

# Analysis of the impact of COVID-19 pandemic on functional gastrointestinal disorders among paediatric population

G. FARELLO<sup>1</sup>, A. DI LUCIA<sup>1</sup>, B. FIORAVANTI<sup>1</sup>, R. TAMBUCCI<sup>2</sup>,  
S. STAGI<sup>3</sup>, R. GAUDINO<sup>4</sup>

<sup>1</sup>Pediatric Clinic, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

<sup>2</sup>Digestive Endoscopy and Surgery Unit, Bambino Gesù Children's Hospital-IRCCS, Rome, Italy

<sup>3</sup>Health Sciences Department, University of Florence, Anna Meyer Children's University Hospital, Florence, Italy

<sup>4</sup>Pediatric Division, Department of Pediatrics, University Hospital of Verona, Verona, Italy

**Abstract. – OBJECTIVE:** Functional gastrointestinal disorders are common gastrointestinal diseases. The pathophysiology is multifactorial and psychosocial distress worsens symptoms severity. Since the end of 2019 the world has been facing COVID-19 pandemic. The associated control measures have affected the psychological health of people. The aim of the present study is to evaluate the impact of the COVID-19 pandemic on the prevalence of functional gastrointestinal disorders among Italian children and adolescents.

**PATIENTS AND METHODS:** The study sample is composed of 407 patients (187 males, 220 females), aged from 10 to 17 years. The mean age is  $14.27 \pm 2.24$  years. The study was conducted through the Italian version of the Questionnaire on Pediatric Gastrointestinal Symptoms–Rome III Version. The prevalence of each disorder has been calculated as the ratio of affected subjects for each disease and the total number of effective cases for that specific disease.

**RESULTS:** The study demonstrates that the prevalence of Functional Gastrointestinal Disorder in Italian children, during the COVID-19 pandemic, is higher, compared with the one reported in the previous studies. The most frequent disorders are Abdominal Migraine and Irritable Bowel Syndrome.

**CONCLUSIONS:** Our study is the first one which provides data of the prevalence of Functional gastrointestinal disorders in sample of Italian adolescents, during the COVID-19 pandemic. The study underlines the need to focus on stress management, in order to reduce the effects of the lockdown on the psychological well-being of the youngest.

*Key Words:*

FGIDs, pandemic, lockdown, Rome III criteria, QPGS – RIII.

## Abbreviations

FGIDs: Functional gastrointestinal disorders; IBS: Irritable Bowel Syndrome; FD: Functional Dyspepsia; QPGS – RIII: Questionnaire on Pediatric Gastrointestinal Symptoms – Rome III version; GBA: Gut – Brain Axis; CNS: Central nervous system; ANS: Autonomic nervous system; ENS: Enteric nervous system; HPA: Hypothalamus – Pituitary – Adrenal Axis; QoL: Quality of life.

## Introduction

Functional gastrointestinal disorders (FGIDs) are gastrointestinal diseases that affect 5-20% of the general population<sup>1,2-4</sup>. The pathophysiology of FGIDs is multifactorial, the dysregulation of the gut-brain axis<sup>5-10</sup> may represent the main cause of the disease. Moreover, low levels of IL-10, polymorphisms of the transporter responsible for the reuptake of serotonin, polymorphisms of G protein and  $\alpha 2$  adrenergic receptor are described<sup>11-14</sup>. FGIDs are stress-sensitive disorders: negative life events may exacerbate the clinical picture<sup>15,16</sup>. Functional Dyspepsia (FD) and Irritable Bowel Syndrome (IBS) are two of the most common disorders<sup>17</sup>.

FGIDs have been defined as symptomatic disorders without known organic abnormalities, leading

to believe that these conditions have a psychosomatic origin<sup>18,19</sup>. In 1980, it was found that psychosocial distress worsened symptoms severity<sup>21,22,23</sup>.

The functional gastrointestinal disorders can induce a major social and economic burden<sup>24</sup>. The prevalence rate of FGIDs varied from 9.9% to 29%. The most frequent FGIDs are cycling vomiting syndrome, IBS and functional constipation<sup>25</sup>.

