



The impact of allergic rhinitis on gastrointestinal disorders among young adults

Sai-Wai Ho Dr, MD^{1,2} | Ching-Pin Lin Dr, MD^{3,4} | Min-Sho Ku Dr, PhD^{1,5} 

¹School of Medicine, Chung Shan Medical University, Taichung, Taiwan

²Department of Emergency Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan

³Institute of Biochemistry, Microbiology and Immunology, Chung Shan Medical University, Taichung, Taiwan

⁴Division of Gastroenterology, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan

⁵Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwan

Correspondence

Min-Sho Ku, School of Medicine, Chung Shan Medical University, and Department of Pediatrics, Chung Shan Medical University Hospital, 110, Section 1, Chien-Kuo North Road, Taichung, Taiwan.
Email: a129184@yahoo.com.tw

Abstract

Background: An association between allergic rhinitis (AR) and digestive diseases (DDs) has been reported; however, studies have only focused on the prevalence of DDs in populations of patients with AR. In individuals with specific DDs, the impact of AR on the frequency of clinical visits for each DD has not been studied. Moreover, the association between topical steroid usage for AR and DDs has not been investigated.

Methods: Data from 16 526 men and 18 438 women, aged 21 to 30 years, were collected from a national database. Individuals were separated into the AR and non-AR groups. Eight common DDs were studied: (1) gastroesophageal reflux disease (GERD), (2) gastritis and duodenitis, (3) peptic ulcers, (4) irritable bowel syndrome, (5) gastric functional disease, (6) intestinal functional disease, (7) gastroenteritis and colitis, and (8) constipation. The rate of each DD was compared between groups. In individuals with specific DDs, the frequency of clinical visits for each DD was also compared between groups. Between users and nonusers of topical steroids in the AR group, the rate of DDs was compared.

Results: Significant associations were observed between all eight DDs and AR in both sexes. In comparison to the non-AR group, women with AR visited clinics more frequently for gastritis/duodenitis, gastric and intestinal functional disease, gastroenteritis/colitis, and constipation, while men with AR visited clinics more frequently for gastritis/duodenitis, gastric functional disease, gastroenteritis/colitis, and constipation. Female topical-steroid users with AR had higher rates of GERD, irritable bowel syndrome, gastric or intestinal functional disease, and gastritis/colitis. Male topical-steroid users with AR had higher rates of GERD and peptic ulcers.

Conclusion: AR was associated with DDs in both sexes. However, the influence of AR on clinical visit frequency varied among specific DD groups. Topical steroid usage for AR was associated with some DDs, but the association requires future evaluation.

KEYWORDS

allergic rhinitis, clinical visit, digestive disease, topical steroid

1 | INTRODUCTION

Similar to lung disease,¹ inflammation occurring in the nasal passage may influence gastrointestinal disease.²⁻⁷ The association between

allergic rhinitis (AR) and irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), and peptic ulcers has been reported.²⁻⁷ However, only one or two digestive diseases (DDs) were investigated in those studies.

Previous studies²⁻⁷ investigated the prevalence rate of DDs in AR and non-AR patients. However, for individual subjects with specific DDs, the influence of AR on the specific DD frequencies has not been studied. Moreover, the role of topical steroids for AR on DD is not completely understood.²⁻⁷

Many factors, such as mood disorders, chronic abdominal disease, and other diseases, can potentially manifest with abdominal signs and symptoms. An increase of IBS occurrence in asthma patients was also reported.⁴ However, these confounding factors have rarely been holistically considered before.²⁻⁷

DD and AR are common and have a negative impact on productivity and quality of life and result in increased medical visits. Therefore, extensively studying their association is worthwhile. By analysing a large set of representative data and adjusting for confounding factors, we aimed to investigate any correlation between AR and eight common DDs. For individual subjects with specific DDs and concomitant AR, we also investigated whether clinical visits for that specific DD are higher than for subjects without AR. In AR subjects, the rates of DD between those who were or were not using topical steroids for AR were also compared to investigate the impact of topical steroids on DD.

