Seasonal Variation in the Incidence of Gastroesophageal Reflux Disease

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Abstract: *Background:* To examine the seasonal variation in the incidence of gastroesophageal reflux disease (GERD) for different gender and age groups and its association with climatic parameters (ambient temperature, relative humidity, atmospheric pressure, rainfall, and hours of sunshine). *Methods:* A total of 76,636 ambulatory care visits for the treatment of GERD between 2001 and 2006 were included. Monthly GERD incidence rates per 10,000 people were calculated over 72 months and categorized by gender and age groupings (19–44, 45–64, and ≥65 years). Seasonality is a general component of time-series patterns. The auto-regressive integrated moving average (ARIMA) regression method was used to evaluate the effects of climatic and monthly factors on GERD incidence rates after adjusting for the time-trend effect. *Results:* Seasonal trends showed an incidence peak in October to December, followed by a sharp decrease in January, and a trough in February; a fairly similar seasonal pattern of GERD incidence was apparent for gender, age, and combined groups. The ARIMA test for seasonality found a significant association for the total group ($P < 0.01$), for female ($P < 0.05$) patients, and for the 45 to 64 years ($P < 0.01$) and >64 years ($P < 0.01$) age groups. The ARIMA models also showed that relative humidity was negatively related to monthly GERD incidence rates for men ($P < 0.01$) and the >64 years ($P < 0.01$) age group. *Conclusion:* Data showed seasonal variations in GERD incidence. Relative humidity was associated with monthly GERD incidence rates for men and the >64 years age group.

Key Indexing Terms: Gastroesophageal reflux disease; Climate; Seasonality. **[Am J Med Sci 2009;338(6):453–458.]**

Gastroesophageal reflux disease (GERD) is a common condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications. A prevalence of 10% to 20% was reported in Western Europe and North America. In the United States, >40% of the population reports the symptoms of GERD atleast sporadically.[1] A survey conducted in New Zealand indicated a 30% prevalence of GERD there. In Asia, the prevalence of erosive esophagitis and complications of GERD have been reported variably, but they are generally less common than in Western countries. A recent study from Japan has reported 24.7% to 42.2% of patients complain of heartburn.[2,3]

The pathophysiology of GERD is multifactorial, including components such as anatomical irregularities of the stomach, gastroesophageal junction and the esophagus itself, the nervous system, lifestyle issues, such as obesity, a high-fat diet, cigarette smoking, consumption of alcohol and coffee, and ingestion of medications such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Also, Locke et al emphasized that a family history of gastroesophageal reflux symptoms or gastroesophageal disease were principal risk factors for gastroesophageal reflux symptoms.[4,5] Although many studies have reported seasonal variation in relapses and hospital admissions for peptic ulcers and irritable bowel disease,[6,7] as far as we know, no study has ever attempted to explore the seasonality of GERD or its association with climate.

Adopting a time-series analysis and using a 6-year nationwide population-based data from Taiwan, this study sets out to examine the possibility of seasonal variations in GERD incidence for different gender and age groups and their associations with climatic parameters. Understanding seasonal patterns of GERD and associated climatic triggers may aid clinicians developing effective strategies for preventing GERD, and also, help policy makers plan for appropriate healthcare resource distribution and seasonal availability during peak-incidence season.

METHODS

Ambulatory Care Data

This study used ambulatory care data from the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institute in 2008. This database consists of 1,073,891 randomly selected subjects, about 5% of all enrollees in the National Health Insurance program. This dataset was created by the Taiwan National Health Research Institute using a systematic method to randomly select a representative database from the entire set of enrollees. There were no statistically significant differences in age, gender, and healthcare costs between the sample group and all enrollees. The principle diagnoses are based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and include up to 3 secondary diagnoses.

