A 8-year population-based cohort study of irritable bowel syndrome in childhood with history of atopic dermatitis

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Accepted 11 December 2017
Published Online First 26 January 2018

To cite: Tsai J-D, Wang I-C, Shen T-C, *et al*. *J Investig Med* 2018;**66**:755–761.

ABSTRACT

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder affecting a large number of people worldwide. Based on the concept of central sensitization, we conducted a population-based cohort analysis to investigate the risk of IBS in children with atopic dermatitis (AD) as one of the first steps in the atopic march. From 2000 to 2007, 1 20 014 children with newly diagnosed AD and 1 20 014 randomly selected non-AD controls were included in the study. By the end of 2008, incidences of IBS in both cohorts and the AD cohort to non-AD cohort hazard ratios (HRs) and CIs were measured. The incidence of IBS during the study period was 1.45-fold greater (95% CI: 1.32 to 1.59) in the AD cohort than in the non-AD cohort (18.8 vs 12.9 per 10 000 person-years). The AD to non-AD HR of IBS was greater for girls (1.60, 95% CI: 1.39 to 1.85) and children≥12 years (1.59, 95% CI: 1.23 to 2.05). The HR of IBS in AD children increased from 0.84 (95% CI: 0.75 to 0.94) for those with ≤3 AD related visits to 16.7 (95% CI: 14.7 to 18.9) for those with >5 visits (P<0.0001, by the trend test). AD children had a greater risk of developing IBS. Further research is needed to clarify the role of allergy in the pathogenesis of IBS.

Significance of this study

What is already known about this subject?

- The high prevalence of childhood irritable bowel syndrome (IBS) has become an economic and quality-of-life burden.
- IBS has considered as central nervous system sensitisation.
- Multiple factors, such as chronic low-grade inflammation within the gut wall, visceral hypersensitivity, and genetic and immunologic factors play roles in the development of IBS.
- Elimination of food antigens has been reported to improve IBS and atopic dermatitis (AD).

What are the new findings?

- The overall IBS incidence rate was 1.45-fold greater in the AD cohort than in the non-AD cohort.
- Children aged ≥12 years and girls had greater of IBS.
- Concurrent allergic rhinitis or asthma did not increase the risk of IBS further in AD cohort.
- Children with great clinical burden of AD and more AD related medical visits had higher risk of IBS.

How might these results change the focus of research or clinical practice?

- Clinicians should be aware of the diagnosis of IBS in children with a past history of AD complain chronic abdominal pain and alterations in bowel habits.
- Early intervention to prevent AD and subsequent risk of IBS need more research in the future.

INTRODUCTION

Functional somatic syndromes are common and disabling conditions that may be related to central nervous system sensitisation.[1 2] Irritable bowel syndrome (IBS) is a common feature of functional somatic syndromes, which is characterized by chronic abdominal pain, abdominal pain relieved with defecation, bloating and alterations in bowel habits.[1–3] IBS affects a large number of people worldwide with a prevalence in the paediatric population ranging from 13.25%–24%,[4–6] and it has become an economic and quality-of-life burden.[7] Although the pathophysiology of IBS is complex and not completely understood, multiple factors, such as chronic low-grade inflammation within the gut wall, visceral hypersensitivity, genetic and immunologic factors and the brain-gut interaction play important roles in IBS pathophysiology.[8] Previous studies reported that ingested or inhaled allergens could cause IBS symptoms in atopic individuals.[9–12] In addition, degranulation of intestinal mast cells, which results from previous enteric infection and/or intestinal allergy, may result in gut hypersensitivity in IBS through various mediators acting on enteric neurons and smooth muscle cells.[13] Moreover, many allergic symptoms occur as a result of alteration in the nervous system and

