Risks of irritable bowel syndrome in children with infantile urinary tract infection: a 13-year nationwide cohort study

Teck-King Tan,[1] Miguel Saps,[2] Cheng-Li Lin,[3,4] Chang-Ching Wei[1,5]

[1]Department of Pediatrics, Children's Hospital, China Medical University Hospital, Taichung, Taiwan
[2]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of Miami Hospital, Miami, Florida, USA
[3]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[4]Department of Public Health, China Medical University, Taichung, Taiwan
[5]School of Medicine, China Medical University, Taichung, Taiwan

Correspondence to
Dr Chang-Ching Wei, School of Medicine, China Medical University, Taichung 40402, Taiwan;
weilonger@gmail.com

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ABSTRACT

Early life events play a crucial role in the development of irritable bowel syndrome (IBS). Some evidence suggests the phenomenon of cross-organ sensitization between bladder and colon. Whether urinary tract infection (UTI) during infancy is a risk factor of childhood IBS remains to be elucidated. In this retrospective cohort study, we selected 31 788 infants who had UTI between 2000 and 2011 as a UTI cohort and selected 127 152 infants without UTI as a comparison cohort, matched by age, sex and level of urbanization of living area. Incidence density and HRs with CIs of IBS between UTI and non-UTI cohorts were calculated by the end of 2012. The incidence density of IBS during the study period was 1.52-fold higher in the UTI cohort (95% CI 1.38 to 1.67) compared with the non-UTI cohort (2.05 vs 1.32 per 10 000 person-years). The HR of IBS was slightly higher for boys (1.53; 95% CI 1.34 to 1.73) than for girls (1.50; 95% CI 1.29 to 1.73). The HRs for IBS in children with UTI were greater for those with more UTI-related medical visits/per year (>5 visits, HR 61.3; 95% CI 51.8 to 72.6), with longer length of stay of hospitalization (>7 days, HR 1.75; 95% CI 1.36 to 2.24) and with vesicoureteral reflux (VUR) (HR 1.73; 95% CI 1.35 to 2.22) (p<0.0001, the trend test). Infants with UTI had higher risks of childhood IBS and the risks elevated further with recurrent UTI or UTI with concurrent VUR.

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.
- Multiple factors have been reported to play a role in the pathophysiology of IBS, such as intestinal inflammation, dysbiosis of the gut microbiota, motility disturbance, food sensitivity, psychological disorders and genetic considerations.
- Early life events play a crucial role in the development of functional gastrointestinal disorders.
- Several studies have addressed the phenomenon of cross-organ sensitization between bladder and colon.

What are the new findings?

- Infants with urinary tract infection (UTI) had 1.52-fold greater risks of childhood IBS than those without UTI.
- Male infants with UTI had slightly greater risk for IBS than female.
- The subsequent risks for IBS in infants with UTI were greater for those with more UTI-related medical visits per year, with longer hospitalization and with vesicoureteral reflux.

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

- Clinicians and researchers should be aware of the early symptoms of IBS in children with a medical history of UTI.
- This study confirms previous investigations that suggested that UTI early in life predispose children to develop IBS.
- Current management of IBS is limited to treatment once symptoms develop. The identification of a population at risk of developing IBS provides a unique opportunity of changing the paradigm and introduce prevention to the management of IBS.
- Early intervention in children with UTI may decrease the subsequent risk of IBS.

INTRODUCTION

Irritable bowel syndrome (IBS) is the most common diagnosis in children with functional abdominal pain disorders (FAPDs).[1] School-based studies reported a prevalence of IBS ranging from 1.3% to 19.8%.[2–6] IBS has a serious impact on quality of life, increase in medical costs and at risk of subsequent psychiatric disorders.[7] The management of IBS is currently limited to the treatment of patients who consult for bothersome symptoms. This approach to the management of IBS frequently result in suboptimal outcomes. An alternative approach to IBS would be to establish prevention strategies. In order to accomplish this change in paradigm, we need to start by identifying the risk factors to the development of IBS.