In order to have more strictly criteria to diagnose FGIDs, in 2006 Rome III criteria have been developed<sup>2,26</sup>.

Since December 2019 the world has been facing an epidemic of coronavirus disease 2019 which was later classified as a pandemic<sup>27</sup>. The control measures as lockdown have affected the psychological health, causing higher levels of stress and depression<sup>28,29</sup>. During pandemic, a sense of fear increases the levels of anxiety and exaggerates the symptoms of individuals<sup>30</sup>. Children exposed to lockdown presented anxiety and behavioural difficulties<sup>31</sup>.

The aim of the present study is to evaluate the impact of lockdown on the prevalence of FGIDs among Italian children and adolescents.

## Patients and Methods

We enrolled 429 patients. 22 subjects were excluded from the analysis. They were either outside the age range required by the study or did not answer all questions in the questionnaire.

We studied 407 patients, aged between 10 and 17 years. Of these, 187 were male and 220 females. The mean age was  $14.27 \pm 2.24$  years.

The study was conducted through the development of a Google Questionnaire. The link to access the Google Questionnaire has been uploaded to the bulletin board of the electronic register of high school students. It was emailed to parents. We have obtained the informed consent of the parents.

### Survey

The prevalence of FGID was assessed using the Italian version of the QPGS-RIII. It has been specifically designed and validated to diagnose FGDI among children and adolescents<sup>32</sup>.

The Questionnaire uses scoring scales to assess the frequency, severity, and duration of symptoms. It is followed by a coding system that identifies all patients who meet the criteria for each functional gastrointestinal disease<sup>32</sup>.

### Data Collection and Statistical Analysis

The prevalence of each FGID was calculated by applying the Rome III criteria and the relative score. In case of insufficient answers given on a specific FGID, the patient was excluded from the analysis. The prevalence of each FGID was estimated as the ratio of affected subjects for each disease and the total number of effective cases for that specific disease.

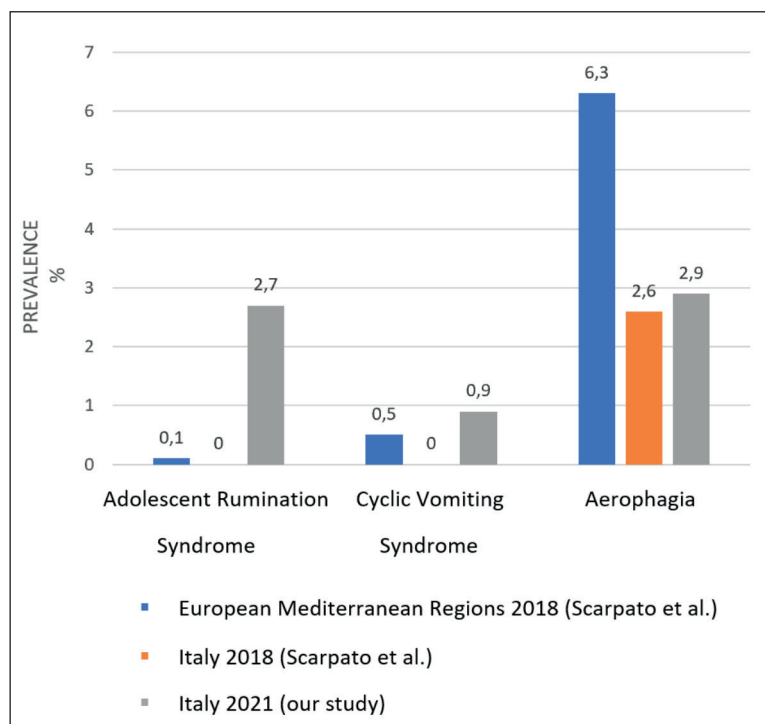
In order to highlight differences in the prevalence of FGIDs before and during the lockdown, we compared the data with a previous study<sup>33</sup> from 2018 concerning the frequency of FGIDs in an Italian population.