Study Sample

Between January 1, 2001, and December 31, 2006, there were 79,661 ambulatory care visits for the treatment of GERD, as identified from the database by a principle diagnosis of reflux esophagitis (ICD-9-CM code 530.11). We excluded data of patients younger than 18 years and revisits for treatment of GERD within 30 days (which were regarded as the same episode). All included patients had been recently diagnosed with GERD during the study period. The Bureau of the National Health Insurance requires that GERD patients be diagnosed by either endoscopy or 24-hour pH-meter inspection

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before proton pump inhibitors' prescriptions can be applied for treatment. Therefore, GERD diagnosis was considered very valid in Taiwan. Ultimately, our study sample included 76,636 cases of GERD patients for the years 2001–2006, inclusive. The mean age of the cohort was 52.9 years with a standard deviation of 16.6 years.

Population Data

This study used data from the NHIRD to calculate the GERD monthly incidence rates per 10,000 people. We defined the monthly GERD incidence rate as the proportion of ambulatory care visits for the treatment of GERD in relation to the total population identified through the NHIRD, which is expressed as a fraction.

Meteorological Data

Meteorological data, including average monthly ambient temperature, relative humidity, atmospheric pressure, rainfall, hours of sunshine, and maximum and minimum temperatures, were obtained from 19 Taiwan Central Weather Bureau observation stations. Although the Central Weather Bureau has 26 observation stations across the island, the meteorological data from 7 stations located in mountainous regions with very sparse population was discarded. By excluding data from the mountain weather stations, the remaining data more closely represents conditions experienced by the majority of the population. Monthly mean values were then calculated by averaging monthly data from the remaining 19 stations. Because Taiwan is a relatively small island, with a total land area slightly $<$36,200 square kilometers, we can use monthly mean values of climatic data to explore its association with GERD incidence.

Statistical Analysis

Monthly GERD incidence rates per 10,000 people were calculated over 72 months and categorized into gender and age groupings (of 19–44, 45–64, and $\geq$65 years). Seasonality is a general component of time-series patterns. Therefore, the seasonality of the data was evaluated using the auto-regressive integrated moving average (ARIMA) method, which describes a univariate time series as a function of its past values. This method has been used to test for the presence of seasonality in earlier, analogous studies.

This study likewise adopted the ARIMA regression method as a means of evaluating the effects of climatic and monthly factors on GERD incidence rates, after adjusting for the time-trend effect. The time trend was a count variable numbered from 1 to 84, according to the time series. Selection of the final parameters was based on the lowest mean absolute percentage error, or mean absolute error, allowing the choice of the best model from the family of ARIMA regression models. All P values of < 0.05 were considered statistically significant in this study.

RESULTS

GERD Incidence Rates

The number of first-time ambulatory care visits (within 30 days) for GERD treatment by year throughout the study period were 7,023 (2001), 7,738 (2002), 8,932 (2003), 13,559 (2004), 17,495 (2005), and 21,889 (2006; Table 1). These figures correspond to annual incidence rates of 112.4, 121.0, 134.4, 202.8, 243.6, and 320.4 per 10,000 people, respectively. Throughout the study period, the monthly GERD incidence (per 10,000 people) ranged from a low of 7.63 in January 2001, to a high of 29.10 in November 2006, with a mean of 15.76 and a standard deviation of 6.57 (Table 2). The mean monthly GERD incidence for men and women was 17.70 and 14.03, respectively.

TABLE 1. Monthly mean values for ambulatory care visits seeking treatment for gastroesophageal reflux disease and meteorological factors, 2001–2006 in Taiwan (n = 76,636)

Variable	Monthly mean	SD	Minimum	Maximum
Reflux esophagitis/10,000 persons, aged 19–44 yr	10.94	5.29	3.85	23.80
Reflux esophagitis/10,000 persons, aged 45–64 yr	20.01	8.15	9.10	37.31
Reflux esophagitis/10,000 persons, aged >64 yr	27.68	7.72	14.86	45.72
Reflux esophagitis/10,000 persons				
Total	15.76	6.57	7.63	29.10
Male	17.70	7.24	7.73	32.02
Female	14.03	6.06	5.76	26.81
Ambient temperature (°C)	23.13	4.00	16.26	29.01
Relative humidity (%)	78.08	2.80	69.70	84.02
Atmospheric pressure (hPa)	998.72	5.04	989.43	1006.91
Rainfall (mm)	189.77	151.79	26.99	944.80
Sunshine (hr)	149.85	40.06	76.76	278.02
Maximum temperature (°C)	31.12	2.81	25.31	35.16
Minimum temperature (°C)	16.72	5.19	6.81	24.01

