World Journal of Clinical Cases

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World J Clin Cases 2018 December 6; 6(15): 944-951

DOI: 10.12998/wjcc.v6.i15.944

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Association between functional abdominal pain disorders and asthma in adolescents: A cross-sectional study

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Author contributions: Kumari MV contributed to designing the study, collected, analyzed, and interpreted the data, and drafted the initial manuscript; Devanarayana NM, Amarasiri L, and Rajindrajith S conceptualized the study, contributed to designing the study, and critically analyzed the final manuscript for important intellectual content. All authors approved the final manuscript.

Institutional review board statement: The Ethics Review Committee of Faculty of Medicine and Allied Sciences of Rajarata University of Sri Lanka has granted the ethical approval for this study.

Informed consent statement: Parental/guardian written informed consent was obtained.

Conflict-of-interest statement: The authors declare no conflict of interest.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Manuscript source: Invited manuscript

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Received: August 13, 2018
Peer-review started: August 13, 2018
First decision: October 5, 2018
Revised: November 10, 2018
Accepted: November 14, 2018
Article in press: November 15, 2018
Published online: December 6, 2018

Abstract

AIM

To find the association between asthma and different types of functional abdominal pain disorders (FAPDs) among teenagers.

METHOD

A cross-sectional study was conducted among 13 to 15-year-old children from six randomly selected schools in Anuradhapura district of Sri Lanka. Data were collected using translated and validated self-administered questionnaires (Rome Ⅲ questionnaire, International Study on Asthma and Allergies in Child-

hood questionnaire, and Pediatric Quality of Life Inventory 4.0) and administered under an examination setting after obtaining parental consent and assent.

RESULTS

Of the 1101 children included in the analysis, 157 (14.3%) had asthma and 101 (9.2%) had at least one FAPDs. Of children with asthma, 19.1% had at least one type of FAPDs. Prevalence rates of functional abdominal pain (FAP) (8.9% *vs* 3.3% in non-asthmatics), functional dyspepsia (FD) (2.5% *vs* 0.7%), and abdominal migraine (AM) (3.2% *vs* 0.4%) were higher in those with asthma ($P < 0.05$, multiple logistic regression analysis), but not in those with irritable bowel syndrome (4.5% *vs* 3.1%, $P = 0.2$). Severe abdominal pain (10.8% *vs* 4.6%), bloating (16.6% *vs* 9.6%), nausea (6.4% *vs* 2.9%), and anorexia (24.2% *vs* 16.2%) were more prevalent among asthmatics ($P < 0.05$). Lower gastrointestinal symptoms did not show a significant difference. Scores obtained for health related quality of life (HRQoL) were lower in those with asthma and FAPDs ($P < 0.05$, unpaired *t*-test).

CONCLUSION

Asthma is associated with three different types of FAPDs, namely, FD, AM, and FAP. HRQoL is significantly impaired in teenagers with asthma and FAPDs.

Key words: Health related quality of life; Functional gastrointestinal disorders; Abdominal pain; Asthma; Children

Core tip: A cross-sectional study was conducted to assess the association between asthma and functional abdominal pain disorders (FAPDs) in teenagers. We observed a strong, independent association between asthma and three types of FAPDs, namely, functional abdominal pain, functional dyspepsia, and abdominal migraine, indicating possibility of common underlying pathophysiology. However, no association was observed with irritable bowel syndrome. Most upper gastrointestinal symptoms were more common among asthmatics than in non-asthmatics, but lower gastrointestinal disorders showed no difference. Health related quality of life was significantly decreased in both asthma and FAPDs, indicating the significant impact of both disorders.

Kumari MV, Devanarayana NM, Amarasiri L, Rajindrajith S. Association between functional abdominal pain disorders and asthma in adolescents: A cross-sectional study. *World J Clin Cases* 2018; 6(15): 944-951 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i15/944.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i15.944

INTRODUCTION

Functional abdominal pain disorders (FAPDs) are a group of disorders characterized by recurrent episodes of abdominal pain with no identifiable organic pathology. There are four recognized types of FAPDs in children, namely, functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), and functional abdominal pain (FAP)[1]. It is estimated that 13.5% of children worldwide suffer from FAPDs[2]. The complex patho-physiology of FAPDs involves gastrointestinal dysmotility, visceral hypersensitivity, dysregulation of mucosal immune system, altered gut microbiota, and complex bidirectional interactions in the brain-gut axis[3].