## Results

A total of 407 individuals, with a mean age of  $14.27 \pm 2.24$  years, including 187 males and 220 females, completed the questionnaire and were enrolled in the study. We analyzed the prevalence of all FGIDs. In the first category, the prevalence of adolescent rumination syndrome, cyclic vomiting syndrome and aerophagia was found to be 2.7%, 0.9%, 2.9%, respectively (Table I, Figure 1). Our case report showed a significant increase in rumination syndrome with a prevalence of 2.7% compared to 0% in previous studies (Table I). The most frequent complaints were functional constipation and abdominal migraine, with a prevalence of 13.6% and 13.9%, respectively. The latter, together with IBS, showed a significant increase in prevalence, compared to previous data in the literature<sup>33</sup>. Regarding IBS, there was an increase from 3.8% to 8.8%. As for abdominal migraine, the increase was 5.1% to 13.9% (Table I, Figure 2). The category that showed the most significant increase in prevalence, compared to previous data<sup>33</sup> reported in 2018, was abdominal pain. For category H3, relating to Constipation and Non-Retentive Fecal Incontinence, no one affected by Non-Retentive Fecal Incontinence was found, while 54 patients with Functional Constipation were identified. (Table I) There was no significant change from previous studies in the literature<sup>33</sup> (Table I, Figure 3). It was found that only one patient retained stools daily for the two months prior to the administration of the questionnaire.

## Discussion

This cross-sectional study is the first to provide a comprehensive review of the prevalence of



**Figure 1.** H1. Vomiting and aerophagia: prevalence in adolescents of Rumination syndrome, cyclic vomiting syndrome and aerophagia in our study and in literature.

FGID in a representative sample of Italian adolescents, during the Lockdown period, related to the COVID-19 pandemic. Their frequency increases with age, varying significantly between different Mediterranean countries<sup>34,35</sup>. In Italy, it emerged that the most frequent disorders were irritable bowel syndrome (3.8%), abdominal migraine (5.1%) and functional constipation (14%)<sup>33</sup>.

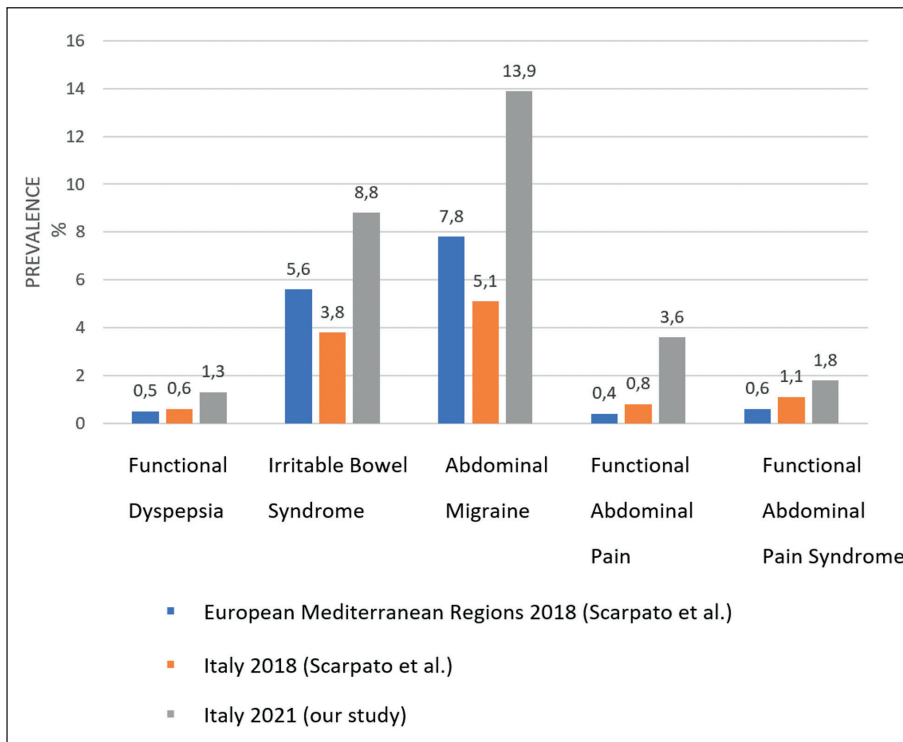
The choice to use the Rome III Criteria instead of the more recent Rome IV depends on the fact

that most of the previous studies in the literature used QPGS-RIII. As our aim was specifically to assess the differences, in terms of prevalence of FGID, between our study and the previously reported data we had to use the Rome III criteria.

