

**Preschoolers with Allergic Diseases have an Increased Risk of
Irritable Bowel Syndrome when Reaching School Age**

Short title: irritable bowel syndrome in allergic diseases

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Abstract

Objectives: To systemically investigate the risk of subsequent irritable bowel syndrome (IBS) in children with antecedent allergic diseases in a population-based case-control study in Taiwan.

Methods: We evaluated 11,242 children (age range: 7–18 years) with IBS and 44,968 age- and sex-matched control subjects who had been examined between 2000 and 2008. IBS odds ratios (ORs) were calculated for children with antecedent allergic diseases, including allergic conjunctivitis (AC), allergic rhinitis (AR), asthma, atopic dermatitis (AD), urticaria, and food allergy (FA).

Results: Children with antecedent allergic diseases had a greater risk of IBS than did control subjects ($p < 0.001$). Among the 6 evaluated diseases, the highest adjusted OR (aOR) of 1.78 was observed with AR (95% confidence interval [CI], 1.69–1.87). With 2 or more allergic diseases, the aORs increased to 2.06 (95% CI, 1.93–2.19) for all subjects, 2.07 (95% CI, 1.88–2.28) for girls, and 2.18 (95% CI, 2.02–2.35) for children ≥ 12 years old.

Conclusions: Preschoolers with a history of allergic disease had an increased risk of subsequent IBS development upon reaching school age. This risk increased in the presence of concurrent allergic disease and a higher clinical allergy burden.

Key Words: allergic conjunctivitis; allergic rhinitis; asthma; atopic dermatitis; food allergy; irritable bowel syndrome

What Is Known

- Patients with a food allergy have a high prevalence of irritable bowel syndrome (IBS) and allergic diseases.
- Adults with asthma have a high prevalence of IBS.
- Children with increasing numbers of allergic disorders have an elevated risk of recurrent abdominal pain.

What Is New

- Children with antecedent allergic diseases (allergic conjunctivitis, atopic dermatitis, allergic rhinitis (AR), asthma, urticaria, and food allergy (FA)) had consistently increasing risks of IBS.
- Among the evaluated allergic diseases, AR presented the greatest risk of IBS, and FA was associated with the shortest time interval to IBS development.

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder in pediatric populations (1). Although IBS is generally benign, associated symptoms such as diarrhea, constipation, abdominal distention, bloating, and abdominal pain are frequently associated with anxiety, school absenteeism, a decreased quality of life, and increased health care burden (1). Currently, the exact etiology and pathophysiology of IBS are unclear (2,3). Although alterations of the brain-gut axis are thought to play a central role in the manifestation of IBS, inflammation, alterations in the gut microbiota, bacterial overgrowth, food hypersensitivities, psychological disorders, and genetic considerations have been reported to associate with IBS pathogenesis (2–6). Recently, increasing evidence has suggested that mucosal inflammation contributes to the development of this disorder (4,5). Mucosal inflammation, characterized by an increased number of immunocytes (e.g., lymphocytes, mast cells, eosinophils, and enteroendocrine cells), has been observed in the lamina propria and epithelium of patients with IBS (4,5). Increased numbers of mast cells and soluble mediators released by activated mast cells, particularly histamine and tryptase, have been reported to associate with food hypersensitivity and visceral hypersensitivity in patients with IBS (6–9).

The association between allergy and IBS has remained controversial for many years. Patients with food allergy (FA) were reported to exhibit a high prevalence of IBS and allergic disease (10,11). One study noted that a food elimination diet effectively reduced IBS symptoms (12). Previous studies have also reported a high prevalence of IBS among patients with asthma (13–16). One study in the USA evaluated adult participants via questionnaires and found a strong association of IBS with atopic manifestations, such as allergic rhinitis and atopic dermatitis (17). This finding contributed to knowledge and ideas regarding the pathophysiology of IBS. However, earlier studies included a limited number of patients and

mainly focused on adults. Although a population-based birth cohort study in Sweden found an association between increasing numbers of allergy-related diseases and an elevated risk of recurrent functional abdominal pain in children, the association of allergic diseases with IBS in Asian pediatric populations remains unknown (18). To investigate whether allergic disease is a risk factor for childhood IBS, we conducted a population-based case-control study to evaluate the hypothesis that children with allergic diseases, including allergic conjunctivitis (AC), allergic rhinitis (AR), asthma, atopic dermatitis (AD), urticaria, and FA, have a greater subsequent risk of IBS development than do those without allergic diseases.