2 | METHODS

2.1 | Database

The National Health Insurance Research Database was created by the National Health Research Institute in Taiwan.^{8,9} The National Health Research Institute randomly sampled a representative database of 1 million subjects in 2010 through systematic sampling. These 1 million samples served as our data source. Ninety-eight percents of them were Han nationality, and the remaining were Taiwanese aborigines. The database provides information on patient identification, numbers, birthdays, sex, diagnostic codes in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format, prescription drugs, medical care facilities, as well as other categories.

2.2 | Data collection, criteria of AR, and gastrointestinal disease

In total, 34 964 people, born between 1982 and 1983, were randomly selected from the National Health Insurance Research Database. From 2002 to 2013, claims data from the entire cohort from 21 to 30 years of age were analysed. The criteria of AR were at least two diagnoses of AR over a period of 10 years recorded by doctors. Because AR is a chronic disease, those with AR duration <180 days were excluded. Those meeting the criteria for AR were classified as AR subjects, and those without were classified as non-AR subjects. Eight major DDs were selected for our study. The diseases included (1) GERD, (2) gastritis and duodenitis, (3) peptic ulcers, (4) IBS 5. gastric functional disease, (6) intestinal functional disease, (7) gastroenteritis and colitis (other and unspecified noninfectious gastroenteritis and colitis), and (8) constipation.

2.3 | The association between AR and common digestive diseases

Rates of the eight DDs between AR and non-AR groups and between genders were compared. More than two diagnoses of each DD in 10 years were used to define those with the individual disease. In AR subjects, the rates of DD between those using topical steroids for AR or not were also compared for each gender.

In those with individual DD, we compared the frequencies of clinical visits between AR and non-AR subjects, for each disease, subdivided by gender. For example, for those with peptic ulcer disease, the mean number of clinical visits for peptic ulcers in the 10-year period, between male and female, and AR and non-AR subjects were compared. Then we could determine, in peptic ulcer disease subjects, if having AR increases the number peptic ulcer clinical visits or not.

The frequency of clinical visits for intestinal infectious diseases between AR and non-AR subjects was also compared with investigate the effect of AR on intestinal infection.

2.4 | Determining the confounding factors

Neurologic diseases, mood, anxiety, and some mental disorders might induce symptoms such as vomiting, diarrhoea, or abdominal pain. Other chronic gastrointestinal disorders, such as inflammatory bowel disease and chronic pancreatic or liver disease might also induce these abdominal symptoms. Together with asthma, other variables including pregnancy, abdominal surgery, gender, urbanization, socio-economic status, and obesity were classified as potential confounding factors and were adjusted for in our study. The criteria of asthma were at least two diagnoses of asthma over a period of 10 years recorded by doctors. Because asthma is a chronic disease, those with asthma duration <180 days were excluded. Socioeconomic status and education level were defined according to the patients' occupations. The occupation classifications were as follows: (1) teacher, public official, or staff employed by companies; (2) other jobs; and (3) peasant or fisherman. Based on Liu's report,¹⁰ urbanization levels were grouped into seven levels. Level 1-2 was grouped to urban citizens, and level 3-7 was grouped to rural citizens. Patients with malignant neoplasms had many abdominal symptoms and signs from either the malignant disease itself or from treatment, and therefore, they were excluded from our study.

2.5 | ICD-9-CM codes and ATC code

The ICD-9-CM codes of the confounding factors were asthma (493), chronic pancreatitis (577.1), chronic cholecystitis (575.11), cholelithiasis (574), viral hepatitis (070), chronic liver disease and cirrhosis (571), inflammatory bowel disease (555, 556), migraine (346), glaucoma (365), disorder of vestibular system (386.0~386.3), mood disorder (293.83, 296), anxiety (293.84, 300.0), and obesity (278). The ICD-9-CM codes of AR and the gastrointestinal diseases were AR (477), GERD (530.11, 530.81), gastritis and duodenitis (535), peptic ulcers (531~534), IBS (564.1), gastric functional disease (536.8, 536.9), intestinal functional disease (564.8, 564.9), gastroenteritis and colitis (558.9), constipation (564.0), and intestinal infectious disease

(001~009). The ATC code R01AD (nasal preparations for topical use, corticosteroids) was used for "topical steroids for AR."