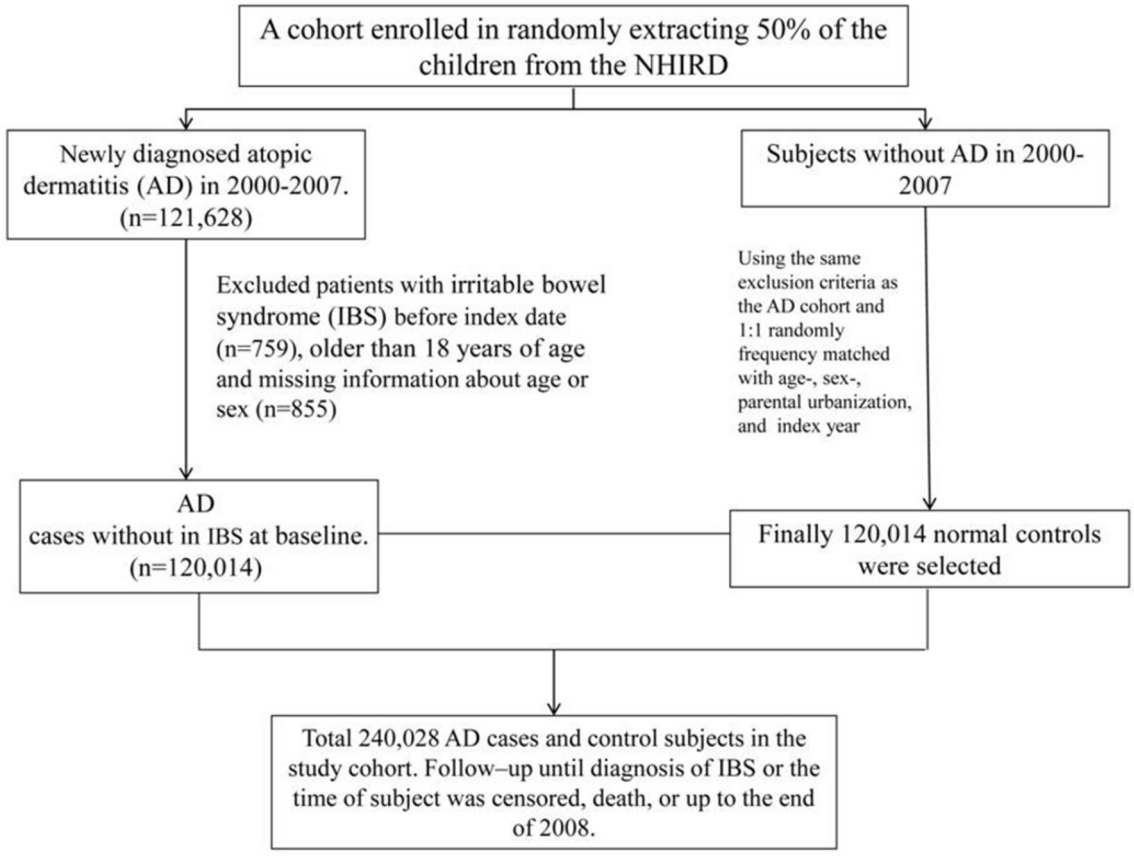

Figure 1 Flow chart for patient enrollment.

these symptoms depend on the organ in which the allergic reaction occurs.[14] These symptoms occur after mediators released during an allergic reaction interact with sensory nerves, change processing in the central nervous system and alter transmission in sympathetic, parasympathetic and enteric autonomic nerves.[14]

Among the atopic disorders, atopic dermatitis (AD) is a chronic, relapsing and highly pruritic inflammatory skin disease and is considered as the beginning of the atopic march, often followed by asthma and allergic disorders.[15 16] The prevalence of AD ranges from 10%–20% in children in developed countries, with an increasing trend in the past three decades.[16] Recent discovery of the filaggrin loss-of-function mutation is associated with AD, allergic sensitization to respiratory allergies and food protein.[16 17]Animal studies suggest that environmental allergens, such as food protein, can make contact with the immune system via antigen-presenting cells in the superficial epidermis of impaired skin barrier, leading to sensitization.[16 17] Children with AD have a higher risk for development of food allergies and gastrointestinal dysfunction.[10] It has been considered that diet plays an important role in the pathogenesis of both IBS and AD; elimination of food antigens has been reported to improve IBS and AD.[18–21] As seen in the literature, a considerable amount of research has focused on allergies and IBS. However, most previous studies were cross-sectional case control studies with limited numbers of patients focusing on adult population. Studies on the association between IBS and AD in children population are scarce.[14 22 23] These observations prompted us to design a population cohort study to investigate the incidence and risk of IBS in children with AD. We hypothesized that children with AD would have an increased future risk of IBS.