Multiple factors have been reported to play a role in the pathogenesis and pathophysiology

of IBS, such as intestinal inflammation, dysbiosis of the gut microbiota, motility disturbance, food sensitivity, psychological disorders, and genetic considerations.[8] Recent studies suggested that early life events, including gastrointestinal infection and inflammation, have been associated with a greater risk for developing pediatric functional gastrointestinal disorders (FGIDs).[9]. However, gastrointestinal factors only explain some cases of IBS and a large proportion of pediatric FGIDs remain unexplained.

Urinary tract infections (UTI) are common in early childhood. Traditionally, UTI in children without genitourinary tract anomalies and renal damage is considered a mild infectious disease that does not result in long-term consequences.[10] Animal and observational human studies have showed the comorbidity of genitourinary (interstitial cystitis) and gastrointestinal disorders (IBS).[11–13] These studies highlight the presence of this association but do not allow establishing causation. Thus, the mechanisms and temporal association between the events affecting both organ systems remain incompletely understood. Some studies suggest that the relation between both systems may be secondary to the phenomenon of cross-organ sensitization between bladder and colon. Cross-talk between both systems could result in an infection in one organ system (such as urinary infection) causing an effect in another organ system (such as the gastrointestinal system).[14 15]

Advancing our knowledge in the relation between urinary tract and gastrointestinal disorders has the potential to uncover new mechanisms and risk factors for FGIDs opening the door to a change in paradigm in IBS that would not be only limited to treatment but could include preventative strategies.

The aim of our study is to survey the future risk of IBS in children with UTI during their first year of life.

METHODS

Data source

In this population-based, retrospective study, we used the children file, derived from the Taiwan National Health Insurance Research Database, which is generated and maintained by the National Health Research Institutes. This population-based claims data were derived from the National Health Insurance program, which has been created since 1995 and covers over 99% of Taiwan's population (http://www.nhi.gov.tw/english/index.aspx).[16–18] Following Taiwan's Personal Information Protection Act, de-identification of personal information was performed before the data set was available for research. Diseases in this study were coded based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study subjects

The aim of this retrospective cohort study was to examine the difference of the incidence rate (IR) and relative risk (incidence rate ratio) between IBS in an UTI infant cohort and a non-UTI infant cohort during 2000–2012. UTI was identified as at least once diagnostic code in any diagnostic field with the ICD-9-CM codes 590 (infection of kidney), 599.0 (urinary tract infection, site not specified) and 771.82 (urinary tract infection of newborn). A total of 31 788 infants (aged <1 year) newly diagnosed with UTI between 2000 and 2012 were defined as the UTI cohort. The baseline index date was the date when UTI was diagnosed. For each infant with UTI, we randomly selected four non-UTI infants, who never had diagnostic code of UTI, matched by sex, urbanization level and baseline year as non-UTI cohort. Children with missing data or those with preexisting IBS before the baseline year were excluded. Because of the chronic and relapsing characteristics of IBS, IBS was defined at least two diagnostic records of ICD-9-CM code 564.1 in any diagnosis field. To ensure an accurate diagnosis of IBS, we excluded any patient who met the following conditions: ever diagnosed celiac disease (ICD-9-CM code 579.0), ever diagnosed inflammatory bowel disease (ICD-9-CM code 555, 556.0–556.6, 556.8, 556.9), and diagnosed pancreatitis (ICD-9-CM code 577.0-–577.1) or giardiasis (ICD-9-CM code 007.1) within 12 months before the IBS diagnosis. Children with congenital urinary tract anomaly (ICD-9-CM code 753) and neurogenic bladder (ICD-9-CM code 596.4 and 596.5) were also excluded from this study. The follow-up time started from the index date and stopped until the development of IBS, withdrawal of insurance, or on 31 December 2012. A diagram showing the flow of participants from enrollment to analysis is summarized in figure 1.

