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***Observational Study***

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

Kumari MV *et al.* Asthma and functional abdominal pain

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**Abstract**

***AIM***

Asthma is reported to be associated with irritable bowel syndrome (IBS) in adults. This study was undertaken to find the association between asthma and different types of functional abdominal pain disorders (FAPDs) among teenagers.

***METHODS***

A cross sectional study was conducted among 13 to 15-year-old from 6 randomly selected schools in Anuradhapura district of Sri Lanka. Data collected using translated and validated self-administered questionnaires (Rome III Questionnaire, International Study on Asthma and Allergies in Childhood questionnaires and Pediatric Quality of Life Inventory 4.0), administered under examination setting after obtaining parental consent and assent.

***RESULTS***

Of the 1101 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 of functional abdominal pain (FAP) (8.9% *vs* 3.3% in non-asthmatics), functional dyspepsia (FD) (2.5% *vs* 0.7%) and abdominal migraine (3.2% *vs* 0.4%) were higher in those with asthma (*P* < 0.05, multiple logistic regression analysis), but not with IBS (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 was associated with three different types of FAPDs, namely FD, abdominal pain and FAP not specified. HRQoL was significantly impaired in teenagers with asthma and FAPDs.

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

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**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 commoner 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.

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**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 interactions between bidirectional 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 in child health and over whelming 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 one type of FAPDs (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, the 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 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 4 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 13-15 years. In the second stage, 2 schools from each type were randomly selected representing all five educational zones in the Anuradhapura district. In the final stage, from every selected school, 6 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 from the children themselves. Previously translated and validated Rome III questionnaire (self-reported form for children 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 questionnaires 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, 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 reported to have both physician diagnosed asthma and having wheezing during the previous 12 mo[20] were categorized as current asthma.

***Computation of HRQoL***

The PedsQL inventory assessed 23 items;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, 4 = almost always a problem). Items were reverse scored and linearly transformed to a zero to 100 scales (0 = 100, 1 = 75, 2 = 50, 3 = 25, 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 with binary logistic regression. *χ*2 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 as significant. PSPP statistical software version 1.0.1 was used in all calculation. 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 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%. Hundred and one (101) adolescents had at least one 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 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 asthma alone. Furthermore, children having FAPDs only had a higher impairment of the quality of life, compared to those with asthma alone. There was no significant statistical difference between FAPDs only group and children with both diseases group.

**Discussion**

For perhaps the first time in the paediatric literature, we have found a strong, independent association between asthma and three different types of FAPDs, namely FAP, FD and AM. Further 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 the age, gender and psychological co-morbidities, the association became insignificant[24]. In their study, the clinical diagnosis for FAPDs was made by a general practitioner and not conforming exactly to standard Rome criteria, which made comparisons difficult. Olen *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 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 to be 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 throughout world, which ranged between 0.8% to 32.6% among adolescents aged 13 to 14 years old[4].Different prevalence rates can be explained by selected age group, sample selection and case definition used.

We observed that adolescents with only asthma, only 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 has 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 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 a 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 burden of disease among these adolescents. Interestingly in our study, children having only FAPDs had a lower total HRQoL score than adolescents with asthma alone. Though 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 diseases 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 only FAPDs.

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 giving 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 (FEV1) was significantly lower and the airway resistance at 5 Hz was significantly higher in them compared to healthy subjects. It supports evidence of 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 the 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 with 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 TH2 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 patho-physiology.

The present study has several strengths. Large sample size and multistage sampling technique shave 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. 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. Other limitation is that 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.

Finding out of the association between FAPDs, and asthma has several implications. Both these disorders are very common in paediatric practice and consider 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 with children with asthma than in non-asthmatics. Our findings suggest the possibility of common underlying patho-physiological mechanism for both disorders. Furthermore, the lower HRQoL of children with FAPDs compared to 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 reported 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 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 asthma and 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 could have been one potential pathophysiological mechanism to explain this association. Furthermore, it is also possible 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.