The fact that we administered the online questionnaire did not allow us to exclude an organic etiology, potentially at the basis of the reported symptoms; however, online administration was a good screening method. Furthermore, it has al-

**Table I.** Prevalence of each FGIDs in our study and in the literature.

Functional gastrointestinal disorder	Prevalence of FGIDs in Adolescents		
	European mediterranean areas, 2018	Italy, 2018	Italy, 2021
<b>Vomiting and aerophagia</b>			
Adolescent Rumination Syndrome	0.1%	0	2.7%
Cyclic Vomiting Syndrome	0.5%	0	0.9%
Aerophagia	6.3%	2.6%	2.9%
<b>FGIDs Related to abdominal pain</b>			
Functional Dyspepsia	0.5%	0,6%	1.3%
Irritable Bowel Syndrome	5.6%	3,8%	8.8%
Abdominal Migraine	7.8%	5.1%	13.9%
Functional Abdominal Pain	0.4%	0.8%	3.6%
Functional Abdominal Pain Syndrome	0.6%	1.1%	1.8%
<b>Constipation and incontinence</b>			
Functional Constipation	13.1%	14%	13.6%
Non-retentive Fecal Incontinence	0.4%	0.1%	0

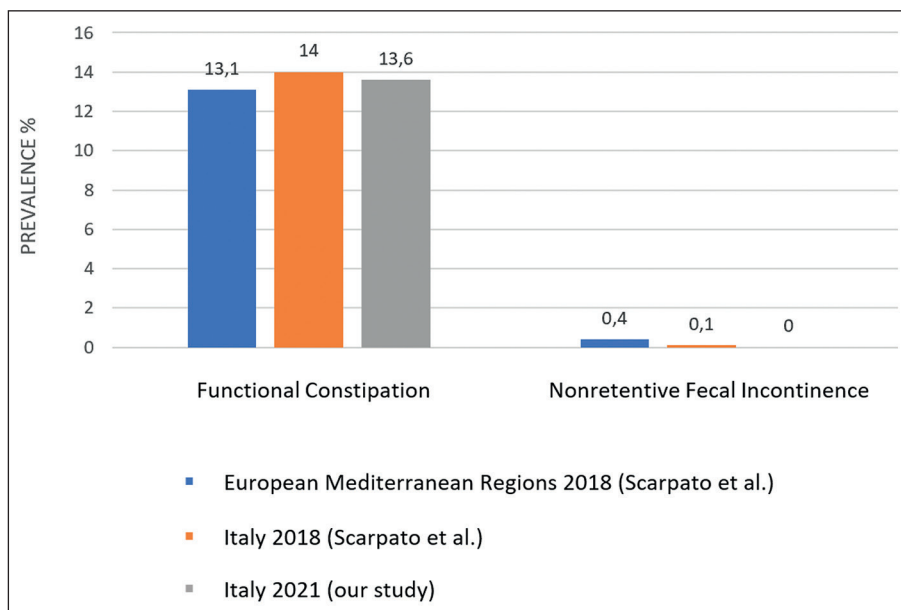


**Figure 2.** H2. FGIDs related to abdominal pain: prevalence of functional dyspepsia, IBS, abdominal migraine, functional abdominal pain in adolescents.

ready been shown that it is highly unlikely that an organic etiology could explain most of the symptoms diagnosed with the Rome III criteria<sup>36</sup>.

Comparing our results with that reported in the study published in 2018 by Scarpato et al<sup>33</sup>, it emerged that the prevalence of almost all FGID in Italian adolescents was found to be higher.

In particular, the prevalence of Adolescent Rumination Syndrome was 2.7%; the prevalence of cycling vomiting syndrome was 0.9% and aerophagia 2.9%. Regarding Functional Constipation, no significant differences emerged; however, the slight reduction in cases of Functional Constipation (13.6% vs. 14%) could be explained



**Figure 3.** H3. Constipation and incontinence: prevalence in adolescents in our study and in literature,

by the change in the hygiene habits of these adolescents: during the lockdown children were forced to stay at home so they lose the instinct to hold back feces, which is very normal behavior during school hours<sup>37</sup>, in fact only one patient retained stools daily in the two months preceding the administration of the questionnaire.