Statistical analysis

The sociodemographic factors in the current study included age, sex, and urbanization level of residential area. Urbanization level was defined based on the population density. The urbanization level was stratified into four levels, from the highest density (Level 1) to the lowest density (Level 4). The data analyses in this study were using SAS software (V.1). The statistically different was defined at $p<0.05$ in two-tailed tests.

Comparison of the differences were tested using the X^2 test for categorical variables and Student's t-test for continuous variables. The Kaplan-Meier method was used to estimate the proportion of study subjects who did not suffer from IBS during the follow-up period for both cohorts. Person-time is the sum of the follow-up times for each one in the cohort study population had been exposed to or were at risk for the conditions of interest. The incidence density rate of IBS is demonstrated as the number of newly diagnosed IBS per person-years in both the UTI and non-UTI population. HRs and 95% CI were calculated by Cox proportional hazard regressions, with the non-UTI control cohort as the reference group, to investigate the association between UTI and the risk of developing IBS. The Cox proportional hazards model was also used to estimate the HRs of IBS by the frequency of UTI-related medical visits and hospitalization. Further analysis assessed whether the association of IBS varied according to the length of the follow-up period after UTI was diagnosed.

RESULTS

This study evaluated 31 788 UTI children eligible for the study and 127 152 non-UTI matched controls. The sociodemographic factors of both cohorts are demonstrated in table 1. The mean age for infants with UTI was 5.57 month old (SD 3.24) and for infants without UTI was

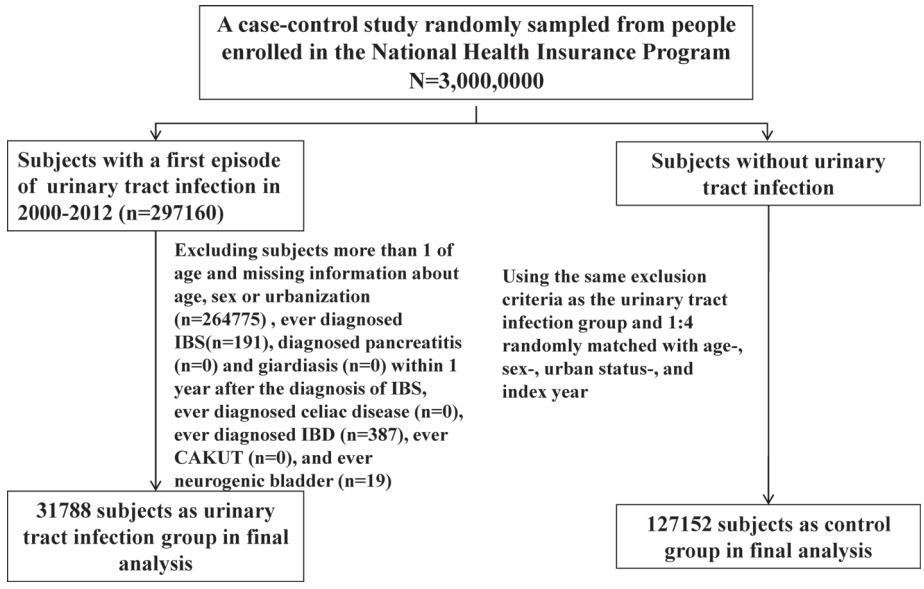

Figure 1 Flow diagram of the enrollment process. CAKUT, congenital anomalies of the kidney and urinary tract; IBD, inflammatory bowel disease.

6.53 month old (SD 3.39). In the UTI cohort, there were more male infants (55.8%), and more living in higher population density areas (60.7%). There were no differences in sex and urbanization of residential area between UTI and non-UTI cohorts. The Kaplan-Meier curve revealed that the IBS rate was greater in the UTI cohort compared with the non-UTI cohort (p=0.001, by log-rank test; figure 2).

