1% of the adult population and is associated with progressive worsening of joint function and increased morbidity and mortality.[2–4] Due to musculoskeletal deficits, patients with RA may experience cumulative comorbidity risks, deteriorating physical function, declining quality of life and substantial medical and socioeconomic burdens.[5 6] Upper gastrointestinal (GI) disease is a recognised, major comorbidity associated with RA and contributes to the increased mortality risk of patients with RA.[7–11] Gastro-oesophageal reflux disease (GORD) is a widely prevalent disorder of the GI tract. It manifests with major upper GI symptoms, heartburn and acid regurgitation due to reflux of gastric contents into the oesophagus.[12] A study from Japan documented a higher prevalence of GORD among patients with RA compared with the general population (24.6% vs 11.5%).[13] A study from the USA showed that GORD was more likely among patients with RA aged <60 years.[14] Antirheumatic medications (particularly, non-steroidal anti-inflammatory drugs (NSAIDs)) have been blamed for the increased burden

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most widely prevalent chronic inflammatory diseases. Although predominantly involving the joints, RA is recognised as a systemic condition with extra-articular

of GI diseases among patients with RA.[15–17] An alternative hypothesis has been recently proposed that GI disorders may be part of the clinical spectrum and pathogenesis of RA disease.[9 18]

The link between GORD and RA may extend beyond shared pathogenic processes. As is well documented, both genetic (eg, heritability and family history[3 19]) and environmental factors (eg, smoking and low socio-economic status or educational attainment[20 21]) are involved in the pathogenesis of RA.[22] Recent studies have suggested a role of the microbiome in RA risk and its progression.[23 24] Studies based on animal models suggest a prominent role of the gut microbiome in the progression of RA.[23] Evidence for the immunological relevance of peptides from gut microbes was strengthened by their detection in synovial tissues and peripheral blood mononuclear cells among patients with newly diagnosed RA.[25] As these evidences examined mainly on lower GI, none has attempted to investigate the potential role of upper GI tract microbiomes (eg, GORD) on RA development. Nevertheless, it would be plausible that chronic inflammation resulting from the repeated acid reflux in GORD may cause mucosal damage and translocation of the microbiome from the gut into the circulation,[26 27] GORD may therefore serve as a facilitating factor for RA pathogenesis, a hypothesis that could be tested by looking for evidence that GORD predates RA and that GORD is associated with disproportionately more new RA diagnoses than among persons without GORD. This study investigates whether GORD is associated with increased risk of a subsequent RA diagnosis over 5-year follow-up using a population-based dataset.

METHODS
Database
Sample patients were selected from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005), hosted by the Taiwan National Health Research Institutes. Taiwan implemented its National Health Insurance (NHI) programme in 1995. The LHID2005 contains registration files and all medical care claims for 1 000 000 enrollees randomly selected from all enrollees (n=23.72 million) listed in the 2005 Registry of NHI Beneficiaries. The LHID2005 allows researchers to longitudinally track medical services provided to the selected enrollees since NHI inception in 1995.

This study was exempt from full review by the Institutional Review Board of Taipei Medical University (TMU-JIRB 201612025) since the LHID2005 consists of de-identified secondary data released without restriction to researchers for research purposes.

Study sample
This nested case–control study included a study group and a comparison group. To select the study group, we first retrieved 21 395 patients who visited clinics or ambulatory care centres for the treatment of GORD (International

Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 530.11 or 530.81) between 1 January 2002 and 21 December 2008. We excluded paediatric patients (<18 years of age, n=594) in order to limit the sample to the adult population. To improve the validity of the GORD diagnoses, we included only those patients who were diagnosed by either endoscopy or 24 hour pH monitoring, and additionally, received a proton-pump inhibitor prescription for more than 30 days (n=13 977). We assigned the first date of the GORD diagnosis as the index date for study patients. Finally, we excluded 332 patients with GORD who had a diagnosis of RA (ICD-9-CM code 714.0) preceding the index date of the GORD diagnosis. The final study group included 13 645 patients with GORD.