2.6 | Statistical analysis

All analyses were performed using SAS version 9.1 for windows (SAS Inc., Cary, NC, USA) and PASW Statistics 18 (IBM, Armonk, NY, U.S.A.). The chi-square test was used for the rate comparisons of DD between groups. A Student's *t* test was used for differences in the frequencies of DD clinical visits between groups. Multivariate logistic regression and multivariate regression analyses were used to adjust for confounding factors. Two-sided *p* values of <0.05 were defined as statistically significant.

3 | RESULTS

3.1 | Demographic data and intestinal infectious disease

The results are presented in Table 1. In total, 34 964 subjects were recruited (16 526 men and 18 438 women). The AR group made up 20.41% (7 135 subjects) of the studied subjects with 2998 men (18.1%) and 4137 women (22.4%). The frequency of clinical visits per subject for intestinal infectious disease in the 10-year period was studied. In males, the number of clinical visits was higher overall in AR subjects (0.66 visit times) than in non-AR subjects (0.37 visit times), with an adjusted *p* value < 0.001. In female, the number of clinical visits was also higher in AR subjects (0.76 visit times) than in non-AR subjects (0.44 visit times), with an adjusted *p* value < 0.001.

3.2 | Rates of DDs between AR and non-AR subjects

The results are presented in Table 2. The rate of all eight diseases was higher in AR subjects of both sexes (male OR 1.87–2.39-fold, female OR 1.65–2.45-fold). The highest and lowest fold differences in the rate of DDs for AR vs non-AR males were intestinal functional disease (OR 2.39) and peptic ulcers (OR 1.87), respectively. The highest and lowest fold-differences for females were GERD (OR 2.45) and intestinal functional disease (OR 1.65), respectively.

TABLE 1 Demographic data of study subjects

	Male (n = 16 526)		Female (n = 18 438)	
	AR (18.1%) n = 2998	Non-AR (81.9%) n = 13 528	AR (22.4%) n = 4137	Non-AR (77.6%) n = 14 301
Urbanization				
1. Urban	1759 (58.7%)	7754 (57.3%)	2410 (58.3%)	8212 (57.4%)
2. Country	1239 (41.3%)	5774 (42.7%)	1727 (41.7%)	6089 (42.6%)
Occupation				
1. Public official, Company employee	1635 (54.5%)	7505 (55.5%)	2249 (54.4%)	8191 (57.3%)
2. Other jobs	1000 (33.4%)	4361 (32.2%)	1386 (33.5%)	4512 (31.5%)
3. Peasant or Fisherman	363 (12.1%)	1662 (12.3%)	502 (12.1%)	1598 (11.2%)

Abbreviation: AR, allergic rhinitis.

3.3 | Frequency of clinical visits for each DD between AR and non-AR subjects with an individual DD

The results are presented in Table 3. In males, 3435 subjects had gastritis and duodenitis, and 26.3% of them had AR. The mean number of clinical visits for gastritis and duodenitis per subject in the 10-year period was 4.9 in AR subjects and 4.4 in non-AR subjects. The mean number of clinical visits was higher in AR subjects with statistical significance. Similar conditions were also noted in gastric functional disease, gastroenteritis and colitis, and constipation in males. In females, 6218 subjects had gastritis and duodenitis and 31.5% of them had AR. Their mean number of clinical visits for gastritis and duodenitis per subject in the 10-year period was 5.9 in AR subjects and 4.7 in non-AR subjects. The mean number of clinical visits was higher in AR subjects with statistical significance. Similar conditions were noted in gastric functional disease, intestinal functional disease, gastroenteritis and colitis, and constipation in females.