The incidence densities of IBS for both cohorts are presented in table 2, along with the UTI to non-UTI HRs for IBS development by sociodemographic status. At the end of a 12-year follow-up, IBS incidence was found to be 1.52-fold greater (95% CI 1.38 to 1.67) in the UTI cohort than in the non-UTI cohort (2.05 vs 1.32 per 1000 person-years). Children with UTI had a significantly greater risk of IBS than those without UTI, regardless of stratification by sex and urbanization. In comparison of gender, it revealed that the incidences of IBS were greater in boys in both cohorts. Boys also had slightly greater adjusted HRs of IBS than girls. The highest and lowest populated areas had increased HR for IBS for the UTI cohort compared with the non-UTI cohort. Compared with the non-UTI cohort, the adjusted HR increased with the frequency of UTI-related medical visits, from 0.97 (95% CI 0.87 to 1.09) for those with ≤3 visits up to 61.3 (95% CI 51.8 to 72.6) for those with >5 visits (p<0.001 for trend) (table 3). In addition, the UTI cohort with longer length of stay of admission for

Table 1 Demographics between children with and without urinary tract infection (UTI)

	Non-UTI (n=127 152)		UTI (n=31 788)		
	n	(%)	n	(%)	P values
Age, months, mean (SD)*	6.53	(3.39)	5.57	(3.24)	<0.001
Sex					
Girl	56 200	(44.2)	14 050	(44.2)	0.99
Boy	70 952	(55.8)	17 738	(55.8)	
Urbanization†					
1 (highest)	37 020	(29.1)	9255	(29.1)	0.99
2	40 136	(31.6)	10 034	(31.6)	
3	24 228	(19.1)	6057	(19.1)	
4 (lowest)	25 768	(20.3)	6442	(20.3)	
Follow-up years, mean (SD)*	9.13	(2.40)	9.09	(2.45)	0.006

*The t-test or X^2 test was used to quantify differences in means or prevalence between the patients with UTI and without UTI for continuous and categorical matching variables.
†The urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized and level 4 as the least urbanized.

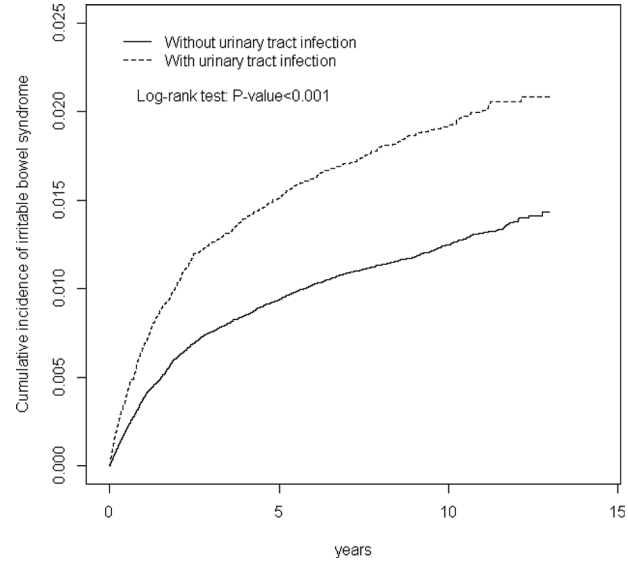

Figure 2 The Kaplan-Meier analysis of cumulative incidence of irritable bowel syndrome for urinary tract infection (UTI) cohort compared with non-UTI cohort.

Table 2 The risk of irritable bowel syndrome in children with urinary tract infection (UTI) compared with children without UTI stratified by demographics in Cox proportional hazard regression

	Non-UTI			UTI			
	Event	Person-years	IR	Event	Person-years	IR	Adjusted HR† (95% CI)
All	1531	1 161 371	1.32	593	289 021	2.05	1.52 (1.38 to 1.67)**
Sex							
Girl	653	512 015	1.28	245	127 574	1.92	1.50 (1.29 to 1.73)**
Boy	878	649 356	1.35	348	161 446	2.16	1.53 (1.34 to 1.73)**
Urbanization							
1 (highest)	481	336 658	1.43	163	84 092	1.94	1.32 (1.11 to 1.58)*
2	482	365 234	1.32	183	90 955	2.01	1.49 (1.26 to 1.77)**
3	269	225 050	1.20	139	55 598	2.50	2.01 (1.64 to 2.48)**
4 (lowest)	299	234 429	1.28	108	58 376	1.85	1.41 (1.13 to 1.76)*

*P<0.01, **P<0.001.
†Variables found to be statistically significant in the univariable model were further examined in the multivariable model. Adjusted for age.
IR, incidence rate, per 1000 person-years.