Seasonality

Spring occurs in Taiwan from March to May, summer from June to August, autumn from September to November, and winter from December to February. Seasonal variations in GERD incidence for each gender group, each age group, and both gender groups combined are given (Figures 1 and 2). In addition, we also present seasonal variations in GERD incidence expressed as percentages for each gender group, age group, and both gender groups pooled (Figure 3). A fairly similar seasonal pattern of GERD incidence was apparent for each gender and age, as well as for the combined groups. Seasonal trends showed incidence peaking in October to December, followed by a sharp decrease in January, and a trough in February. Then an upward trend started, which peaked in March. The ARIMA test for seasonality found significant patterns for the total group ($P < 0.01$), for female patients ($P < 0.05$), and for the 45 to 64 years ($P < 0.01$) and >64 years ($P < 0.01$) age groups (Tables 2 and 3).

Climatic Influences

Mean monthly figures for the 5 climatic variables across the entire 6-year study period were 23.1°C temperature, 78.1% relative humidity, 998.7 hPa atmospheric pressure, 189.8-mm rainfall, and 149.9 monthly hours of sunshine (Table 1). After adjustment for the time trend, the ARIMA regression models showed that relative humidity was negatively related to monthly GERD incidence rate for men ($P < 0.01$) and the >64 years ($P < 0.01$) age group, whereas rainfall was positively related to only the >64 years ($P < 0.05$) age group.

DISCUSSION

Our study demonstrates that the incidence of GERD has been rising consistently during the past few years in Taiwan. According to the study conducted by Locke et al,[8] it is esti-

TABLE 2. ARIMA regression analysis by gender group

Independent variable	Total			Male			Female		
	β	SE	t	β	SE	t	β	SE	t
Intercept	57.178	148.636	0.38	167.610	161.456	1.03	104.903	151.307	0.69
Atmospheric pressure	−0.042	0.143	−0.29	−0.139	0.154	−0.89	−0.097	0.147	−0.65
Ambient temperature	−0.014	0.213	−0.06	−0.027	0.208	−0.12	−0.159	0.250	−0.63
Relative humidity	−0.224	0.119	−1.86	−0.398	0.131	−3.02[a]	−0.105	0.124	−0.84
Rainfall	0.002	0.002	0.76	0.003	0.002	1.11	0.001	0.002	0.31
Hours of sunshine	−0.006	0.011	−0.53	−0.016	0.012	−1.30	0.002	0.012	0.16
Trend	0.447	0.066	6.75[b]	0.501	0.037	13.44[b]	0.411	0.060	6.76[b]
AR1	0.761	0.167	4.54[b]	0.902	0.038	23.37[b]	0.556	0.211	2.62[c]
MA1	−0.402	0.256	−1.56	−0.997	0.090	−10.99[b]	−0.012	0.272	−0.04
SAR12	0.388	0.154	2.50[a]	0.188	0.147	1.27	0.373	0.144	2.58[c]
Akaike info criterion		3.7193			3.8311			3.8523	
Schwarz criterion		4.0714			4.1832			4.2045	
R^2		0.958			0.959			0.945	

Selection of the final parameters was based on the lowest Akaike info criterion and Schwarz criterion.
[a] $P < 0.01$.
[b] $P < 0.001$.
[c] $P < 0.05$.
AR1, autoregressive lag 1; MA1, moving average lag 1; SAR12, seasonal correlation lag 12; ARIMA, auto-regressive integrated moving average.

mated that around 20% of American adults experience heartburn weekly. It is generally believed that GERD is less common among Asians. However, the findings of this study show that, if present trends continue, GERD will become a considerable medical burden in the near future in Taiwan. The causes of increasing numbers of patients seeking medical care for GERD are not completely known. However, an increasingly westernized diet and lifestyle in Taiwan are potential explanatory factors. Meanwhile, in addition to classic symptoms, physicians' attention is increasingly drawn to extraesophageal manifestations,[9] hence, fewer patients suffering from GERD are neglected. All the above phenomena contribute to an increasing number of patients diagnosed with GERD in Taiwan.