Methods

Data Sources

The National Health Insurance (NHI) program in Taiwan, a single-payer, social insurance plan, was implemented in 1995 (19). The Bureau of the NHI (BNHI) has contracts with 99% of hospitals, and the NHI program covers up to 99% of the Taiwanese population. The NHI program also provides datasets from the National Health Research Insurance Database (NHIRD) to researchers interested in healthcare programs and treatment outcomes (<http://www.nhi.gov.tw/english/index.aspx>) (19–21). The childhood dataset (age <18 years) used in this study was derived from the NHIRD and comprised a randomly selected sample of half of all insured children in Taiwan (22). Diseases were coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). All insurance claims were subjected to peer review and investigation by medical reimbursement specialists. To comply with personal electronic data privacy regulations, insurants' identifications were encrypted prior to being accessed by the research team. This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH104-REC2-115).

Study Subjects

The IBS group comprised children aged 7–18 years who had received a new IBS diagnosis between 2000 and 2008. Children younger than 7 years were excluded because of the concern that they might not have been able to express themselves clearly enough to ensure a correct diagnosis. Because of the chronic and relapsing characteristics of IBS, we required at least 2 claims to have been coded (ICD-9-CM: 564) in any diagnosis field during the inpatient or ambulatory claim process. In Taiwan, diagnostic criteria for IBS are based on the Rome II criteria. To ensure an accurate diagnosis of IBS, we excluded any patient who met the following criteria: diagnosis with celiac disease or inflammatory bowel disease any time before or after the diagnosis of IBS, and a diagnosis of pancreatitis or giardiasis within 12 months before the IBS diagnosis. For each IBS patient, four control subjects with no history of IBS were matched according to age (within a 1-year interval), sex, and urbanization level.

Definitions of Variables and Comorbidity

To avoid recall bias, all allergic diseases were diagnosed by a physician. Allergic diseases, including AC (ICD-9-CM: 372.05, 372.10, and 372.14), AR (ICD-9-CM: 477), asthma (ICD-9-CM: 493), and AD (ICD-9-CM: 691.8), were defined by at least 3 codes in the primary diagnosis field during the inpatient or ambulatory claim process with respect to the ICD-9-CM. Allergic urticaria (ICD-9-CM: 708.0) and FA (ICD-9-CM: 995.6, 995.7, 693, 558.3, 558.4, and 477.1) were defined by at least 1 code in the primary diagnosis field during the inpatient or ambulatory claim process with respect to the ICD-9-CM. Patients with incompletely recorded age or sex information were excluded.

Statistical Analysis

The chi-square and *t* tests were used to compare demographic data between the IBS and non-IBS control groups, and multivariate logistic regression models were used to

calculate the odds ratios (OR) and 95% confidence intervals (CI) and thus determine associations between allergic diseases and IBS, after adjusting for age, sex, and urbanization of residential area. SAS 9.1 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses, and a p value <0.05 was considered statistically significant.

Results

The mean annual incidence rate of IBS among children aged 7–18 years during the study period was 4.60 (range: 2.50–6.54) per 10,000 children, and a decreasing trend in this parameter was observed. A total of 11,242 subjects with IBS were identified. The mean (standard deviation; SD) age at IBS diagnosis was 13.5 (3.03) years. The occurrence rates of the following allergic diseases were higher in the IBS group than in the non-IBS group: AC (16.7% vs. 11.0%), AR (22.8% vs. 14.4%), asthma (8.4% vs. 5.7%), AD (2.1% vs. 1.5%), urticaria (4.3% vs. 2.8%), and FA (0.57% vs. 0.37%; Table 1). The age at IBS diagnosis and the time interval between physician diagnoses of allergic disease and IBS are shown in Table 1. Compared with the other 5 allergic diseases, FA was associated with the shortest time interval (2.35 years, SD = 1.8 years) prior to IBS development (Table 1).