METHODS

Data sources

The National Health Insurance Research database (NHIRD), maintained by the National Health Research Institutes, is population-based and derived from the claims data of the National Health Insurance programme, a mandatory-enrollment, single-payment system created in 1995, now covering over 99% of Taiwan's population.[24 25] To ensure the accuracy of disease diagnosis, the National Health Insurance Bureau of Taiwan has randomly reviewed medical charts of 1/100 ambulatory and 1/20 inpatient claims. The high validity of the diagnostic data from the NHIRD has been reported.[26–28] The validation of using ICD-9 codes for AD had been addressed in our previous study.[25] The NHIRD contains records of insurance claims, including medications, prescriptions, and treatment costs for both inpatient and outpatient visits. This study used the children file derived from NHIRD with the information of a half of all children randomly selected from all insured population in Taiwan. The datasets generated during and/or analysed during the current study are available in the NHIRD (http://www.nhi.gov.tw/english/index.aspx). Because of the personal electronic data-privacy regulation, the identification of

insurant was encrypted before being sent to researcher. The study was approved the Institutional Review Board in China Medical University Hospital (CRREC-103–048). All methods were performed in accordance with the relevant guidelines. The International Classification of Disease, Ninth Revision (ICD-9) was used for the diagnosis codes.

Study design and subjects

Children (under 18 years of age) who was newly diagnosed AD (at least one inpatient claim record or three ambulatory claims in primary diagnosis field with respective ICD-9-CM code 691.8) from 2000 to 2007 were identified as the AD cohort. The baseline index date was the date of AD diagnosis. Matching is a technique used to avoid confounding in a study design. Childhood stressors from socioeconomic environment and residential area of industrialization or urbanization have been argument of risk factors of IBS for decades.[2] Hence, in this matching cohort study, for each child with AD, we randomly selected one non-AD (never having ICD-9-CM code 691.8 in any diagnosis field) children matched by sex, age (within a 1 year interval), urbanized residence area, parental occupation, and baseline year as non-AD cohort. Any patient who had diagnosis with celiac disease or inflammatory bowel disease any time before or after the diagnosis of IBS (at least three claims in any diagnostic field with respective ICD-9-CM code 564.1 by at least on gastroenterologist), and a diagnosis of pancreatitis or giardiasis within 12 months before the IBS diagnosis was excluded. The diagnostic criteria for IBS are based on the Rome criteria II during study period.[3] Each child was followed up from the index date until the development of IBS, withdrawal of insurance, or conclusion of follow-up person-years on December 31, 2008. The flow chart of this study was summarized in figure 1.

Statistical analysis

The sociodemographic variables in this study were sex, age, and urbanization. Urbanization was categorized into four levels based on the population density of the residential area: level one was the most urbanized and level four was the least urbanized. All data analyses were performed using the SAS software version 9.1 (SAS Institute Inc., Carey, NC). Statistical significance was set at $P<0.05$ in 2-tailed tests. To describe the baseline distributions of the AD and non-AD cohorts, means and SD were used for continuous variables and counts and percentages were used for categorical variables.

Differences were examined using the chi-square test for categorical variables and the *t* test for continuous variables. The Kaplan–Meier method was used to estimate the proportion of study subjects in both cohorts who did not develop IBS during the follow-up period. The incidences were calculated for each cohort. Hazard ratios (HRs) and 95% CIs were calculated using multivariable Cox proportional hazard regression models, with the non-AD cohort as the reference group, to assess the association between AD and the risk of developing IBS. Patients with atopic dermatitis (AD) are at a higher risk for progressing in the atopic march to allergic rhinitis and asthma.[15 16] These allergic diseases, while sharing genetic and environmental risk factors, may develop sequentially along an atopic pathway or may co-occur in many patients. Hence, differences in the presence of these comorbid conditions, allergic rhinitis or asthma, may be important confounders when comparing risk of IBS between AD and non-AD group.