To select comparison patients from the remaining patients of the LHID2005 dataset, we first excluded patients with any claim showing a diagnosis of GORD since initiation of the NHI program in 1995 and all paediatric patients. We used propensity score matching to select 13 645 comparison patients (one for every study patient with GORD). The selected variables, age, sex, monthly income (NT$0~15 840, NT$15 841~25 000≥NT$25 001; average exchange rate in 2008, US$1.00≈New Taiwan (NT)$29), geographical location (Northern, Central, Southern and Eastern), urbanisation level of the patient's residence, the year of the index date and medical comorbidities, were entered into a multivariable logistic regression model as predictors to calculate each patient's expected probability of receiving a GORD diagnosis. Residential urbanisation level is classified by the Taiwanese National Health Research Institute into five levels (one being the most urbanised and five least urbanised). Medical comorbidities were identified using ICD-9-CM codes and included hyperlipidaemia (272.0–272.4), diabetes (250), hypertension (401–405), coronary heart disease (410–414 or 429.2), stroke (430–438) and obesity (278, 278.0, 278.00 or 278.01). The diagnosis of tobacco use disorder (305.1) in the claims data was used to identify severe current smokers. These comorbid conditions were included only if the condition occurred in an inpatient claim or in two or more ambulatory care claims within 2 years before the index date.

For the study group, the year of the index date was the year in which they received their first-time diagnosis of GORD. To create the comparison group, comparison patients were selected based on matched propensity scores for receiving a GORD diagnosis. We then assigned their first healthcare use that occurred in the index year of the matched study patient as the index date for the comparison patient. All comparison patients' prior claims were screened to ensure that none of them had a history of RA prior to their index date.

The study included 13 645 study patients and 13 645 comparison patients. We tracked each patient's claims over a 5-year period from their index date to identify those who subsequently received a diagnosis of RA (ICD-9-CM code 714.0). To enhance validity of the RA diagnosis, we

identified only those patients who showed a RA diagnosis in at least two distinct medical encounter claims.

Statistical analysis

We used the SAS system for statistical analyses. We used Pearson's X^2 tests to examine differences between GORD patients and comparison patients on sociodemographic characteristics and medical comorbidities. We performed a log-rank test to examine the difference in 5-year RA-free survival between the two groups. We performed Cox proportional hazard regressions to calculate the HR and 95% CI for the subsequent occurrence of RA over 5-year follow-up.

We verified that the data were consistent with the proportional hazards assumption by confirming that the survival curves for both strata (GORD and comparison patients) had hazard functions that were proportional over time. Finally, we censored patients who died or were lost to follow-up during the study (787 study patients (5.77% of patients with GORD) and 801 comparison patients (5.87% of the comparison group)). A significance level of 0.05 was used.

RESULTS

Table 1 shows the sample demographic distribution stratified by the presence or absence of GORD. Because of propensity score matching, there was no significant difference in age, sex, monthly income, urbanisation level, geographic region and medical comorbidities between patients with GORD and comparison patients (all p>0.05). However, there was a significant difference in the number of ambulatory care visits within 1 year of the index date (p<0.001).

The incidence of RA during 5-year follow-up is presented in table 2. RA incidence was 2.81 (2.42–3.24) per 1000 person-years of observation among patients

Table 1	Demographic and clinical characteristics of sampled patients (n=27 290)				
	Patients who received a diagnosis of GORD, n=13 645		Comparison patients n=13 645		
Variable	Total number	Column %	Total number	Column %	p Value
Males	6490	47.6	6474	47.5	0.846
Age, mean (SD)	48.2±15.0		48.1±16.1		0.064
Urbanisation level					
1 (most)	4512	33.1	4430	32.5	0.780
2	3852	28.2	3907	28.6	
3	1964	14.4	2011	14.7	
4	1827	13.4	1817	13.3	
5 (least)	1490	10.9	1480	10.9	
Monthly income					
NT$0–15 840	4688	34.4	4782	35.0	0.204
NT$15 841–25 000	4800	35.2	4837	35.5	
≥NT$25 001	4157	30.5	4026	29.5	
Geographical region					
Northern	6615	48.5	6707	49.1	0.168
Central	4013	29.4	3827	28.0	
Southern	2724	20.0	2740	20.1	
Eastern	293	2.1	281	1.8	
Hypertension	4218	30.9	4121	30.2	0.202
Diabetes	1922	14.1	1864	13.7	0.310
Tobacco use disorder	428	3.1	392	2.9	0.202
Hyperlipidaemia	4095	30.0	3976	29.1	0.114
Obesity	245	1.8	219	1.6	0.223
Stroke	1240	9.1	1165	8.5	0.109
Coronary heart disease	1483	10.9	1473	10.8	0.846
Number of ambulatory care visits within 1 year after index date	28.6±22.6		18.7±18.1		<0.001

Note: The average exchange rate in 2008 was US$1.00≈New Taiwan (NT)$29.
GORD, gastro-oesophageal reflux disease.