In the overall study population, the greatest subsequent risk of IBS was observed among children with AR, with an adjusted odds ratio (aOR) of 1.78 (95% confidence interval [CI], 1.69–1.87), followed by aORs of 1.64 for AC (95% CI, 1.54–1.74), 1.56 for urticaria (95% CI, 1.40–1.73), 1.54 for FA (95% CI, 1.15–2.05), 1.52 for asthma (95% CI, 1.40–1.64), and 1.40 for AD (95% CI, 1.21–1.62; Table 2). An increased subsequent risk of IBS was observed for both sexes (Table 2). In a comparison of patients with and without allergic diseases, the aORs for IBS increased along with the number of allergic comorbidities, regardless of sex or age (Table 2). In a multivariate logistic regression analysis, the aOR increased with the number of allergic diseases from 1.51 (95% CI, 1.43–1.59) for

those with only 1 allergic disease to 2.06 (95% CI, 1.93–2.19) for those with at least 2 allergic diseases (p for trend <0.001 ; Table 2). In addition, the aOR increased to 2.07 (95% CI, 1.88–2.28) for girls with at least 2 allergic diseases, and to 2.18 (95% CI, 2.02–2.35) for adolescents (≥ 12 years old) with at least 2 allergic diseases (Table 2). We further examined the association between the annual frequency of allergic disease-related medical visits and the risk of IBS development. Table 3 showed the aOR increased while FA was concurrent with the presence of all other allergic diseases, except AD.

Discussion

This study is one of a few that have systemically evaluated the association between common allergic diseases in preschool-aged children and the subsequent risk of IBS development upon reaching school age. Previous studies have reported a high prevalence of IBS among patients with asthma (13–16). These studies were limited, however, by a primary focus on adult patients and investigation of a single relationship: the association between asthma and IBS. Accordingly, the risk of IBS development borne by children with other types of allergic diseases remains unknown. In this study, we analyzed a large spectrum of common allergic diseases, including AR, AD, AC, asthma, urticaria, and FA, and confirmed a consistent increase in the risk of IBS among children with antecedent allergic diseases. Among the 6 evaluated allergic diseases, AR was associated with the greatest risk of subsequent IBS; children with AR had a 77% increase in the risk of subsequent IBS. In addition, the risk of IBS increased with the number of concurrent allergic diseases and frequency of medical visits for allergic diseases, indicating that a larger burden of clinically evident allergic disease might associate with a higher prevalence of IBS.

Although IBS is less common in children than in adults, it can begin in childhood. Very few epidemiological studies have estimated the incidence of childhood IBS within a

large population. In Italy, the reported prevalence of IBS among children from birth to 12 years of age was 13.9% (23). In Moscow, the prevalence of IBS among adolescents ranged from 14% to 24% (24). The prevalence of IBS among adolescents and children in China was 13.25%, with a boy-to-girl ratio of 1:1.8 (25). A recent meta-analysis of the epidemiology of pediatric functional abdominal pain disorders determined a global pooled prevalence for IBS of 8.8% (26). In our population-based study, the mean annual incidence rate of IBS among children aged 7–18 years was 4.6 (2.5–6.5) per 10,000 children. In the IBS group, 76.1% of patients experienced IBS onset between 13 and 18 years of age, and the ratio of boys to girls was 1:1.1. Our results revealed that school-aged girls with allergic diseases, except AR and AD, had a higher risk of developing IBS relative to boys.

Environmental factors such as allergen exposure or gut microbiota have been reported to trigger symptoms of IBS and allergic diseases (27–33). Patients with food hypersensitivity were found to exhibit a high prevalence of IBS and allergic diseases (10,11). Food elimination diets could effectively reduce IBS symptoms (12). Perturbations of the intestinal microbiota composition due to lifestyle changes might interfere with the development of immunologic tolerance and thus might be linked to the development of atopic diseases (27–29). The role of gut microbiota has also been considered among several important factors that contribute to the etiology and pathophysiology of IBS in animal and human studies (30–33). Some mechanisms, such as visceral hypersensitivity, mucosal inflammation, and motility, or the interplay of dysregulated microbiota with other IBS targets such as the gut–brain axis might explain the association between allergy and IBS (27–33). Reduced intestinal colonization with *Lactobacillus spp.* and *Bifidobacterium spp.* or increased colonization with *Clostridium difficile* have also been reported to increase the risks associated with allergic diseases and lead to the development of IBS (27–33).