Table 1 Demographics between children with and without atopic dermatitis (AD)

	Non-AD (n=1 20 014)	AD (n=1 20 014)	
	n (%)	n (%)	P value
Age, years, mean (SD)*	4.98 (4.83)	4.94 (4.85)	0.05
Stratified age, years			0.99
≤5	72 320 (60.3)	72 320 (60.3)	
6–11	30 016 (25.0)	30 016 (25.0)	
≥12	17 678 (14.7)	17 678 (14.7)	
Sex			0.99
Girl	54 559 (45.5)	54 559 (45.5)	
Boy	65 455 (54.5)	65 455 (54.5)	
Urbanization†			0.99
1 (highest)	42 190 (35.2)	42 190 (35.2)	
2	35 407 (29.5)	35 407 (29.5)	
3	20 026 (16.7)	20 026 (16.7)	
4 (lowest)	22 391 (18.7)	22 391 (18.7)	
Follow-up time, years, mean (SD)*	4.85 (2.31)	4.86 (2.30)	
Allergic rhinitis			<0.001
No	105 938 (88.3)	89 107 (74.3)	
Yes	14 076 (11.7)	30 907 (25.8)	
Asthma			<0.001
No	112 223 (93.5)	100 781 (84.0)	
Yes	7791 (6.49)	19 233 (16.0)	

χ^2 test, and *t-test comparing subjects with and without atopic dermatitis
†The urbanization level was categorized by the population density of the residential area into four levels, with level one as the most urbanized and level four as the least urbanized.

RESULTS

This study evaluated 120014 AD cases and 1 20 014 non-AD controls. No differences in the sociodemographic variables were noted between groups. Majority of AD children were boy (54.5%), aged ≤5 years (60.3%), and lived in higher urbanization regions (35.2%) (table 1). AD cohort had higher occurrence rate of allergic rhinitis (25.8% vs 11.7%) and asthma (16.0% vs 6.5%) than no-AD cohort (table 1). There were no differences in age group, sex, urbanization of living areas, or follow-up period between the two cohorts. Kaplan–Meier analysis showed that the accumulated incidence rate of IBS was significantly greater in the AD cohort than in the non-AD cohort (log-rank test $P<0.0001$; figure 2).

The incidence of IBS in both cohorts and the AD to non-AD HRs of IBS by sociodemographic status are presented in table 2. Overall, the IBS incidence was 1.45-fold greater (95% CI: 1.32 to 1.59) in the AD cohort than in the non-AD cohort (18.8 vs 12.9 per 100 000 person-years) at the end of follow-up period. The increased AD to non-AD HRs of IBS was consistent regardless of age and sex. The age-specific AD to non-AD HRs for IBS was highest 1.59 (95% CI: 1.23 to 2.05) for the children aged ≥12 years.

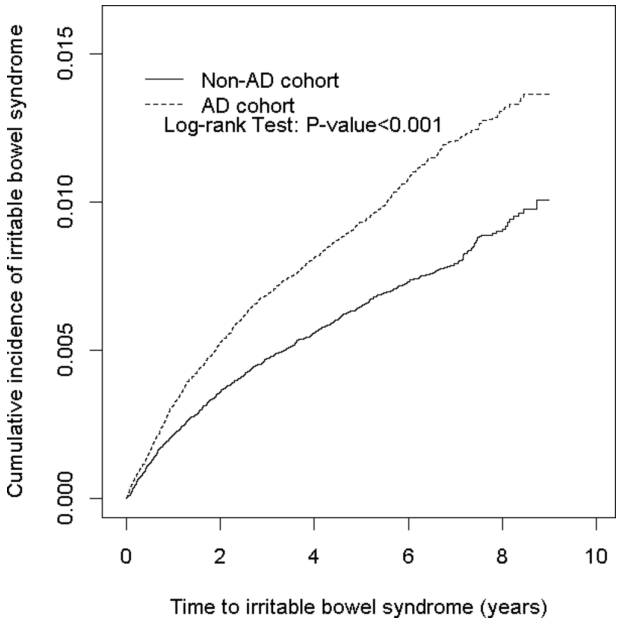

Figure 2 Cummulative incidence of irritable bowel syndrome for patients with atopic dermatitis (dashed line) or without atopic dermatitis (solid line).