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**REFERENCES**

1 **Rasquin A**, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006; **130**: 1527-1537 [PMID: 16678566 DOI: 10.1053/j.gastro.2005.08.063]

2 **Korterink JJ**, Diederen K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. *PLoS One* 2015; **10**: e0126982 [PMID: 25992621 DOI: 10.1371/journal.pone.0126982]

3 **Korterink J**, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. Childhood functional abdominal pain: mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 159-171 [PMID: 25666642 DOI: 10.1038/nrgastro.2015.21]

4 **Lai CK**, Beasley R, Crane J, Foliaki S, Shah J, Weiland S; International Study of Asthma and Allergies in Childhood Phase Three Study Group. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009; **64**: 476-483 [PMID: 19237391 DOI: 10.1136/thx.2008.106609]

5 **Ozier A**, Allard B, Bara I, Girodet PO, Trian T, Marthan R, Berger P. The pivotal role of airway smooth muscle in asthma pathophysiology. *J Allergy* (Cairo) 2011; **2011**: 742710 [PMID: 22220184 DOI: 10.1155/2011/742710]

6 **Barnes PJ**. Th2 cytokines and asthma: an introduction. *Respir Res* 2001; **2**: 64-65 [PMID: 11686866]

7 **Devanarayana NM**, Rajindrajith S, Benninga MA. Quality of life and health care consultation in 13 to 18 year olds with abdominal pain predominant functional gastrointestinal diseases. *BMC Gastroenterol* 2014; **14**: 150 [PMID: 25145589 DOI: 10.1186/1471-230X-14-150]

8 **Gibson PG**, Henry RL, Vimpani GV, Halliday J. Asthma knowledge, attitudes, and quality of life in adolescents. *Arch Dis Child* 1995; **73**: 321-326 [PMID: 7492196]

9 **Park R**, Mikami S, LeClair J, Bollom A, Lembo C, Sethi S, Lembo A, Jones M, Cheng V, Friedlander E, Nurko S. Inpatient burden of childhood functional GI disorders in the USA: an analysis of national trends in the USA from 1997 to 2009. *Neurogastroenterol Motil* 2015; **27**: 684-692 [PMID: 25809794 DOI: 10.1111/nmo.12542]

10 **O'Neill S**, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, Bucknall C, Chaudhuri R, Thomson NC, Brightling CE, O'Neill C, Heaney LG; British Thoracic Society Difficult Asthma Network. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2015; **70**: 376-378 [PMID: 24917087 DOI: 10.1136/thoraxjnl-2013-204114]

11 **Amra B**, Hoseini-Asl MK, Rahmani AR, Golshan M, Mohamad-Zadeh Z. Correlation between asthma and irritable bowel syndrome in a general population in Iran in 2003. *Respir Med* 2006; **100**: 110-114 [PMID: 16338596 DOI: 10.1016/j.rmed.2005.03.036]

12 **Yazar A**, Atis S, Konca K, Pata C, Akbay E, Calikoglu M, Hafta A. Respiratory symptoms and pulmonary functional changes in patients with irritable bowel syndrome. *Am J Gastroenterol* 2001; **96**: 1511-1516 [PMID: 11374691 DOI: 10.1111/j.1572-0241.2001.03748.x]

13 **Shen TC**, Lin CL, Wei CC, Chen CH, Tu CY, Hsia TC, Shih CM, Hsu WH, Sung FC, Kao CH. Bidirectional Association between Asthma and Irritable Bowel Syndrome: Two Population-Based Retrospective Cohort Studies. *PLoS One* 2016; **11**: e0153911 [PMID: 27093172 DOI: 10.1371/journal.pone.0153911]

14 **Amarasiri WA**, Pathmeswaran A, de Silva AP, Dassanayake AS, Ranasinha CD, de Silva HJ. Gastric motility following ingestion of a solid meal in a cohort of adult asthmatics. *J Neurogastroenterol Motil* 2013; **19**: 355-365 [PMID: 23875103 DOI: 10.5056/jnm.2013.19.3.355]

15 **Amra B**, Emami MH, Drooshi B, Golshan M. Airway resistance in irritable bowel syndrome as measured by impulse oscillometry. *Indian J Gastroenterol* 2006; **25**: 185-187 [PMID: 16974031]

16 **Wallaert B**, Desreumaux P, Copin MC, Tillie I, Benard A, Colombel JF, Gosselin B, Tonnel AB, Janin A. Immunoreactivity for interleukin 3 and 5 and granulocyte/macrophage colony-stimulating factor of intestinal mucosa in bronchial asthma. *J Exp Med* 1995; **182**: 1897-1904 [PMID: 7500035]