There was a marked increase in the prevalence of FGID related to abdominal pain and, among these, data on abdominal migraine almost tripled (13.9% vs. 5.1%) and data on bowel syndrome emerged strongly. Irritable, more than doubled (8.8%) against 3.8%.

These findings could be the direct consequence of the limitations and restrictions imposed during the COVID-19 pandemic, as already demonstrated by previous studies on adult samples. In the study by Oshima et al<sup>38</sup>, over 20% of adults with FD or IBS reported worsening of symptoms during the COVID-19 pandemic. Deterioration was most often related to psychological comorbidities and occupational problems<sup>38</sup>.

Mohammed et al<sup>30</sup>, reported the presence of stress in two thirds of their patients, who were suffering from IBS and an impairment of daily activities in 75% of the same patients, during the period of the pandemic<sup>30</sup>.

In fact, although Sars-CoV 2 most often causes an asymptomatic or mild infection, with a low mortality rate<sup>39</sup>, COVID-19 disease has an incredible impact on psychological health<sup>40</sup>. Fear of the unknown increases anxiety in healthy people and exacerbates it in people with pre-existing mental illness<sup>41</sup>.

On the one hand, the current crisis offers great opportunities for family cohesion. However, segregation and marginalization, with school closures, restrictions on social contacts, sport and recreation, pose a significant threat to the mental health of children and adolescents and a major source of stress<sup>42</sup>. Stress, together with changes in daily routine, is an important trigger for the onset of Abdominal Migraine episodes and for the recurrence of symptoms related to Irritable Bowel Syndrome<sup>36,43</sup>.

## Conclusions

Clinical studies show that stressful stimuli have a great impact on the sensitivity, motility, secretion, permeability and immune activation of the intestinal mucosa. This is due to the remarkable bi-directional connections of the Gut-Brain Axis

(GBA). These connections develop through the Central Nervous System (CNS), the Autonomic Nervous System (ANS), the Enteric Nervous System (ENS) and the hypothalamic-pituitary-adrenal (HPA) axis<sup>44</sup>.

Recent scientific evidence shows FGIDs are linked to a reduction in the quality of life (QoL) and psychological diseases that can determine the persistence of symptoms even in adulthood<sup>36</sup>.

It would be interesting, in future studies, to expand our data, also considering the levels of stress and the incidence of depression, anxiety and other psychological diseases in Italian adolescents, and to correlate these factors with the prevalence of FGID themselves.

Our study underlines the need to focus on stress management and all the consequences it could have on the well-being of Italian children and adolescents, especially during the critical period of the pandemic we are facing today. The use of telemedicine and the coordinated intervention of psychologists, gastroenterologists and pediatricians would be desirable, in order to reduce the dangerous effects of the Lockdown on the fragile psychological structure of the youngest.

---

### Funding

No funding was received.

---

### Conflict of Interest

The Authors declare that they have no conflict of interests.

---

### Availability of Data

The data are available upon request by Giovanni Farello..

---

### Author's Contributions

G.F. and A.D.L. conceptualized and designed the study; B.F. and R-T. designed the data collection instruments, collected data, carried out the initial analysis; S.S. and R.G. conceptualized and designed the study and critically review the manuscript.

---

### Ethics Approval

The Local Ethics Committee of the Pediatric Clinic approved the study (No. 13/2021).

---

### Consent to Participate

All study participants and their parents gave their informed consent.

### Consent for Publication

All authors gave their consent for publication.