UTI (>7 days) had greater adjusted HR (1.75; 95% CI 1.36 to 2.24) than those with shorter length of stay (≤7 days) (HR 1.30; 95% CI 1.10 to 1.54). The UTI cohort with VUR had greater adjusted HR (1.73; 95% CI 1.35 to 2.22) than those without VUR (1.49; 95% CI 1.35 to 1.65) (table 3). Compared with the non-UTI cohort, the adjusted HR for IBS decreased slightly with the follow-up years, from adjusted HR (1.59; 95% CI 1.42 to 1.77) for follow-up within the first 4 years to 1.35 (95% CI 1.12 to 1.62) after the 4-year follow-up (table 4).

DISCUSSION

Early life events are key in the development of FGIDs. Animal studies have shown that early life stimulation alters the activity of hypothalamo-pituitary-adrenal axis system, and that as adults, rats that were exposed to adverse events early in life have an exaggerated response to stress.[19] Rat models have also showed that transient colonic irritation in neonates results in chronic visceral allodynia and hyperalgesia during adulthood.[20] Early life events such as psychological stress, painful events, and adverse environmental factors have been identified as risk factors for the development of FGIDs in children.[9] However, many children with FGIDs appear to have none of these risk factors to explain their symptoms.

Table 3 The risk of irritable bowel syndrome stratified by urinary tract infection (UTI)-related medical visits and hospitalization and vesicoureteral reflux (VUR) in Cox proportional hazard regression

	Event	Person-years	IR	Adjusted HR† (95% CI)
UTI-related medical visits, per year				
0	1531	1161371	1.32	1.00 (reference)
1–3	370	2 84 788	1.30	0.97 (0.87 to 1.09)
4–5	70	2669	26.2	17.3 (13.6 to 22.0)*
>5	153	1564	97.9	61.3 (51.8 to 72.6)*
P for trend <0.001				
UTI-related hospitalization days				
0	312	152 166	2.05	1.53 (1.35 to 1.73)*
≤7	145	813 578	1.78	1.30 (1.10 to 1.54)*
>7	67	27 217	2.46	1.75 (1.36 to 2.24)*
UTI association with VUR				
No VUR	527	261 291	2.02	1.49 (1.35 to 1.65)*
VUR	66	27 730	2.38	1.73 (1.35 to 2.22)*

*P<0.001.
†Variables found to be statistically significant in the univariable model were further examined in the multivariable model. Adjusted for age.
IR, incidence rate, per 1000 person-years.

The urinary and gastrointestinal tracts are closely related. Both anorectum and urinary bladder are developed from the cloaca in the human embryo. The lower urinary tract (LUT) and colorectum share the same peripheral nervous system for their sensory and motor function (eg, pelvic nerve controls both the micturition and defecation).[14] Moreover, the sensory function of the LUT and colon are closely related at the level of the central nervous system. This includes the brain central processing and the afferent and efferent pathways of the spinal cord.[21] Additionally, neural bidirectional cross-organ sensitization may play an important role in the association between bladder and colon disorders[15] by explaining how pathological changes in an organ system can result in long-term increased pain sensitivity in the other system.