17 **Friesen CA**, Sandridge L, Andre L, Roberts CC, Abdel-Rahman SM. Mucosal eosinophilia and response to H1/H2 antagonist and cromolyn therapy in pediatric dyspepsia. *Clin Pediatr* (Phila) 2006; **45**: 143-147 [PMID: 16528434 DOI: 10.1177/000992280604500205]

18 **Barbara G**, Wang B, Stanghellini V, de Giorgio R, Cremon C, Di Nardo G, Trevisani M, Campi B, Geppetti P, Tonini M, Bunnett NW, Grundy D, Corinaldesi R. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* 2007; **132**: 26-37 [PMID: 17241857 DOI: 10.1053/j.gastro.2006.11.039]

19 **Walker LS**, Caplan A, Rasquin A. Manual for the questionnaire on pediatric gastrointestinal symptoms. Nashville TN: Department of Pediatrics, Vanderbilt University Medical Center, 2000. Available from: URL: https://scholar.google.com/citations?user=ONkF3HkAAAAJhl=en#d=gs\_md\_cita-dp=u=%2Fcitations%3Fview\_op%3Dview\_citation%26hl%3Den%26user%3DONkF3HkAAAAJ%26citation\_for\_view%3DONkF3HkAAAAJ%3A2osOgNQ5qMEC%26tzom%3D-480

20 **Ellwood P**, Asher MI, Beasley R, Clayton TO, Stewart AW. ISAAC Steering Committee International Study of Asthma and Allergies in Childhood Phase Three Manual. Auckland, New Zealand, 2000. Available from: URL: http:// isaac.auckland.ac.nz/phases/phasethree/phasethreemanual.pdf

21 **Danansuriya MN**, Rajapaksa LC, Weerasinghe A. Genetic, familial and environmental correlates of asthma among early adolescents in Sri Lanka: a case control study. *World Allergy Organ J* 2015; **8**: 19 [PMID: 26140077 DOI: 10.1186/s40413-015-0068-x]

22 **Varni JW**, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 2003; **3**: 329-341 [PMID: 14616041 DOI: 10.1367/1539-4409(2003)0032.0.CO;2]

23 **Ozol D**, Uz E, Bozalan R, Türkay C, Yildirim Z. Relationship between asthma and irritable bowel syndrome: role of food allergy. *J Asthma* 2006; **43**: 773-775 [PMID: 17169830 DOI: 10.1080/02770900601031789]

24 **Jones MP**, Walker MM, Ford AC, Talley NJ. The overlap of atopy and functional gastrointestinal disorders among 23,471 patients in primary care. *Aliment Pharmacol Ther* 2014; **40**: 382-391 [PMID: 24961872 DOI: 10.1111/apt.12846]

25 **Olén O**, Neuman Å, Koopmann B, Ludvigsson JF, Ballardini N, Westman M, Melén E, Kull I, Simrén M, Bergström A. Allergy-related diseases and recurrent abdominal pain during childhood - a birth cohort study. *Aliment Pharmacol Ther* 2014; **40**: 1349-1358 [PMID: 25270840 DOI: 10.1111/apt.12965]

26 **Caffarelli C**, Deriu FM, Terzi V, Perrone F, De Angelis G, Atherton DJ. Gastrointestinal symptoms in patients with asthma. *Arch Dis Child* 2000; **82**: 131-135 [PMID: 10648366 DOI: 10.1136/adc.82.2.131]

27 **Tollefsen E**, Langhammer A, Bjermer L, Romundstad P, Holmen TL. Allergy: a systemic disease? The HUNT and Young-HUNT study, Norway. *Pediatr Allergy Immunol* 2008; **19**: 730-736 [PMID: 18312534 DOI: 10.1111/j.1399-3038.2008.00732.x]

28 **Ronchetti R**, Villa MP, Matricardi PM, La Grutta S, Barreto M, Pagani J, Mortella S, Falasca C, Ciofetta G, Poggi B. Association of asthma with extra-respiratory symptoms in schoolchildren: two cross-sectional studies 6 years apart. *Pediatr Allergy Immunol* 2002; **13**: 113-118 [PMID: 12000483 DOI: 10.1034/j.1399-3038.2002.01036.x]

29 **Powell N**, Huntley B, Beech T, Knight W, Knight H, Corrigan CJ. Increased prevalence of gastrointestinal symptoms in patients with allergic disease. *Postgrad Med J* 2007; **83**: 182-186 [PMID: 17344573 DOI: 10.1136/pgmj.2006.049585]