### References

- 1) Oshima T, Miwa H. Epidemiology of Functional Gastrointestinal Disorders in Japan and in the World. *J Neurogastroenterol Motil* 2015; 21: 320-329.
- 2) Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. *Gastroenterology* 2016; 16: 223-227.
- 3) Engel GL. The need for a new medical model: a challenge for biomedicine. *Science* 1977; 196: 129-136.
- 4) Wood JD, Alpers DH, Andrews PL. Fundamentals of neurogastroenterology. *Gut* 1999; 45: 6-16.
- 5) Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. *Gastroenterology* 2016; 150: 1257-1261.
- 6) Mayer EA, Labus J, Aziz Q, Tracey I, Kilpatrick L, Elsenbruch S, Schweinhardt P, Oudenhove LV, Boorsok D. Role of brain imaging in disorders of brain-gut interaction: a Rome Working Team Report. *Gut* 2019; 68: 1701-1715.
- 7) Vanner S, Greenwood-Van Meerveld B, Mawe G, Shea-Donohue T, Verdu EF, Wood J, Grundy D. Fundamentals of Neurogastroenterology: Basic Science. *Gastroenterology* 2016; 130: 1391-1411.
- 8) Van Oudenhove L, Crowell MD, Drossman DA, Halpert AD, Keefer L, Lackner JM, Murphy TB, Naliboff BD, Levy RL. Biopsychosocial Aspects of Functional Gastrointestinal Disorders. *Gastroenterology* 2016; 150: 1355-1367.
- 9) Gaman A, Kuo B. Neuromodulatory processes of the brain-gut axis. *Neuromodulation J Int Neuromodulation Soc* 2008; 11: 249-259.
- 10) Barbara G, Feinle-Bisset C, Ghoshal UC, Quigley EM, Santos J, Vanner S, Vergnolle N, Zoetendal EG. The Intestinal Microenvironment and Functional Gastrointestinal Disorders. *Gastroenterology* 2016; 150: 1305-1318.
- 11) Yeo A, Boyd P, Lumsden S, Handley A, Stubbins M, Knaggs A, Asquith S, Taylor I, Bahari B, Crocker N, Rallan R, Varsani S, Montgomery D, Alpers DH, Dukes GE, Purvis I, Hicks GA. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut* 2004; 53: 1452-1458.
- 12) Camilleri M, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, Viramontes BE, McKinzie S, Urrutia R. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2002; 123: 425-432.
- 13) Holtmann G, Siffert W, Haag S, Mueller N, Langkafel M, Senf W, Zotz R, Talley NJ. G-protein beta 3 subunit 825 CC genotype is associated with unexplained (functional) dyspepsia. *Gastroenterology* 2004; 126: 971-979.
- 14) Kim HJ, Camilleri M, Carlson PJ, Cremonini F, Ferber I, Stephens D, McKinzie S, Zinsmeister AR, Urrutia R. Association of distinct alpha(2) adrenoceptor and serotonin trans-porter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders. *Gut* 2004; 53: 829-837.
- 15) Fond G, Loundou A, Hamdani N, Boukouaci W, Dargel A, Oliveira J, Roger M, Tamouza R, Leboyer M, Boyer L. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci* 2014; 264: 651-660.
- 16) Bulut Çakmak B, Özkula G, Işıklı S, Özkan Göncüoğlu İ, Öcal S, Altınöz AE, Taskintuna N. Anxiety, depression, and anger in functional gastrointestinal disorders: A Cross-sectional observational study. *Psychiatry Res* 2018; 268: 368-372.
- 17) Oshima T, Fukui H, Watari J, Miwa H. Childhood abuse history is associated with the development of dyspepsia: a population-based survey in Japan. *J Gastroenterol* 2015; 50: 744-750.
- 18) Holtmann G, Shah A, Morrison M. Pathophysiology of Functional Gastrointestinal Disorders: A Holistic Overview. *Dig Dis Basel Switz* 2017; 35: 5-13.
- 19) Van Oudenhove L, Vandenberghe J, Demyttenaere K, Tack J. Psychosocial factors, psychiatric illness and functional gastrointestinal disorders: a historical perspective. *Digestion* 2010; 82: 201-210.
- 20) Tack J, Drossman DA. What's new in Rome IV? *Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc* 2017; 29.
- 21) Levy RL, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, Creed F. Psychosocial aspects of the functional gastrointestinal disorders. *Gastroenterology* 2006; 130: 1447-1458.
- 22) Drossman DA. Irritable bowel syndrome: a multifactorial disorder. *Hosp Pract Off Ed* 1988; 23: 119-133.
- 23) Whitehead WE, Bosmajian L, Zonderman AB, Costa PT, Schuster MM. Symptoms of psychologic distress associated with irritable bowel syndrome. Comparison of community and medical clinic samples. *Gastroenterology* 1988; 95: 709-714.
- 24) Talley NJ. Functional gastrointestinal disorders as a public health problem. *Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc* 2008; 20: 121-129.
- 25) Boronat AC, Ferreira-Maia AP, Matijasevich A, Wang Y-P. Epidemiology of functional gastrointestinal disorders in children and adolescents: A systematic review. *World J Gastroenterol* 2017; 23: 3915-3927.
- 26) Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. *J Gastrointest Liver Dis JGLD* 2006; 15: 237-241.
- 27) Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. *Bio-med J* 2020; 43: 328-333.