Asthma is a chronic inflammatory disorder of airways with airway hyper- responsiveness and airflow limitation. It is a major public health problem affecting 300 million people worldwide. In children, the global prevalence of asthma ranges from 0.8% to 32.6%[4]. Patho-physiology of asthma involves complex immunological reactions, environmental triggers, smooth muscle dysfunction, and psychological factors[5,6].

Both FAPDs and asthma are known to have significant repercussion on child health and overwhelming effects on their health related quality of life (HRQoL)[7,8]. These lead to high healthcare expenditure taxing a significant proportion of health budgets[9,10]. The association between asthma and FAPDs has been previously assessed only in IBS[11-13], but not in other types (FD, AM, and FAP). Furthermore, this association has not been previously studied in paediatric age groups. Exact reason for association between FAPDs and asthma is not clear. However, smooth muscle dysfunction[14,15] and altered immune reactions[16-18] are possible shared patho-physiological mechanisms for both disorders. Therefore, the main objective of this study was to evaluate the association between asthma and different types of FAPDs in the paediatric population and the effects of these disorders on their HRQoL.

MATERIALS AND METHODS

Study population

A cross-sectional survey was conducted in the largest district of Sri Lanka, Anuradhapura. A list of schools in the Anuradhapura district was obtained from the Provincial Educational Department, North Central province, Sri Lanka. Multi-stage sampling technique was used to select the study population. There are four types of schools recognized by the Ministry of Education, Sri Lanka. They are Type 1AB, 1C, Type 2, and Type 3. This categorization is mainly based on the number of academic grades available in a school. In the first stage, all the schools from Type 1AB, 1C, and Type 2 in the district were selected, representing adolescents aged

Table 1 Prevalence of functional abdominal pain disorders according to asthma (*n* = 1101) *n* (%)

Disease category	Asthmatics	Non-asthmatics	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)	*P*-value
BS	7 (4.5)	29 (3.1)	1.6 (0.7-3.8)	1.7 (0.7-4.0)	0.2
FD	4 (2.5)	7 (0.7)	3.9 (1.1-13.6)	3.9 (1.1-13.5)	0.03
AM	5 (3.2)	4 (0.4)	8.5 (2.2-32.4)	10.2 (2.6-39.5)	0.001
FAP	14 (8.9)	31 (3.3)	3.1 (1.6-5.9)	3.1 (1.6-6.0)	0.001
With any type of FAPDs	30 (19.1)	71 (7.5)	2.9 (1.8-4.6)	2.9 (1.8-4.7)	< 0.0001

IBS: Irritable bowel syndrome; FD: Functional dyspepsia; AM: Abdominal migraine; FAP: Functional abdominal pain; FAPDs: Functional abdominal pain disorders.

13-15 years. In the second stage, two schools from each type were randomly selected, representing all five educational zones in the Anuradhapura district. In the final stage, from every selected school, six classes were randomly selected. All the students aged 13 to 15 years present in a selected class on the day of the survey were included.

Data collection

Consent was obtained from the school administration, parents, and the children themselves. Previously translated and validated Rome Ⅲ questionnaire (self-reported form for children above 10 years)[7,19] and International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire[20,21] were used to diagnose FAPDs and asthma, respectively. HRQoL was evaluated using translated and pretested Pediatric Quality of Life Inventory 4.0 (PedsQL - Generic Core Scales) self-report form for teens[7,22]. All parts of the questionnaire were distributed among students in an examination setting, to ensure confidentiality and privacy. The principal investigator and trained research assistants were present and explanations were given while filling the questionnaire.

Identification of children with FAPDs or asthma

Types of FAPDs (IBS, FD, AM, and FAP) were categorized using Rome Ⅲ criteria[1]. Severity of abdominal pain was coded using a 4-point scale (no pain, mild, moderate, and severe). Students reporting to have both physician diagnosed asthma and wheezing during the previous 12 mo[20] were categorized as current asthma.