Our study also found that there were seasonal variations in GERD incidences for the total group, for female patients, and for the 45 to 64 years and >64 years age groups. Seasonal

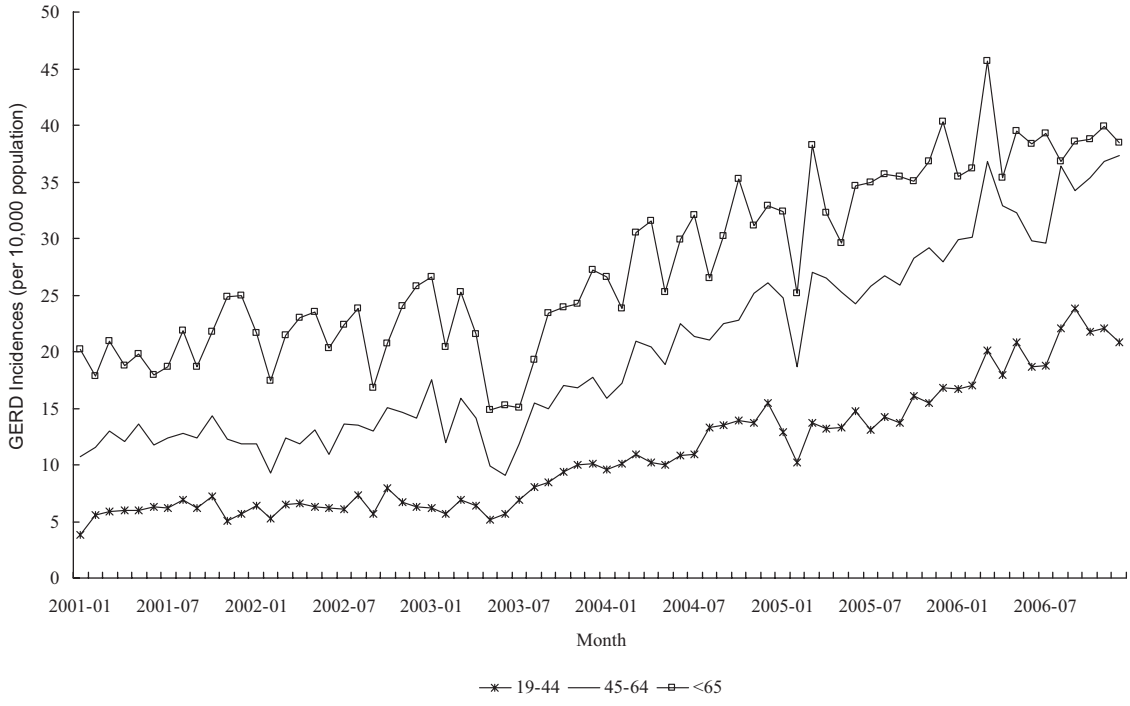

FIGURE 1. Monthly reflux esophagitis incidences per 10,000 population by age group in Taiwan, 2001–2006.