Recently, increasing evidence suggests that disrupted mucosal immune responses play a role in chronic intestinal inflammation (e.g., inflammatory bowel disease), IBS, and allergic gastroenteritis (e.g., eosinophilic gastroenteritis and allergic IBS) (34,35). In a normal situation, the intestinal mucosa constantly comes into contact with large amounts of antigens, including bacterial antigens derived from the microbiota and food, without initiating a pro-inflammatory immune response. Toll-like receptors (TLRs) are pattern recognition receptors expressed by various cells in the gastrointestinal tract. Differences in intestinal TLR expression and signaling have been reported either to affect tolerance induction or promote intestinal inflammation. Mast cells play a well-known primary role in allergic diseases. In addition, mast cell activation is a component of visceral hypersensitivity, a main characteristic of IBS (36,37). Activated mast cells release various neurotransmitters and pro-inflammatory mediators (36) that can alter intestinal motility, increase intestinal mucosal permeability, and modulate intestinal inflammation (37). A mast cell stabilizer (ketotifen) that is traditionally used to treat allergic diseases has been shown to increase the threshold of discomfort in patients with IBS with visceral hypersensitivity and to reduce IBS symptoms (38).

Activation of the gastrointestinal mucosal immune system is considered among the causative factors in IBS pathogenesis (4,5). Food antigens, bacterial infection, and commensal microbial flora can trigger such activation (2-6). To date, only a few epidemiological studies of childhood IBS and FA have been published. One birth cohort study in Sweden revealed an association between allergic diseases and recurrent abdominal pain at 12 years of age (18). This increased risk of abdominal pain was particularly significant in children sensitized to food allergens but without self-reports of FA events at the time of sensitization. Another hospital-based case-control study demonstrated an association between a cow-milk allergy in infancy and an increased risk of the development of functional gastrointestinal disorders in childhood (39). Our results revealed that FA and the other allergic diseases evaluated were all

associated elevated risk of IBS development. Among the 6 evaluated allergic diseases, FA was associated with the shortest time interval to IBS development. This suggests that food allergens might activate gastrointestinal mucosal immune system more directly than other allergic diseases, possibly leading to IBS development.

A recent meta-analysis of the epidemiology of pediatric functional abdominal pain disorders reported a global pooled IBS prevalence of 8.8% (26). However, prevalence varied widely across studies (26). Our results indicated a lower incidence rate than those obtained through previous hospital-based or questionnaire-diagnosed studies. The strength of the current study was the population-based design that minimized the selection bias inherent in case-control studies. In addition, the diagnosis of IBS by a physician rather than by questionnaire minimized both selection and recall bias. The underdiagnosis of IBS might be attributable to the following factors. First, mild or infrequent symptoms of IBS might not be recognized by children's caregivers or may be only treated with over-the-counter medications. Second, a physician's specialization might interfere with the diagnosis. For example, gastroenterologists might be more alert with regard to IBS symptoms. Third, some physicians might record non-specific diagnosis codes, such as constipation, gastroenteritis, abdominal pain, and abdominal distention, for children with IBS.

In this study, physician-diagnosed FA was defined by ICD-9-CM codes. The worldwide accumulative prevalence of FA varies from approximately 3% to 6%, depending on age, geographic location, and diagnostic methods (40). FA appeared to be underestimated in the current study, with prevalence rates of 0.37% in the non-IBS group and 0.57% in the IBS group. The following reasons might explain this result. In children, mild wheals and nonspecific GI symptoms such as vomiting, abdominal cramps, and/or diarrhea may not be recognized as FA symptoms by caregivers. Accordingly, caregivers might not seek medical care when children suffer from mild FA symptoms. Although children with FA might present

with hives or eczema, these reactions to food allergens might not be recognized as causing a few hives or worsening AD. Accordingly, these cases might be classified as acute urticaria or AD, and FA codes would not be recorded.

This study revealed consistent associations of all 6 evaluated allergic diseases with a risk of IBS. In addition, the risk of IBS increased with the number of concurrent allergic diseases, indicating that a higher burden of clinically evident allergic disease was associated with a higher prevalence of IBS. However, surveillance bias might exist, as children with allergic diseases might participate in more clinic visits than those without allergic diseases, and are also more likely to receive an IBS diagnosis. In addition, patients with mild symptoms might not visit a physician, leading to undiagnosed cases. Accordingly, selection bias might exist, as the undiagnosed cases might be randomly selected as comparison controls.