Table 2 HRs for rheumatoid arthritis (RA) among sampled patients during the 5-year follow-up period

Presence of RA	Total sample, n=27 290	Patients who received a diagnosis of GORD, n=13 645	Comparison patients, n=13 645
Five-year follow-up period			
Yes, n (%)	242 (0.89)	186 (1.36)	56 (0.41)
Incidence rate per 1000 person-years (95% CI)	1.82 (1.60 to 2.06)	2.81 (2.42 to 3.24)	0.84 (0.64 to 1.09)
HR (95% CI)	–	3.35*** (2.48 to 4.52)	1.00
Adjusted HR* (95% CI)		2.84*** (2.09 to 3.85)	1.00

*Adjustments were made for the number of ambulatory care visits within 1 year after the index date.
The HR was calculated by a Cox proportional hazard regression.
***p<0.01.
GORD, gastro-oesophageal reflux disease.

with GORD and 0.84 (0.64–1.09) per 1000 person-years among comparison patients. The log-rank test showed that patients with GORD were more likely to be diagnosed with RA than comparison patients (p<0.001). Table 2 also shows the Cox HRs for RA. The HR for RA among patients with GORD relative to comparison patients over 5-year follow-up was 2.84 (95% CI 2.09 to 3.85) after censoring deaths and loss to follow-up and adjusting for the number of ambulatory care visits within 1 year of the index date. For the 242 sample patients who received an RA diagnosis during the follow-up, the mean gap between the index date and RA diagnosis was 756 days (SD 502 days), being 839 and 481 days, respectively, for patients with and without GORD.

We conducted a stratified proportional hazard analysis, stratifying on sex (table 3). For females with GORD, the HR for RA was higher (adjusted HR 3.36, 95% CI 2.30 to 4.91) than males (adjusted HR 2.00, 95% CI=1.18 to 3.37).

We used sensitivity analysis to assess the possible role of surveillance bias, which may increase the likelihood of chronically ill patients being subsequently diagnosed with other diseases due to their greater frequency of medical encounters than healthier patients. Patients with GORD may visit doctors more often than comparison patients and therefore have a greater chance of being diagnosed with RA, while those in the comparison group may disregard mild symptoms and remain undetected for some time. Table 4 presents the results of sensitivity analysis. After excluding patients who were newly diagnosed with RA within 60 days following the index date and adjusting for the number of ambulatory care visits in the first year of follow-up, the adjusted HR was 2.81 (95% CI 2.06 to 3.83), closely similar to the unadjusted HR.

DISCUSSION

To our knowledge, this study is the first to investigate the 5-year risk of RA among patients with GORD. Propensity score matching (using age, sex, monthly income, geographical location, residential urbanisation level, year

Table 3 HRs for rheumatoid arthritis (RA) during the 5-year follow-up period by sex

Development of RA	Sex				
	Males		Females		
	Patients who received a diagnosis of GORD, (n=6490) n, %	Comparison patients, (n=6474) n, %	Patients who received a diagnosis of GORD (n=7155) n, %	Comparison patients, (n=7171) n, %	
Five-year follow-up period					
Yes	50 0.77	21 0.32	136 1.90	35 0.49	
Incidence rate per 1000 person-years (95% CI)	1.58 (1.18 to 2.09)	0.68 (0.42 to 1.04)	3.93 (3.29 to 4.64)	0.98 (0.68 to 1.36)	
HR (95% CI)	2.39*** (1.43 to 3.98)	1.00	3.95*** (2.72 to 5.74)	1.00	
Adjusted HR* (95% CI)	2.00*** (1.18 to 3.37)	1.00	3.36*** (2.30 to 4.91)		

*Adjustments were made for the number of ambulatory care visits within 1 year after the index date.
The HR was calculated by a Cox proportional hazard regression.
***p<0.01.
GORD, gastro-oesophageal reflux disease.