Computation of HRQoL

The PedsQL inventory assessed 23 items, including physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). A 5-point response scale was applied to assess the responses (0 = never a problem; 1 = almost never a problem, 2 = sometimes a problem, 3 = often a problem, and 4 = almost always a problem). Items were reverse scored and linearly transformed to a 0 to 100 scales (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0) final HRQoL scores were computed out of 100 so that higher scores indicate better HRQoL.

Statistical methods

The sample size was calculated based on an expected prevalence of 20%, absolute precision of 5%, and standard normal deviation of 1.96 for a confidence level of 95%. The minimum sample size required for determining the prevalence of FAPDs and prevalence of asthma was 672.

Data from all schools were pooled for the initial analysis. A logistic regression model was used to evaluate an independent association between asthma and FAPDs. The association between asthma and severity of abdominal pain was assessed using binary logistic regression. The chi-square statistic and odds ratios with 95%CI were calculated to compare the prevalence of upper and lower gastrointestinal symptoms between asthmatics and non-asthmatics. One-way ANOVA was used with Bonferroni correction to compare HRQoL scores between groups. $P < 0.05$ was considered significant. PSPP statistical software version 1.0.1 was used in all calculations. Statistical review of the study was performed by a biomedical statistician.

RESULTS

A total of 1113 questionnaires were distributed and all of them were returned. Of them, properly filled 1101 (98.9%) questionnaires were included in the final analysis. The study population consisted of 509 boys (46.2%) with a mean age of 14.03 years (range 13-15 years, SD of 0.8 years). In this study, the prevalence of current asthma was 14.3%. One hundred and one adolescents had at least one type of FAPD (9.2%). According to Rome Ⅲ criteria, FAP was identified in 45 (4.1%), 36 (3.3%) had IBS, 11 (1%) had FD, and 9 (0.8%) had AM.

Association between asthma and FAPDs

Of children with asthma, 19.1% had at least one type of FAPD. Logistic regression analysis showed a strong, independent association between asthma and FAP, FD, and AM after adjusting for age and sex (Table 1). There was also a significant association between asthma and severity of abdominal pain (Table 2).

Gastrointestinal symptoms among asthmatics

Upper gastrointestinal symptoms which showed a

Table 2 Severity of abdominal pain according to asthma (*n* = 1101) *n* (%)

Abdominal pain severity	Asthmatics	Non-asthmatics	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)	*P*-value
Mild	38 (24.2)	225 (23.8)	1.1 (0.7-1.8)	1.1 (0.7-1.7)	0.49
Moderate	36 (22.9)	217 (23.0)	1.1 (0.7-1.7)	1.1 (0.7-1.8)	0.48
Severe	17 (10.8)	43 (4.6)	2.7 (1.4-5.1)	2.8 (1.5-5.3)	0.001

Table 3 Prevalence of gastrointestinal symptoms among asthmatics (*n* = 1101) *n* (%)

	Asthmatics	Non asthmatics	Odds ratio (95%CI)	*P*-value
Upper gastrointestinal symptom				
Abdominal pain	33 (21)	109 (11.5)	2.0 (1.3-3.1)	0.002
Bloating	26 (16.6)	91 (9.6)	1.8 (1.1-2.9)	0.01
Loss of appetite	38 (24.2)	153 (16.2)	1.6 (1.1-2.4)	0.02
Nausea	10 (6.4)	27 (2.9)	2.3 (1.0-4.8)	0.04
Vomiting	7 (4.5)	54 (5.7)	0.7 (0.3-1.7)	0.6
Early satiety	15 (9.6)	119 (12.6)	0.7 (0.4-1.2)	0.3
Lower gastrointestinal symptom				
Increased frequency of defecation	17 (10.8)	82 (8.7)	1.2 (0.7-2.2)	0.3
Decreased frequency of defecation	14 (8.9)	70 (7.4)	1.2 (0.6-2.2)	0.5
Frequency of passage of hard stool	10 (6.4)	76 (8.1)	0.7 (0.3-1.5)	0.4
Frequency of passage of loose stool	18 (11.5)	92 (9.7)	1.1 (0.7-2.0)	0.5

Table 4 Health related quality of life scores in children with each disease category and controls (*n* = 1101)