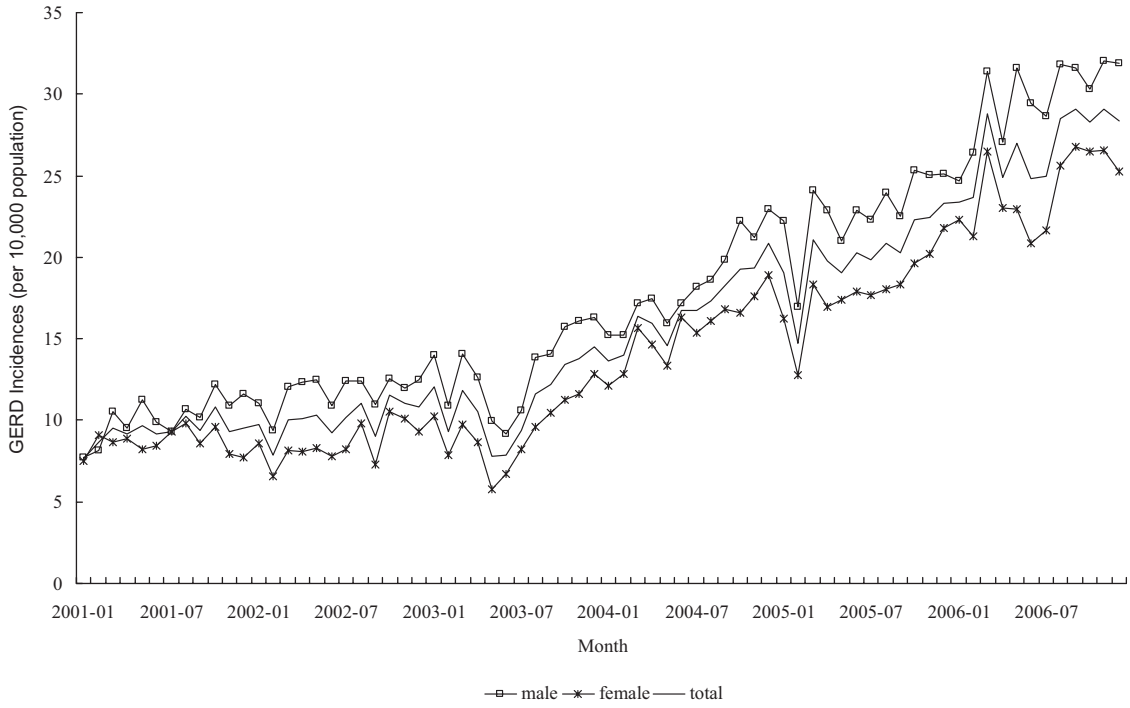

FIGURE 2. Monthly reflux esophagitis incidence per 10,000 population by gender group in Taiwan, 2001–2006.

patterns of GERD incidence were rather similar for these groups: a trough in January and February, followed by a rebound in March. This finding is compatible with the custom of not seeking medical care during the Chinese new year months of January or February. Another likely explanation for consistently low incidences of GERD in February is that there are fewer days in the month. Patients crowd into the hospital seeking treatment for GERD after a long vacation, and hence a March surge develops.

Other possible explanations include the possibility that seasonal variation in body weight may affect the occurrence of GERD. First, several studies have confirmed the role of obesity in GERD, and body mass index positively correlates with symptom severity.[10,11] In theory, obesity influences GERD by