Table 4 HRs for rheumatoid arthritis (RA) among sampled patients during the 5-year follow-up period after excluding sampled patients who received an RA diagnosis within 60 days after the index date

Presence of RA	Total sample, n=27 279	Patients who received a diagnosis of GORD, n=13 636	Comparison patients, n=13 643
Five-year follow-up period			
Yes, n (%)	231 (0.85)	177 (1.30)	54 (0.40)
HR (95% CI)	–	3.31*** (2.43 to 4.49)	1.00
Adjusted HR* (95% CI)		2.81*** (2.06 to 3.83)	1.00

*Adjustments were made for the number of ambulatory care visits within 1 year after the index date.
The HR was calculated by a Cox proportional hazard regression.
***p<0.01.
GORD, gastro-oesophageal reflux disease.

of the index date and medical comorbidities) was done to select comparison patients without GORD in order to mitigate selection bias. During the 5-year follow-up, we documented RA incidence per 1000 person-years of 2.81 for patients with GORD and 0.84 for comparison patients. We also observed that after mitigating surveillance bias, GORD was independently associated with 2.84-fold higher risk of RA during 5-year follow-up, after adjusting for the number of ambulatory care visits within 1 year of the index date. Our findings may support previously documented animal model evidence that implicated a pathogenetic role of GORD in RA risk and its progression.

Upper GI diseases are major comorbid medical conditions contributing to the impaired quality of life and increased mortality risk experienced by patients with RA.[7-11]

A Japanese study specifically linked RA with GORD, a common GI condition among patients with RA. The authors reported that the prevalence of GORD was significantly higher among patients with RA, compared to the general population.[13] GI disease has been, thus far, considered an adverse effect of RA treatment, particularly NSAIDs.[15 16 28 29] No study has examined whether GORD is simply a comorbid illness occurring after the RA diagnosis due to treatment. In recent years, it has been suggested that GORD may be implicated at a much earlier stage in shaping the disease risk, in light of increasing research on the role of environmental factors in the pathogenesis of RA (eg, microbiome effects[23 24]). Our study presents epidemiological evidence that GORD is associated with a subsequent RA diagnosis over 5-year follow-up. Given that GORD predated the RA diagnosis by a substantial period of time (more than 2 years in average), it appears unlikely that GORD was merely an early manifestation of underlying, asymptomatic RA pathology.

In additional analysis that classified the sample by sex, we observed that the RA increased RA risk of patients with GORD relative to comparison patients is heightened among females (males OR 2.00, 95% CI 1.18 to 3.37; females OR 3.36, 95% CI 2.30 to 4.91). The magnitude of difference between the sexes is consistent with the known sex bias of RA incidence; approximately 70% of patients with RA are women.[30] No statistically significant findings were observed on stratification by age.

How the RA risk is intensified among patients with GORD has not been articulated. Tentative evidence, though mainly focusing on lower GI, suggests the possibility that the microbiome may play a role in many autoimmune diseases, including RA.[23 24] Clinical studies and laboratory research have investigated various factors in the pathogenesis of RA, including environmental factors, genetic factors and inflammatory pathways. One currently prevailing hypothesis is that specific organisms in the mouth or gut microbiota may influence mucosal and systemic immune responses affecting the joints in patients with RA.[31–33] Stool samples from patients with recent-onset RA, compared with patients with chronic RA, psoriatic arthritis or healthy individuals, show that *Prevotella copri* in the gut microbiota is overmagnified.[34] While dysbiosis is documented in patients with RA,[35] a recent study in mice confirmed that dysbiosis contributes to arthritis development through activation of autoreactive T cells in the intestines.[36] Alterations in microbial populations in oral, salivary and other GI sites that were associated with C-reactive protein and autoantibodies against citrullinated peptides status and were also identified in human patients.[37] Further, by liquid chromatography tandem mass spectrometry, Pianta *et al* attempted to examine whether overmagnification of *P. copri* in the gut of human patients may alter immune cell functions at both mucosal and systemic sites, contributing to the pathogenesis of RA disease.[25] They found that among 42% of patients with RA, Th1 responses could be stimulated in vivo by an human leucocyte antigen-antigen D related-presented peptide stemming from a *P. copri* 27-kD protein (Pc-p27). *P. copri* provoked differential antibody responses to the whole organism or this specific protein in a considerable fraction of patients with RA. As this evidence on lower GI revealed the immunological relevance of the microbiota in the pathogenesis of RA, none has attempted to examine the role of upper GI illnesses, such as GORD in our study. How the occurrence of GORD may be linked with RA remains unknown. But presumably, GORD, a chronic oesophageal injury that occurs due