Quality of life domain	Children with FAPDs only mean (SD) *n* = 70	Children with asthma only mean (SD) *n* = 129	Children with both asthma and FAPDs mean (SD) *n* = 30	Controls mean (SD) *n* = 872
Physical functioning	77.0 (14.5)[b]	80.8 (14.0)[b]	72.7 (13.6)[b,c]	88.4 (10.5)
Emotional functioning	69.0 (20.2)[b]	75.3 (16.8)	69.8 (14.4)[a]	78.1 (16.0)
Social functioning	78.6 (19.1)[b,c]	85.6 (14.3)[a]	83.3 (15.2)	88.9 (12.0)
School functioning	74.7 (17.8)[a]	77.2 (15.7)[a]	68.5 (16.4)[b,c]	81.1 (14.1)
Total HRQoL score	75.1 (14.0)[b,c]	79.9 (11.1)[b]	73.4 (11.0)[b,c]	84.7 (10.1)

HRQoL: Health related quality of life; FAPDs: Functional abdominal pain disorders. [a]$P < 0.05$ *vs* controls, [b]$P < 0.0001$ *vs* controls, [c]$P < 0.05$ *vs* asthmatics.

significant association with bronchial asthma were abdominal pain, bloating, nausea, and loss of appetite. However, lower gastrointestinal symptoms were not associated with asthma (Table 3).

HRQoL among affected adolescents

Children with both diseases had lower overall HRQoL scores compared to controls (Table 4). Children with both FAPDs and asthma had significantly lower quality of life than those with asthma alone. Furthermore, children having FAPDs only had a higher impairment of the quality of life, compared to those with asthma alone, but there was no significant difference between children with FAPDs only and those with both diseases.

DISCUSSION

For perhaps the first time in the paediatric literature, we found a strong, independent association between asthma and three different types of FAPDs, namely, FAP, FD, and AM. Furthermore, the severity of abdominal pain in FAPDs was an independent predictive factor of having asthma. In contrast to previous studies among adults, we did not note a significant association between IBS and asthma. This finding is probably not surprising as most of the studies have specifically studied the association between asthma and patients with IBS only[11,12,23]. One study using data from General Practice has shown a weak association between IBS and asthma. However, when adjusted to age, gender, and psychological co-morbidities, the association became insignificant[24]. In their study, the clinical diagnosis of FAPDs was made by a general practitioner and not conforming exactly to standard Rome criteria, which made comparisons difficult. Olén *et al*[25] studied a birth cohort of 2610 children at the age of 12 years in Sweden. They found that the presence of asthma during the first 2 years was significantly associated with abdominal pain of functional origin at 12 years. They looked at the association between asthma and non-specific abdominal pain, but did not attempt to look at the exact association with specific FAPDs.

In our study, the gastrointestinal symptoms independently associated with asthma were abdominal pain, bloating, nausea, and loss of appetite. Our finding was supported by a case-control study that reported that abdominal pain and vomiting were significantly more prevalent in asthmatic children than in controls[26].

In contrast to our study, they showed that lower gastrointestinal symptoms were also significantly more prevalent. Another study among adolescents showed a significant association between allergic wheeze and abdominal pain[27]. Further studies found higher prevalence of gastrointestinal symptoms in patients with allergic rhinitis and wheeze[28,29].

In our study, the prevalence of FAPDs (9.3%) among teenagers was less than the study that had reported 16.5% of prevalence among Sri Lankan adolescents aged 13-18 years[7]. In contrast, a recent meta-analysis has shown a worldwide pooled prevalence of FGIDs of 13.5% in children[2]. Regional differences in the dietary patterns, life styles, differences in survey methods, inclusion of different age groups, and changing diagnostic criteria would have contributed to these differences. The prevalence of asthma in this study is more than that previously reported by Danansuriya *et al*[21] (10.7%) in Sri Lankan adolescents aged 12-14 years. However, the prevalence rate of asthma reported in this study is within the range reported by the ISAAC studies carried out throughout the world, which ranged between 0.8% to 32.6% among adolescents aged 13 to 14 years[4]. Different prevalence rates can be explained by selected age group, sample selection, and case definition used.