In conclusion, children with childhood allergic diseases have a higher risk of IBS development later in life, indicating that physicians should pay close attention to complaints of diarrhea, constipation, abdominal distention, or abdominal pain. Future research on the common immunological aberrancies associated with these disorders is recommended.

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Table 1 Frequency of allergic diseases between children with and without irritable bowel syndrome (IBS); age of IBS diagnosis; time interval between physician-diagnosed allergic diseases and physician-diagnosed IBS

	Non-IBS (N=44968)	IBS (N=11242)	Age of IBS (years)	Time interval between allergic diseases and IBS (years)
Allergic diseases	n (%)	n (%)	Median(IQR) (Range)	Mean (SD)
Allergic conjunctivitis	4948 (11.0)	1882 (16.7)	13.9(11.0-15.6) (7.0-17.9)	3.1 (2.1)
Allergic rhinitis	6495 (14.4)	2559 (22.8)	13.9(10.7-15.6) (7.0-17.9)	3.5 (2.3)
Asthma	2575 (5.7)	941 (8.4)	12.5(9.4-14.8) (7.0-17.9)	4.2 (2.3)
Atopic dermatitis	694 (1.5)	241 (2.1)	12.5(9.2-15.0) (7.0-17.9)	3.9 (2.4)
Urticaria	1268 (2.8)	486 (4.3)	14.2(11.8-15.6) (7.0-17.8)	2.9 (2.0)
Food allergy	167 (0.4)	64 (0.6)	14.3(12.4-15.8) (7.5-17.8)	2.4 (1.8)

IQR: interquartile range; SD: standard deviation

Table 2 Association between allergic diseases and irritable bowel syndrome by sex , odds ratio (OR) and 95% confidence interval (CI)

	All(n=56210)	Girls (n=29735)	Boys (n=26475)	Age < 12(n=13420)	Age≥12(n=42790)
Allergic diseases	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Allergic conjunctivitis	1.64 (1.54, 1.74)**	1.68 (1.55, 1.82)**	1.60 (1.47, 1.74)**	1.46 (1.30, 1.64)**	1.70 (1.59, 1.82)**
Allergic rhinitis	1.78 (1.69, 1.87)**	1.77 (1.64, 1.91)**	1.79 (1.66, 1.92)**	1.55 (1.40, 1.71)**	1.87 (1.76, 1.99)**
Asthma	1.52 (1.40,1.64)**	1.55 (1.38, 1.75)**	1.49 (1.34, 1.65)**	1.55 (1.37, 1.76)**	1.49 (1.35, 1.65)**
Atopic dermatitis	1.40 (1.21, 1.62)**	1.30 (1.05, 1.61)*	1.50 (1.22, 1.85)**	1.45 (1.14, 1.85)*	1.37 (1.14, 1.65)**
Urticaria	1.56 (1.40, 1.73)**	1.57 (1.36, 1.82)**	1.54 (1.32, 1.81)**	1.21 (0.97, 1.50)	1.70 (1.50, 1.92)**
Food allergy	1.54 (1.15, 2.05)**	1.36 (0.91, 2.04)	1.76 (1.16, 2.67)*	0.89 (0.45, 1.77)	1.78 (1.29, 2.45)**
Number of concurrent allergic disease					
1	1.51 (1.43, 1.59)**	1.53 (1.42, 1.65)**	1.48 (1.37, 1.59)**	1.29 (1.15, 1.43)**	1.58 (1.49, 1.68)**
2+	2.06 (1.93, 2.19)**	2.07 (1.88, 2.28)**	2.04 (1.87, 2.23)**	1.76 (1.57, 1.98)**	2.18 (2.02, 2.35)**

*p<0.01, **p<0.001

Table 3 Association between food allergy concurrent with other allergic diseases and risks of irritable bowel syndrome, odds ratio (OR) and 95% confidence interval (CI)

Food allergy (N=231)	OR (95% CI)
Food allergy + allergic conjunctivitis (n=60)	2.50 (1.49, 4.21)**
Food allergy + allergic rhinitis (n=75)	2.13 (1.33, 3.43)*
Food allergy + asthma (n=26)	2.94 (1.35, 6.40)*
Food allergy + atopic dermatitis (n=25)	0.76 (0.26, 2.22)
Food allergy + urticaria (n=32)	2.75 (1.36, 5.57)*

*p<0.01, **p<0.001