to intermittent, abnormal reflux of gastric contents into the oesophagus, may damage the oesophageal mucosa.[38] Bacteria may then be translocated from the gut to the bloodstream and induce immune responses.[26] Bacterial translocation, defined as the movement of viable bacteria from the gastrointestinal tract to extraintestinal locations such as the bloodstream, may be promoted through three mechanisms of: (a) intestinal bacterial overgrowth, (b) augmented permeability of the intestinal mucosal barrier and (c) deficits in host immune defences.[26 27] GORD may, therefore, be associated with a subsequently increased RA risk, as observed in our epidemiological study. The pathobiological pathways underlying these observations remain unknown and should be explored in future studies.

Our findings have important clinical and public health implications for managing GORD. Typically, patients with RA exhibit tender and swollen joints of recent onset, morning joint stiffness, and abnormal laboratory findings such as elevated blood levels of C-reactive protein or erythrocyte sedimentation rates. However, none of these features are specific to RA, which impedes early diagnosis in many patients. Given that early diagnosis and prompt treatment of RA is emphasised,[1] the treating medical team, if aware of the possible pathogenic link, may be able to arrive at the diagnosis sooner and initiate appropriate treatment.

A unique strength of this study was the use of a population-based dataset, which allowed us to track all cases of GORD and RA during the study period. Moreover, the large sample size provided adequate statistical power to detect differences between the two groups.

Despite the strengths, the findings should be interpreted with caution due to certain limitations. First, an inherent limitation of a claims dataset is that only patients who sought medical treatment for GORD and RA were represented in this study. It is unlikely that incident cases of RA were missed because of the joint swelling, pain and discomfort that significantly impacts daily functioning, causing patients to seek medical care. Another potential source of bias is diagnostic misclassification of GORD or RA. In the absence of standardised criteria to define cases, GORD is particularly liable to be underdiagnosed due to its wide range and severity of manifestations and subjective perceptions of patients some of whom may not seek treatment.[39] Such misclassification of GORD status would result in more undiagnosed patients with GORD among the comparison group and would potentially bias our results towards the null. Plausibly, therefore, the actual hazard of RA among patients with GORD may be higher than the observed HR in our study.

Second, the claims dataset lacks clinical information and did not allow us to distinguish study patients by the severity of GORD or RA. Third, there is no data on personal history such as family history of RA, body mass index, history of previous infections, exposure to air pollution and insecticides and occupational exposure to mineral oil or silica, which may contribute to RA.[1] Given that smoking is an important risk factor for RA,[21 40] the

diagnosis of tobacco use disorder in the claims data was used to account for severe smoking behaviours, while leaving less intense smoking unaccounted for in the analysis. Another unavoidable confounder in retrospective studies is that patients with arthralgia or joint symptoms may consume more NSAIDS which directly increases the risk of GORD. Information on the prior existence of such conditions and on NSAID consumption or other relevant medications is not available in the dataset. Therefore, the current study design does not permit an unequivocal inference of a causal relationship between GORD and RA. Finally, the generalisability of our study findings may be limited to ethnic Chinese populations. Future studies will need to include other ethnic groups for evaluation.

Our findings extend the significance and implications of previously reported evidence regarding comorbid GORD among RA. It offers evidence that GORD, a common GI disease, is associated with increased risk of subsequent RA occurrence, using a large, population-based, national dataset. Although our exploratory study offers epidemiological evidence of an association using a retrospective case–control approach, replication of the finding in other settings is required, as well as studies to better characterise the link and verify the directionality and causal link, if any. Biomedical research is essential to elucidate the underlying pathways connecting GORD with RA to interpret the clinical significance of these epidemiological findings.

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