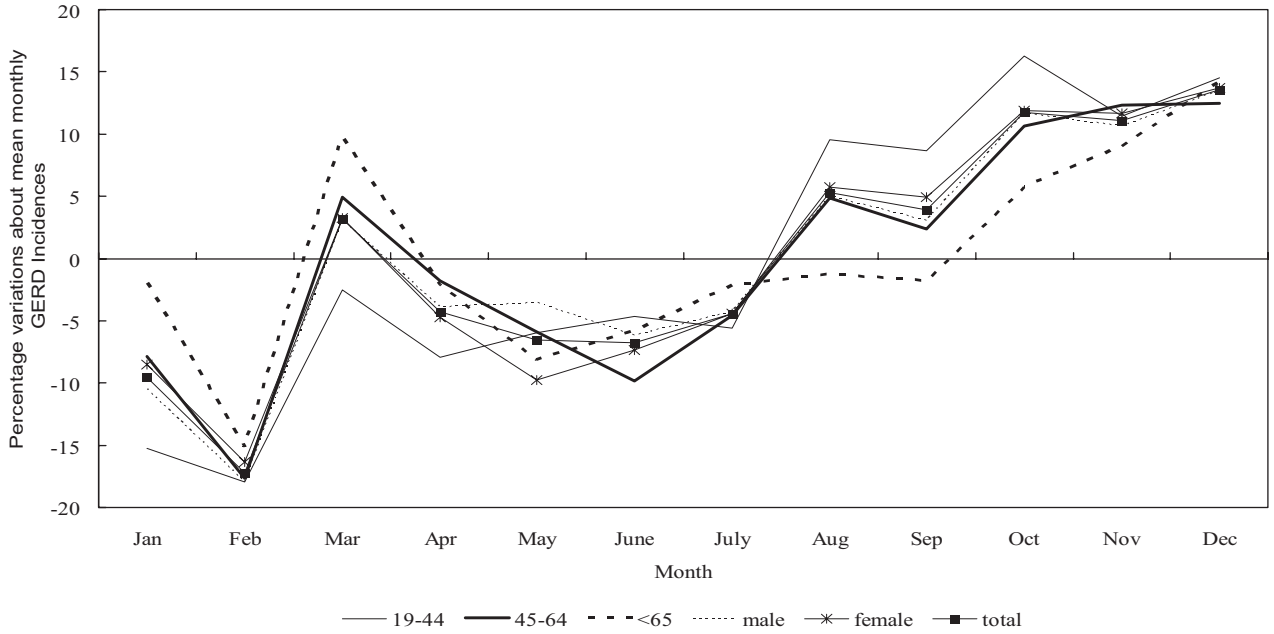

FIGURE 3. Mean monthly average percentage variations in reflux esophagitis incidences per 10,000 population according to age and gender groups.

TABLE 3. ARIMA regression analyses by age group

Independent variable	Age (yr)								
	19–44			45–64			>64		
	β	SE	t	β	SE	t	β	SE	t
Intercept	16.303	115.449	0.14	42.879	210.628	0.20	278.609	301.834	0.92
Atmospheric pressure	−0.007	0.110	−0.06	−0.024	0.205	−0.11	−0.201	0.292	−0.68
Ambient temperature	0.132	0.142	0.92	−0.180	0.355	−0.50	−0.379	0.434	−0.87
Relative humidity	−0.184	0.092	−1.99	−0.249	0.161	−1.54	−0.727	0.236	−3.07[a]
Rainfall	0.001	0.002	0.18	0.002	0.003	0.53	0.011	0.004	2.47[b]
Hours of sunshine	−0.012	0.008	−1.38	0.003	0.016	0.18	−0.018	0.022	−0.80
Trend	0.343	0.057	5.98[c]	0.560	0.076	7.33[c]	0.385	0.086	4.43[c]
AR1	0.871	0.100	8.69[c]	−0.145	0.291	−0.49	0.697	0.222	3.13[a]
MA1	−0.566	0.198	−2.84[a]	0.569	0.252	2.25[b]	−0.312	0.292	−1.06
SAR12	0.062	0.180	0.34	0.436	0.136	3.18[a]	0.365	0.126	2.88[a]
Akaike info criterion		3.4244			4.5139			5.1336	
Schwarz criterion		3.7765			4.8660			5.4857	
R^2		0.952			0.940			0.876	

Selection of the final parameters was based on the lowest Akaike info criterion and Schwarz criterion.
[a] $P < 0.01$.
[b] $P < 0.05$.
[c] $P < 0.001$.
AR1, autoregressive lag 1; MA1, moving average lag 1; SAR12, seasonal correlation lag 12; ARIMA, auto-regressive integrated moving average.

increasing upper abdominal pressure, provoking gastroesophageal reflux. Furthermore, losing weight has actually been reported to have a beneficial effect on GERD.[12] Also, Westerterp[13] reported that body weight showed a pronounced seasonal variation, with a maximum in winter and a minimum in summer. Ma et al[14] likewise concluded that body weight varied in different seasons, with a peak in the winter, and greater variation was found especially in subjects of middle age. Such weight gain may increase abdominal pressure and contribute to the development of GERD.

Second, several investigators have explored the relation between diet and GERD, finding that high-fat meals induce GERD by reducing the lower esophageal sphincter (LES) pressure.[15,16] Importantly, transient LES relaxation plays a critical role in the pathophysiology of GERD. Dietary fat has been shown to release cholecystokinin and subsequently trigger transient LES relaxation.[17] It is plausible to suppose that changes in diet could likewise contribute to seasonal variations in the incidence of GERD. In fact, 1 previous report found significant increased mean dietary intake of fat in winter compared with that in summer.[18] Furthermore, this increase also resulted in increased body mass index in the winter. Okawa et al[19] also reported that 13% of healthy Japanese show apparent increasing appetite and body weight during winter compared with summer. In summary, the seasonality of GERD is closely linked to body weight and fat content of the diet.