Table 3 The risk of irritable bowel syndrome among average frequency for medical visits of atopic dermatitis (AD) in Cox proportional hazard regression

Average frequency for medical visit, per years	Event	Person-years	IR	Adjusted HR† (95% CI)
All				
None	751	582 059	12.9	1.00(Reference)
≤3	591	546 667	10.8	0.84 (0.75 to 0.94)
4–5	129	20 477	63.0	4.63 (3.84 to 5.58)*
>5	374	16 285	229.7	16.7 (14.7 to 18.9)*
p for trend				<0.001
Girl				
None	308	264 049	11.7	1.00(Reference)
≤3	287	248 989	11.5	0.99 (0.85 to 1.17)
4–5	52	8868	58.6	4.75 (3.54 to 6.38)*
>5	155	6752	229.6	18.3 (15.0 to 22.2)*
p for trend				<0.001
Boy				
None	443	318 010	13.9	1.00(Reference)
≤3	304	297 678	10.2	0.73 (0.64 to 0.85)
4–5	77	11 608	66.3	4.51 (3.53 to 5.74)*
>5	219	9533	229.7	15.5 (13.2 to 18.3)*
p for trend				<0.001

*p<0.001
Adjusted HR†, adjusted for age and sex.
IR, incidence rate, per 10 000 person-years.

The sex-specific AD to non-AD HRs was greater for girls 1.60 (95% CI: 1.39 to 1.85) than for boys 1.35 (95% CI: 1.19 to 1.53). Concurrent allergic rhinitis or asthma did not increase the risk of IBS further in AD cohort (table 2). The HR for IBS in AD children increased from 0.84 (95% CI: 0.75 to 0.94) for those with ≤3 AD related visits to 16.7 (95% CI: 14.7 to 18.9) for those with >5 visits (P<0.0001, by the trend test) and the trend was consistent in both sex (table 3). Table 4 demonstrates that AD cohort had a slightly higher adjusted HR1.46 (95% CI: 1.21 to 1.77) for being diagnosed with IBS within the first 4 years than more than 5 years 1.42 (95% CI: 1.16 to 1.74) after being diagnosed with AD.

DISCUSSION

This is one of few studies that provides evidence on the incidence and relative risk of IBS in children with AD in a

Table 2 The risk of irritable bowel syndrome compared with children without atopic dermatitis (AD) stratified by demographics in Cox proportional hazard regression

	Non- AD			AD			
	Event	Person-years	IR	Event	Person-years	IR	Adjusted HR† (95% CI)
All	751	582 059	12.9	1094	583 428	18.8	1.45 (1.32 to 1.59)*
Stratified age							
≤5	505	360 071	14.0	708	361 118	19.6	1.40 (1.25 to 1.57)*
6–11	148	164 053	9.02	230	164 268	14.0	1.55 (1.26 to 1.91)*
≥12	98	57 935	16.9	156	58 042	26.9	1.59 (1.23 to 2.05)*
Sex							
Girl	308	264 049	11.7	494	264 609	18.7	1.60 (1.39 to 1.85)*
Boy	443	318 010	13.9	600	318 819	18.8	1.35 (1.19 to 1.53)*
Allergic rhinitis							
No	657	518 043	12.7	834	436 145	19.1	1.50 (1.35 to 1.66)*
Yes	94	64 016	14.7	260	147 283	17.7	1.21 (0.96 to 1.54)
Asthma							
No	709	545 153	13.0	945	486 037	19.4	1.49 (1.35 to 1.64)*
Yes	42	36 906	11.4	149	97 391	15.3	1.35 (0.96 to 1.90)

*p<0.001.
Adjusted HR†, adjusted for age and sex.
IR, incidence rate, per 10 000 person-years.