3.4 | Rates of DDs in AR subjects either using or not using topical steroids for AR

The results are presented in Table 4. In male AR subjects, the rates of GERD (OR 1.78) and peptic ulcers (OR 1.31) were higher in those who used topical steroids for AR than those who did not. In females, the rates of GERD (OR 1.89), IBS (OR 1.51), gastric functional disease (OR 1.17), intestinal functional disease (OR 1.20), and gastroenteritis and colitis (OR 1.23) were higher in those using topical steroids for AR than those did not.

4 | DISCUSSION

Our study found that AR subjects had higher rate of the eight DDs. The increase ranged from 1.65 to 2.45-fold and varied between different DD and genders. Intestinal conditions were reported to influence the immune system.¹¹ A previous study demonstrated that the association between atopy and IBS, functional dyspepsia, and constipation could be partially explained by the presence of mood disorders (anxiety and depression).³ In our study, after adjusting for the confounding factors of mood disorders, we still found a strong relationship

TABLE 2 The rate of digestive disease between AR and non-AR subjects

		AR, %	Non-AR, %	Adjusted P Value ^a	Odds Ratio 95% CI
Gastroesophageal reflux, %	Male	6.2	2.7	<0.001	2.36 (1.97–2.83)
	Female	7.3	3.1	<0.001	2.45 (2.01–2.84)
Gastritis and duodenitis, %	Male	30.1	18.7	<0.001	1.87 (1.71–2.05)
	Female	47.3	29.8	<0.001	2.12 (1.97–2.27)
Peptic ulcers, %	Male	15.5	9.0	<0.001	1.87 (1.67–2.1)
	Female	19.4	10.2	<0.001	2.12 (1.93–2.33)
Irritable bowel syndrome, %	Male	5.0	2.2	<0.001	2.29 (1.88–2.8)
	Female	5.6	2.9	<0.001	1.97 (1.67–2.32)
Gastric functional disease, %	Male	26.4	13.1	<0.001	2.38 (2.17–2.62)
	Female	41.4	24.3	<0.001	2.2 (2.05–2.37)
Intestinal functional disease, %	Male	9.8	4.4	<0.001	2.39 (2.06–2.76)
	Female	17.1	11.1	<0.001	1.65 (1.5–1.82)
Gastroenteritis and colitis, %	Male	45.2	28.0	<0.001	2.13 (1.96–2.31)
	Female	51.0	33.2	<0.001	2.09 (1.95–2.25)
Constipation, %	Male	6.7	3.1	<0.001	2.37 (1.99–2.82)
	Female	31.5	21.2	<0.001	1.71 (1.58–1.84)

^aAdjusted for neurologic diseases, mood, anxiety, some mental disorders, other chronic digestive disease, pregnancy (female), abdominal surgery, sex, urbanization, socio-economic status, obesity, and asthma.

Abbreviations: AR, allergic rhinitis; CI, confidence interval.

TABLE 3 The mean number of clinical visits per subject for each digestive disease in the 10-year period surveyed among AR and non-AR subjects

	Male			Female		
	Number ^a AR, %	Visit Frequency (AR/non-AR)	Adjusted P Value ^c	Number ^a AR, %	Visit Frequency (AR/non-AR)	Adjusted P Value ^c
Gastroesophageal reflux	558 (33.5%)	4.8/4.6	0.905	751(40.4%)	4.8/4.0	0.094
Gastritis and duodenitis	3435 (26.3%)	4.9/4.4	0.044 ^b	6218(31.5%)	5.9/4.7	<0.001 ^b
Peptic ulcers	1679 (27.8%)	6.5/5.7	0.096	2264(35.5%)	5.8/5.1	0.070
Irritable bowel syndrome	451 (33.0%)	5.0/4.6	0.903	645(35.7%)	4.2/3.9	0.789
Gastric functional disease	2560 (30.9%)	5.7/4.9	0.015 ^b	5192(33.0%)	5.8/5.0	<0.001 ^b
Intestine functional disease	883 (33.3%)	4.6/4.1	0.337	2291(30.8%)	5.1/4.4	0.015 ^b
Gastroenteritis and colitis	5138 (26.4%)	4.1/3.7	0.035 ^b	6862(30.8%)	4.7/3.9	<0.001 ^b
Constipation	602 (33.6%)	6.2/4.6	0.033 ^b	4340(30.1%)	8.3/6.8	<0.001 ^b