In addition to dietary factors, several medications promote gastroesophageal reflux by decreasing the pressure of LES. The LES-relaxing effect is quite evident in nitroglycerins, anticholinergics, β-adrenergic agonists, aminophyllines, α-adrenergic antagonists, nicotine derivatives, tricyclic antidepressants, chlorpromazines, and calcium-channel blockers.[20] Association has been reported between the use of LES-relaxing drugs and esophageal adenocarcinoma, probably via promoting gastroesophageal reflux.[20] Anticholinergics, β-adrenergic agonists, and aminophyllines are commonly used in treatment for chronic obstructive pulmonary disease. Aminophyllines and β-adrenergic agonists are also used in the management of asthma. Exacerbations of these 2 diseases demand more medication. Not surprisingly, increasing medication usage during acute exacerbations of chronic obstructive pulmonary disease and asthma would increase the occurrence of GERD. According to Johnston's study,[21] young adults more frequently experience exacerbations in winter months. However, there is still a peak in late summer and early autumn, a pattern of distribution fairly similar to our own.

For older adults, winter is the most prominent period of exacerbation of GERD, although a small increase occurs in early autumn. The prescription of NSAIDs for GERD is an issue under investigation. Accumulated evidence suggests that NSAIDs may damage the esophageal mucosa by breaking the esophageal mucosal barrier.[22] Furthermore, Kotzan et al[23] confirms that NSAIDs are associated with GERD, especially for females, alcohol and tobacco users, and patients with asthma, hiatal hernia, or obesity. There is general agreement that acute upper respiratory tract infection exhibits seasonal variation and commonly peaks in winter.[24] The potential use of NSAIDs for acute upper respiratory tract infection during winter might likewise play a part in seasonal fluctuation of GERD. Therefore, widespread use of the above medications is responsible for development of GERD as well. Taken together, the seasonality of GERD probably reflects, in part, the side effects of various drugs used to treat a range of primary diseases that fluctuate seasonally.

This is the first study to report an association between GERD incidence and weather conditions. This study found that seasonal variations in GERD incidence are correlated with climate in Taiwan: relative humidity was negatively related to monthly GERD incidence for men and for the >64 years age group, and rainfall is positively related to GERD in the >64 years age group,

after adjusting for time trends and month effects. However, the mechanisms underling these associations are not clear. Large-scale prospective studies by clinical and biological researchers should be initiated to clarify the biological mechanisms linking the GERD incidence and relative humidity.

There are a couple of limitations to our study. First, we cannot obtain adequate information regarding diet composition, body weight, and use of NSAIDs or LES-relaxing drugs. Because multiple factors are involved in the development of GERD, we recommend prospective studies that clarify reasons for the seasonality of GERD. Second, the GERD incidence reported here may underestimate actual incidence, because some patients may not seek medical help for the treatment for GERD. However, we believe our data affords a very good estimate of the actual GERD incidence, because of the very low out-of-pocket payments for ambulatory care under Taiwan's universal health care coverage.

Despite these limitations, our study is the first to report an incidence of increased GERD in the autumn and winter for each gender and age, as well as the combined groups. Clinicians can become increasingly aware of periods of potentially increased risk; clinicians diagnose GERD by not only paying attention to typical GERD symptoms but also to others such as chronic pharyngitis or chronic cough. In addition, clinicians could improve hygienic education for patients, their food habits, and lifestyle during this period. If needed, clinicians will give prophylactic medication to high-risk patients in the seasons of autumn and winter. We also found that after adjusting for time trends, relative humidity was negatively related to monthly GERD incidence for men and the >64 years age group. We recommend future studies to be conducted in other regions and among other ethnic groups to explore the associations between climatic parameters and GERD incidence patterns, to reveal general patterns worldwide.

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