Table 4 Trends of irritable bowel syndrome event risk in atopic dermatitis (AD) by stratified follow-up years

	Non-AD			AD			Adjusted HR† (95% CI)
Follow time	Event	Person-years	IR	Event	Person-years	IR	
≤2 years	417	230 023	18.1	612	230 588	26.5	1.46 (1.29 to 1.65)*
3–4 years	179	177 571	10.1	262	177 995	14.7	1.46 (1.21 to 1.77)*
≥5 years	155	174 465	8.88	220	174 845	12.6	1.42 (1.16 to 1.74)*

*p<0.001.
Adjusted HR†, adjusted for age and sex.
IR, incidence rate, per 10 000 person-years.

large population. Caffarelli *et al* reported the prevalence of IBS showed no significant difference between allergic and healthy children. However, they found that allergic children with a positive skin prick test to food were associated with IBS.[22] Tobin *et al* conducted a prospective study in 125 adult patients and found the frequency of IBS was higher (51%) in AD patients compared with (18%) non-AD controls, with an OR of 3.85 (95% CI, 1.72 to 8.60). Besides, their result showed that AD was an independent predictor of IBS diagnosis.[14] However, these two studies were cross-sectional studies with a limited number of patients and revealed inconsonant association between AD and IBS. In addition, the latter study essentially focused on the adult population. Hence, the exact incidence rate and relative risks of IBS in children with AD remains unclear. In 2015, Jones *et al* conducted a cohort study from 30 000 primary care records on the incidence and risk of atopic disorders in IBS, functional dyspepsia and constipation patients over a minimum 5 year period across the UK. Their result showed that AD was present in 28% of IBS patients and in 21.4% of non-IBS controls, with OR of 1.46 (OR: 1.46; 95% CI, 1.33 to 1.61). Their result, though patients were mostly adults, showed patients with IBS are at risk of AD and suggested that IBS and AD share a connection, which could be possibly explained by mood disorders, such as anxiety and depression.[23] If the increased risk of IBS is consistent before and after AD onset, common environmental triggers, genetic factors and aberrant immunological responses might play an important role in the development of both disorders. Our results suggest that children with AD are more likely to develop IBS regardless of sex and age. Girls with AD and those aged ≥12 years had higher incidence of IBS. It implies that AD has more impact on girls than on boys in the development of IBS. Although all children with AD are at risk of IBS, children with the earlier onset of AD did not show a higher incidence and risk of IBS, and the risk of IBS was greater within the first 4 years of AD diagnosis. Besides, children with AD who have more frequent AD-related medical visits had relatively higher incidence and risks of IBS. Therefore, physicians need to pay more attention to IBS symptoms once children are diagnosed with AD and to those with more frequent medical visits for AD.

Although IBS is less common in children than in adults, it can begin in childhood, and the prevalence of IBS range from 13.25%–24% in the paediatric population,[4–6] and in increases gradually with age, though it is not statistically significant.[29] Our study showed that the incidence rate of childhood IBS was 12.9 of 10 000 person-years in the non-AD cohort and 18.8 of 10 000 person-years in the AD cohort. Previous report showed that Asian girls are at a higher risk for developing IBS compared with boys, and the result is similar in adults.[29 30] Our study showed that girls with AD in all ages have a higher tendency towards developing IBS compared with boys with AD. However, our result showed that boys with AD have higher incidence rate of IBS at age 6 years, especially at age 2 years. This may be explained by the fact that 60% of AD occur during the first year of life and up to 85% of AD occur before the age of 5 years.[31]