We observed that adolescents with only asthma or FAPDs together with adolescents suffering from both disease conditions had significantly lower HRQoL compared to controls. To our knowledge, this is the first study which reported the impact of asthma on quality of life among Sri Lankan adolescents. An Australian study found that asthma caused mild to moderate quality of life impairment among adolescents[8]. A Brazilian study observed a significant impairment of quality of life among adolescents with severe asthma[30]. Another study reported that asthma impairs quality of life not only among asthmatic children but also among their primary caregivers[31].

Pain predominant FGIDs showed lower scores for all four domains of HRQoL in affected adolescents. Similarly, several previous studies have reported lower HRQoL in children with FAPDs[7,32]. We found that adolescents with both diseases (FAPDs and asthma) had lower HRQoL than children with asthma alone. This can be explained by the dual disease burden among these adolescents. Interestingly, in our study, children having only FAPDs had a lower total HRQoL score than adolescents with asthma alone. Although asthma is a chronic condition similar to FAPDs, the impact of FAPDs on quality of life appears to be greater than that of asthma. Youssef *et al*[32] showed that children with FAPDs had lower HRQoL, compared to those with inflammatory bowel disease and gastro-oesophageal reflux disease. We could possibly conclude that FAPDs have a more devastating impact on HRQoL than other chronic diseases which have at least reasonable therapeutic options. In fact, FAPDs have minimal therapeutic options despite decades of research. This could also contribute to the lower HRQoL in adolescents with FAPDs only.

Why asthma and FAPDs, two different disorders involving two different systems, are associated with each other? One hypothesis is that the generalized smooth muscle dysfunction in both gastrointestinal and respiratory systems gives rise to symptoms simultaneously. Gastric motility is maintained by gastric smooth muscle, and disturbance in gastric motility is well reported in children with all types of FAPDs[33,34]. A study assessing gastric motility in adult asthmatics noted a significant delay in gastric emptying rate and lower antral motility index compared to controls[14]. Similarly, disturbance in airway resistance has been demonstrated in patients with IBS[12,15]. Amra *et al*[15] studied IBS patients with no respiratory symptoms and reported that forced expiratory volume in the first second (FEV_1) was significantly lower and the airway resistance at 5 Hz was significantly higher in them compared to healthy subjects. It supports the evidence of a subclinical increase in airway resistance and airway smooth muscle dysfunction in patients with IBS, indicating a possible association between these two entities.

An immunological link between the lung and gut, and therefore, disordered immune response common to both biological systems, can play a role in the association between FAPDs and asthma. In asthma, airway inflammation results in increased numbers of activated eosinophils, mast cells, and T lymphocytes in the airway mucosa[35]. The same immunological reactions have been detected in small bowel biopsy specimens of asthmatics[16]. Similar cellular immune responses have been shown in the gut of patients with FGIDs. Friesen *et al*[17] found that 71% of children evaluated for FD have significant eosinophil infiltration in the duodenal mucosa including intraepithelial eosinophils. Another study showed increased mast cell infiltration in the small and large intestine of patients with IBS, compared to healthy controls[36]. Infiltrated mast cells in gut mucosa spontaneously release mediators like histamine in close proximity to visceral sensory nerves and these substances in turn may lower the sensory threshold for pain, inducing visceral hypersensitivity[18]. Several studies conducted in patients with IBS have found a correlation between the number of activated mast cells present in the gut mucosa and increased severity of abdominal pain and bloating[37,38]. On the other hand, mast cells in airways release the same immune mediators like histamine which have a profound effect on airway smooth muscle cells inducing bronchial hyper responsiveness[39]. Further, TH_2 related immune activation is also known to be associated with both of these disorders[6,40]. These studies indicate the possibility of FAPDs and asthma sharing the same immunological mechanisms and perhaps similar underlying pathophysiology.