In a rodent model, chemical-induced cystitis in the neonatal period led to colonic hypersensitivity in adult rats.[22] Alagiri *et al* demonstrated a higher incidence of IBS in adults with interstitial cystitis.[11] However, few studies investigated the association between genitourinary disorders and FGIDs in the pediatric population. Burgers *et al* showed that children with LUT symptoms are at risk of defecation disorders, including functional constipation and incontinence,[23] but they did not evaluate the association between LUT symptoms and FAPDs. Rosen *et al* demonstrated that UTI in infancy is linked to the development of chronic functional abdominal pain in children,[24] but their sample size was not powered enough to demonstrate the association between UTI and IBS.

Our data suggest the strong evidence of the association between IBS and infantile UTI. These data showed that the incidence of IBS was 1.52-fold higher in the cohort that had a UTI during their first year of life, compared with the non-UTI cohort. (table 2). The HRs for IBS in children with UTI were higher for those with more UTI-related medical visits per year, longer hospital stay for UTI, and those who

Table 4 The risk of irritable bowel syndrome in children with urinary tract infection (UTI) compared with children without UTI stratified by follow-up years in Cox proportional hazard regression

	Non-UTI			UTI			
Follow-up years	Event	Person-years	IR	Event	Person-years	IR	Adjusted HR† (95% CI)
<4	1076	52 906	2.14	442	125 293	3.53	1.59 (1.42 to 1.77)*
≥4	455	658 464	0.69	151	163 728	0.92	1.35 (1.12 to 1.62)*

*P<0.001.
† Variables found to be statistically significant in the univariable model were further examined in the multivariable model. Adjusted for age.
IR, incidence rate, per 1000 person-years.

had UTI combined with VUR (table 3). The results imply that children with greater severity of UTI during their first year of life may have a higher risk to develop IBS.

About two-thirds of the children with IBS were diagnosed within 4 years of follow-up (table 4), that is, during their first 5 years of life. It implies infantile UTI has greater influence on the development of IBS in toddlers and the influence decreases when children grow older. The urinary and gastrointestinal tracts are closely related in embryogenesis and nerve innervation.[15 21 25] Previous studies have showed a negative correlation between age and the prevalence of IBS in school-age children, which are consistent with our findings.[26–28]

Previous studies have shown that intestinal infection and non-infectious inflammation in children increases the risk of IBS later in life.[29 30] Our study is the first study which suggest that non-intestinal infection in early childhood increases the risk of IBS years later. There are several strengths in this study. First, the cohort is a national-based cohort, with a large sample size and long-term follow-up. Moreover, the diagnosis of IBS was made by physician rather than patient-reported or parents-reported questionnaires.

A possible cofounder in this study is the use of antibiotics as those have been thought to alter the gut microbiota and predispose to FGIDs. However, a smaller study that investigated perinatal risk factors for IBS showed that antibiotic exposure is not associated with IBS in adults.[31] Another Swedish birth cohort study with a large sample size also showed that antibiotic treatment in the first year of life was not associated with FAPDs in children.[32] A cohort study that investigated the association between the use of broad-spectrum antibiotics and IBS in adults showed that only macrolides and tetracycline are linked to IBS,[33] but these antibiotics are seldom prescribed to treat infants with UTI in Taiwan. Therefore, the use of antibiotics during the first year of life seems to not associate with pediatric IBS.

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 behavioral 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, our study is the first study to demonstrate the association between UTI in infancy and childhood IBS. Our data suggests that UTI in early life increases the risk of subsequent IBS, and patients with greater severity of UTI would have higher risk to develop IBS compared with those with only mild disease. The use of antibiotic in infancy does not seem to be a confounder of our study though its influence cannot be excluded. These results might help explain the pathogenesis and pathophysiology of a subset of children with IBS and develop novel preventative and treatment strategies for the management of IBS. The possible mechanisms that may include the cross-organ sensitization of the pelvic organs and the overlapping nervous system connectivity of bladder and colon or other unknown mechanisms should be investigated in future studies.

Contributors T-KT drafted the initial manuscript. C-LL carried out the analysis, reviewed and approved the final manuscript as submitted. MS and C-CW conceptualized and designed the study; coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

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Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval The Institutional Review Board of the China Medical University Hospital (CRREC-103-048).

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