AD is a chronic or relapsing inflammatory skin disease that is often followed by asthma and allergic disorders. More than 50% of children with AD will develop asthma and/or allergic rhinitis.[32] Therefore, AD represents the beginning of the atopic march,[16]and the AD cohort represents an important model to investigate the impact of atopy on certain diseases. Recent studies showed that skin barrier abnormalities and immune dysregulation are related to the pathogenesis of AD,[16] and the genetic predisposition of an individual to create immunoglobulin E (IgE) antibody responses to common environmental or food allergens is strongly associated with AD.[32] Three possible explanations of our findings are that AD has a positive influence on the development of IBS or that the two disorders may share common early life determinants. Recent evidence has showed that genetic variations play a role in the linkage between atopy and its impact on local mucosal immune function in IBS. Furthermore, histologically, immune alterations in the intestinal mucosa, showing increased mast cells in duodenal and colonic mucosa, were reported by previous studies.[33 34] Visceral hypersensitivity, promoted by chronic stress on the immune system, is considered as a common underlying factor in atopy and IBS,[3 35 36]and it is the mast cell that plays a crucial role in regulating visceral hypersensitivity.[3 35 36] Mast cells are positioned near enteric neurons and they have surface receptors enabling the binding of IgE. Once an antigen binds to the mast cell, it will lead to mast cell degranulation and release of inflammatory mediators, such as histamine, serotonin and proinflammatory cytokines. This sequential reaction regulated by mast cells induces hypersensitivity, resulting in clinical manifestations associated with atopy.[37 38] In addition, mast cells also promote prolonged hypersensitivity by responding to tryptase, a mast cell-derived mediator effecting type two protein-activated receptors.[3 35 39] Further evidence also showed that mast cells are implicated in intestinal mucosal barrier changes and that they alter small intestine permeability in IBS patients with allergic symptoms, especially diarrhoea-predominant IBS patients.[10 40 41] Besides, serum level of IgE in IBS patients with allergic symptoms was raised with

significantly increased numbers of duodenal IgE-positive cells, indicating that an underlining IgE or mast cell mediated component might be a contributory factor.[42] Based on the above observation, a study administrating ketotifen, a mast cell stabilizer, to patients with IBS has been shown to reduce visceral sensation compared with placebo.[43] A case report also showed that after administering omalizumab to a patient with severe asthma and IBS resulted in not only asthma improvement but also in an almost complete resolution of IBS symptoms.[37] Omalizumab, an anti- IgE monoclonal antibody, has been developed for treatment of patients with refractory allergic asthma,[44]and has also been administered to patients with AD.[45] These findings support our results with respect to the relationship between AD and IBS. Some authors have proposed the concept of atopic IBS for the subgroup of patients with IBS and atopic manifestations.[14] However, determining whether these are independent subgroups still requires further investigation.

The strength of our study is that this is the first population-based cohort study to investigate the precise quantification of IBS incidence in children with AD. Our results revealed an increased incidence rate and risk of IBS in the cohort of children with AD. The severity of AD symptoms is associated with further increased risk of IBS, and the relationship was consistent regardless of age, sex and other atopic disorders. Second, this is a population-based study, minimizing the selection bias inherent in case–control studies. Third, the diagnosis of AD was made by a physician rather than through a questionnaire; this minimized both selection and recall bias. Fourth, we adjusted for possible confounding factors, including age, gender, urbanization of residence area and other atopic disorders, such as asthma and allergic rhinitis.

There are potential limitations to this study that should be acknowledged. First, we are unable to present information that is not captured in administrative claims databases such as genetic and behavioural factors, practice setting, laboratory data, over-the-counter medications, or medication response. Second, problems related to coding accuracy and financial incentives may also lead to bias when using ICD-9 codes for diagnosis in large insurance claims data for research. These potential limitations are partly countered by the strengths of a huge sample size of IBS children in this study.

In conclusion, this population-based cohort study revealed a significantly increased incidence rate and risk of IBS in children with AD. Additional research should be conducted to investigate the contribution of AD to the development of IBS and provide diagnosis and treatment potential strategies.

Contributors I-CW and J-DT made equal contribution to this study. C-CW, J-DT, and T-CS conceptualized and designed the study, drafted the manuscript, and approved the final manuscript as submitted. C-LL conducted the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. C-CW and J-DT coordinated and supervised the data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

Funding The study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004), China Medical University Hospital (DMR-106-053), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10601010036), Taiwan Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo AoshimaMemorial Funds, Japan.

Competing interests None declared.

Patient consent Guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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