^aNumber: numbers of the individual digestive disease; AR(%): rate of AR subjects in the individual digestive disease.

^b $p < 0.05$.

^cAdjusted for neurologic diseases, mood, anxiety, some mental disorders, other chronic digestive disease, pregnancy (female), abdominal surgery, sex, urbanization, socio-economic status, and obesity.

Abbreviations: AR, allergic rhinitis.

between AR and the eight DDs. At the genetic level, variations in specific genes including *TLR9*, *IL6*, and *CDH1* have been reported to influence local mucosal immune function in IBS.¹² These three genes are also associated with atopic disease. At the histological level, people with allergies may have low-grade inflammation in the gut,¹³ increased colonic permeability,¹⁴ and other factors that might explain the association.

At the immunological level, the number of eosinophils is higher in the gastrointestinal tract in functional dyspepsia patients¹⁵ and those with gastroesophageal disease.¹⁶ Serum total immunoglobulin E and house dust mite-specific immunoglobulin E are reported to be positively correlated with gastrointestinal symptoms in atopic patients.⁷ In the AR patients in our study, the intestinal infectious disease rates were higher. Gut infection has been reported to be associated with functional dyspepsia.¹⁷ Therefore, gut infection might play a role in

DD in AR subjects. Environmental and dietary factors may change human microbiomes and lead to the increase of atopic diseases.^{18,19} Urbanization in Taiwan (Table 1; 58.4% of AR subjects lived in urban area) also showed an evidence of the increase in presence of AR in urban area.

The prevalence of functional gastrointestinal disorders and constipation was reported to be higher in women.²⁰ In our study, the rates of IBS, gastric/intestinal functional disease, and constipation were higher in females as well. However, AR's influence on the four diseases mentioned above was stronger among males compare to females (higher OR in males; Table 2). The reasons behind these differences require future studies.

The studies before were focused on the prevalence rate of DD in AR and non-AR subjects. However, for patients with individual DD, understanding if AR increases their DD severity (frequency of clinical

TABLE 4 In AR subjects, the rate of digestive disease between topical-steroid and nontopical steroid users

		Drug Use, %	No Drug Use, %	Adjusted P Value ^a	Odds Ratio 95% CI
Gastroesophageal reflux, %	Male	8.4	4.9	0.001 ^b	1.78(1.33–2.40)
	Female	10.3	5.7	<0.001 ^b	1.89(1.49–2.39)
Gastritis and duodenitis, %	Male	31.7	29.2	0.214	1.13(0.96–1.32)
	Female	49.3	46.3	0.145	1.13(0.99–1.28)
Peptic ulcers, %	Male	17.7	14.2	0.014 ^b	1.31(1.07–1.60)
	Female	20.7	18.8	0.291	1.13(0.96–1.32)
Irritable bowel syndrome, %	Male	5.9	4.4	0.120	1.36(0.98–1.89)
	Female	7.0	4.8	0.009 ^b	1.51(1.15–1.97)
Gastric functional disease, %	Male	25.7	26.8	0.214	0.94(0.80–1.12)
	Female	43.9	40.1	0.031 ^b	1.17(1.03–1.33)
Intestinal functional disease, %	Male	9.2	10.2	0.212	0.89(0.69–1.14)
	Female	18.8	16.1	0.038 ^b	1.20(1.02–1.42)
Gastroenteritis and colitis, %	Male	47.2	44.0	1.114	1.14(0.98–1.32)
	Female	54.4	49.2	0.003 ^b	1.23(1.08–1.40)
Constipation, %	Male	6.1	7.5	0.185	0.86(0.63–1.15)
	Female	31.4	31.6	0.832	0.99(0.86–1.14)

^aAdjusted by neurologic diseases, mood, anxiety, some mental disorder, other chronic digestive disease, pregnancy (female), abdominal surgery, sex, urbanization, socio-economic status, and obesity.