The present study has several strengths. Large sample size and multistage sampling technique have increased the validity of our results. Further, we used standard questionnaires (Rome Ⅲ questionnaire for

children and ISAAC tool to diagnose asthma in children) in data collection, which were translated and validated for Sri Lanka. Limitations of this study include not conducting a physical examination and investigations of these children to confirm the diagnosis of asthma and FAPDs. We could not perform lung function testing and bronchodilator reversibility test to confirm the diagnosis of asthma and basic investigation to exclude organic pathologies causing abdominal pain due to this large sample size. In addition, by the time this study was conducted, Rome Ⅳ criteria were not released and therefore we used Rome Ⅲ criteria for diagnosis of FAPDs. However, the pathophysiological mechanisms are unlikely to be affected by the use of older criteria and therefore, unlikely to have a significant effect on our conclusions.

Identifying the association between FAPDs and asthma has several implications. Both these disorders are very common in paediatric practice and considered as emerging global health problems in children. Further, it is quite possible that the association between these two conditions would reduce the HRQoL and increase healthcare expenditure in children possibly in an additive manner than either disease alone. Therefore, clinicians need to be aware of the association between these two disorders as well as the association between asthma and upper gastrointestinal symptoms to provide holistic clinical care to the affected children. Finally, our findings would suggest the possibility of a common patho-physiological mechanism for both disorders.

In conclusion, this is the first report of a strong independent association between asthma and three different types of FAPDs, namely, FAP, FD, and AM in the pediatric literature. Upper gastrointestinal symptoms are significantly more common among children with asthma than in non-asthmatics. Our findings suggest the possibility of a common underlying patho-physiological mechanism for both disorders. Furthermore, the lower HRQoL of children with FAPDs compared to those with other diseases demands novel and innovative therapeutic modalities to manage children with this disorder.

ARTICLE HIGHLIGHTS

Research background

Both functional abdominal pain disorders (FAPDs) and asthma are highly prevalent diseases among children and have a significant individual and public health impact. Chronic recurrent nature of both diseases is known to impair the health related quality of life (HRQoL) of affected individuals and drain a large amount of public funds in treating exacerbations and long-term follow-up.

Research motivation

Studies among adults have shown a potential association between irritable bowel syndrome and bronchial asthma and suggested the possibility of common patho-physiology for both disorders. However, no studies have attempted to evaluate the association between these two highly prevalent diseases in children.

Research objectives

The main objective of our study is to explore the association between FAPDs and asthma in children and their impact on HRQoL.

Research methods

A cross-sectional survey was conducted among school children aged 13-15 years. Multi-stage sampling technique was used to select the study population. We used validated Rome III questionnaire and International Study on Asthma and Allergies in Childhood questionnaire to assess gastrointestinal and respiratory symptoms. Pediatric quality of life inventory (PedsQL Generic Core Scale) was used to assess HRQoL. Rome III criteria were used to diagnose FAPDs. Students reporting to have both physician diagnosed asthma and wheezing during the previous year were categorized as having asthma. HRQoL was computed using the standard protocol.

Research results

A total of 1101 questionnaires were included in the final analysis. We found asthma in 14.3% of children and at least one type of FAPD in 9.2% of children. The logistic regression analysis model showed an independent association between asthma and functional abdominal pain (FAP), functional dyspepsia (FD), and abdominal migraine (AM). Upper gastrointestinal symptoms such as abdominal pain, bloating, nausea, and loss of appetite were significantly associated with asthma. Quality of life scores in both children with asthma and those with FAPDs were lower when compared to normal children.

Research conclusions

We found a clear association between asthma and three FAPDs, namely, FAP, FD, and AM, suggesting the possibility of asthma and FAPDs sharing same pathophysiological mechanisms. Generalized smooth muscle dysfunction in both gastrointestinal and respiratory tracts could be triggered simultaneously through autonomic dysfunction, which could have been one potential pathophysiological mechanism to explain this association. Furthermore, it is also possible that common immunological phenomena such as mast cell dysfunction and altered TH2 response could drive the pathophysiology of both disorders.

Research perspectives

In this study we highlighted the potential association between two common pediatric disorders (asthma and FAPDs). Future studies should be directed to explore underlying pathophysiological basis for this association, especially focusing on smooth muscle dysfunction and immune dysregulation of both gastrointestinal and respiratory systems.

ACKNOWLEDGMENTS

The authors would like to thank Mr. SMAB Samarakoon, Computer Application Assistant, Department of Physiology, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka for his assistance in typing and preparing questionnaires in native languages and other required documents for data collection.

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