30 **Matsunaga NY**, Ribeiro MA, Saad IA, Morcillo AM, Ribeiro JD, Toro AA. Evaluation of quality of life according to asthma control and asthma severity in children and adolescents. *J Bras Pneumol* 2015; **41**: 502-508 [PMID: 26785958 DOI: 10.1590/S1806-37562015000000186]

31 **Dean BB**, Calimlim BC, Sacco P, Aguilar D, Maykut R, Tinkelman D. Uncontrolled asthma: assessing quality of life and productivity of children and their caregivers using a cross-sectional Internet-based survey. *Health Qual Life Outcomes* 2010; **8**: 96 [PMID: 20825674 DOI: 10.1186/1477-7525-8-96]

32 **Youssef NN**, Murphy TG, Langseder AL, Rosh JR. Quality of life for children with functional abdominal pain: a comparison study of patients' and parents' perceptions. *Pediatrics* 2006; **117**: 54-59 [PMID: 16396860 DOI: 10.1542/peds.2005-0114]

33 **Devanarayana NM**, Rajindrajith S, Bandara C, Shashiprabha G, Benninga MA. Ultrasonographic assessment of liquid gastric emptying and antral motility according to the subtypes of irritable bowel syndrome in children. *J Pediatr Gastroenterol Nutr* 2013; **56**: 443-448 [PMID: 23201712 DOI: 10.1097/MPG.0b013e31827f7a3d]

34 **Devanarayana NM**, Rajindrajith S, Rathnamalala N, Samaraweera S, Benninga MA. Delayed gastric emptying rates and impaired antral motility in children fulfilling Rome III criteria for functional abdominal pain. *Neurogastroenterol Motil* 2012; **24**: 420-425, e207 [PMID: 22273006 DOI: 10.1111/j.1365-2982.2011.01871.x]

35 **Hamid Q**, Tulic M. Immunobiology of asthma. *Annu Rev Physiol* 2009; **71**: 489-507 [PMID: 19575684 DOI: 10.1146/annurev.physiol.010908.163200]

36 **Walker MM**, Talley NJ, Prabhakar M, Pennaneac'h CJ, Aro P, Ronkainen J, Storskrubb T, Harmsen WS, Zinsmeister AR, Agreus L. Duodenal mastocytosis, eosinophilia and intraepithelial lymphocytosis as possible disease markers in the irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther* 2009; **29**: 765-773 [PMID: 19183150 DOI: 10.1111/j.1365-2036.2009.03937.x]

37 **Barbara G**, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004; **126**: 693-702 [PMID: 14988823 DOI: 10.1053/j.gastro.2003.11.055]

38 **Cremon C**, Gargano L, Morselli-Labate AM, Santini D, Cogliandro RF, De Giorgio R, Stanghellini V, Corinaldesi R, Barbara G. Mucosal immune activation in irritable bowel syndrome: gender-dependence and association with digestive symptoms. *Am J Gastroenterol* 2009; **104**: 392-400 [PMID: 19174797 DOI: 10.1038/ajg.2008.94]

39 **Bradding P**, Walls AF, Holgate ST. The role of the mast cell in the pathophysiology of asthma. *J Allergy Clin Immunol* 2006; **117**: 1277-1284 [PMID: 16750987 DOI: 10.1016/j.jaci.2006.02.039]

40 **Kindt S**, Van Oudenhove L, Broekaert D, Kasran A, Ceuppens JL, Bossuyt X, Fischler B, Tack J. Immune dysfunction in patients with functional gastrointestinal disorders. *Neurogastroenterol Motil* 2009; **21**: 389-398 [PMID: 19126184 DOI: 10.1111/j.1365-2982.2008.01220.x]

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**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) | 0.20 |
| 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.

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Abdominal pain severity** | **Asthmatic**  | **Non-asthmatic**  | **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 symptoms** |  |  |  |  |
| 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 symptoms** |  |  |  |  |
| 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 domains**  | **Children with only FAPDs** | **Children with only asthma** | **Children with both asthma and FAPDs** | **Controls** |
| **mean (SD)*****n* = 70** | **mean (SD)*****n* = 129** | **mean (SD)*****n* = 30** | **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* control, and b*P* < 0.0001 *vs* controls. c*P <* 0.05 *vs* asthmatics.