^b $p < 0.05$.

Abbreviations: AR, allergic rhinitis; CI, confidence interval.

visit) is as clinically important as understanding the DD prevalence rate in the population. We found that, for example, in gastritis/duodenitis female patients, those with AR had a higher frequency of clinical visits for the disease (5.9 clinical visits per subject in 10 years) than that for non-AR subjects (4.7 clinical visits). Similar conditions were also noted for the other four DDs in females and four DDs in males (Table 3). On the contrary, although AR increased the rate of all eight DDs, AR increased clinical visit frequencies for only some specific DDs, rather than for all eight DDs.

Little is known about the impact of topical steroids for AR on DD. We found that for AR subjects with topical steroid treatment, two DD's rate in male and five DD's rate in female were increased. Nasally administered corticosteroids may reach the gastrointestinal tract and then induce DD. Orally inhaled steroids were reported to have a slight risk of adverse gastrointestinal events such as gastritis, ulcers, and gastrointestinal bleeding,²¹ but with controversy.²² On the other hand, increased use of nasal steroids reflects overall increase in immunologic inflammation. Immunologic inflammation can impact the digestive tract^{7,13–16} and might induce adverse gastrointestinal events. Therefore, further studies are required to explore this relationship and the mechanism.

There are some limitations to our study. First, our data come from a database. There were no clinical criteria, clinical symptoms, or degree for AR and DD. Second, among AR subjects, clinical visits were more frequent than among subjects in the control group, and therefore, medical records regarding DD were also more frequently recorded during these clinical visits. Third, there were no laboratory data or image or endoscopic results for AR and DD. Fourth, we only investigated the effect of topical steroid in our study. Patient's medications such as nonsteroidal anti-inflammatory drug, antiplatelet, H1, and H2 blockers did not take into account. Therefore, the result of effect of topical steroid on DD should be read with caution.

There are also some strengths in our study. First, the study size was large (34 964 people). Second, the medical records from

physicians rather than patient's self-reports prevent missing data and recall bias. Third, our study investigated a wide profile of DDs rather than one or a few DDs, which has been the focus in other studies. Fourth, in comparison to other studies, our study adjusted for more confounding factors, including mood disorders and other factors. Thus, we could cleanly explore the influence of AR alone on DD. Fifth, we studied the influence of AR on clinical visit frequencies for DDs. Thus, we not only explored the association of AR and DDs but also practically explored the clinical manifestations of that association.

5 | CONCLUSION

The impact of AR on other diseases such as asthma has been well studied,¹ but information on AR's impact on DD is currently scarce. Through our study, the association between AR and DD was elucidated at a broader and more thorough level. The rates of the eight DDs were all higher in AR subjects. For individual subjects with specific DD, an increased frequency of clinical visits was noted in specific DDs if they also had AR. According to these results, patients should likely be informed that if they have any of the DDs mentioned above, their DD-related clinical visits may increase if they also have AR. Doctors could also pay more attention to those with DD-AR overlap conditions because their DD severity might increase. Treatment of one disease (AR) was reported to be helpful for the control of other disease (asthma).²³ We guess that treatment of AR might also be helpful for the control of DD. Studying the impact of AR on DD, including its mechanism, its influence on DD treatment, and its variation between different age groups, is our future objective.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Min-Sho Ku  <https://orcid.org/0000-0002-6654-4372>

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