- 28) Guessoum SB, Lachal J, Radjack R, Carretier E, Minassian S, Benoit L, Moro MR. Ado-lescent psychiatric disorders during the COVID-19 pandemic and lockdown. *Psychiatry Res* 2020; 291: 1-6
- 29) Majumdar P, Biswas A, Sahu S. COVID-19 pandemic and lockdown: cause of sleep dis-ruption, depression, somatic pain, and increased screen exposure of office workers and students of India. *Chronobiol Int* 2020; 37: 1191-1200.
- 30) Alzahrani MA, Alshamrani AS, Ahmasani IM, Alahmari FS, Asiri AH, Alshehri AM, Alsamghan AS, Awadalla NJ. Coronavirus disease 2019 pandemic stress and its effects on irrita-ble bowel syndrome patients in Saudi Arabia. *Medicine* 2020; 99
- 31) Cusinato M, Iannattone S, Spoto A, Poli M, Moretti C, Gatta M, Miscioscia M. Stress, Resilience, and Well-Being in Italian Children and Their Parents during the COVID-19 Pandemic. *Int J Environ Res Public Health* 2020; 17: 82-97.
- 32) Walker LS. Rome III Diagnostic Questionnaire for the Pediatric Functional GI Disorders 2000; 961-990.
- 33) Scarpato E, Kolacek S, Jojkic-Pavkov D, Konjik V, Živković N, Roman E, Kostovski A, Zdraveska N, Altamimi E, Papadopoulou A, Lampoudi TK, Shamir R, Bar Lev MR, Koleilat A, Mneimneh S, Bruzzese D, Leis R, Staiano A, MEAP Group. Prevalence of Functional Gastroin-testinal Disorders in Children and Adolescents in the Medi-terranean Region of Europe. *Clin Gas-troenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2018; 16: 870-876.
- 34) Scarpato E, Quitadamo P, Roman E, Jojkic-Pavkov D, Kolacek S, Papadopoulou A, Ro-ma E, Shamir R, Bar Lev MR, Lutovac B, Djuricic V, Orel R, Koleilat A, Mneimneh S, Coppola V, Corazziari E, Staiano A. Functional Gastrointestinal Disorders in Children: A Survey on Clini-cal Approach in the Mediterranean Area. *J Pediatr Gastroenterol Nutr* 2017; 64: 142-146.
- 35) Miele E, Simeone D, Marino A, Greco L, Auricchio R, Novek SJ, Staiano A. Functional gastrointesti-nal disorders in children: an Italian prospective survey. *Pediatrics* 2004; 114: 73- 78.
- 36) Lewis ML, Palsson OS, Whitehead WE, van Til-burg MAL. Prevalence of Functional Gastrointestinal Disorders in Children and Adolescents. *J Pediatr* 2016; 177: 39-43.
- 37) Vriesman MH, Koppen IJN, Camilleri M, Di Loren-zo C, Benninga MA. Management of functional constipation in children and adults. *Nat Rev Gas-troenterol Hepatol* 2020; 17: 21-39.
- 38) Oshima T, Siah KTH, Yoshimoto T, Miura K, To-mita T, Fukui H, Miwa H. Impacts of the COVID 2019 pandemic on functional dyspepsia and irri-table bowel syndrome: A population-based survey. *J Gastroenterol Hepatol* 2020; 36: 1820-1827.
- 39) Wang Y, Wang Y, Chen Y, Qin Q. Unique epide-miological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol* 2020; 92: 568-576.
- 40) Ornell F, Schuch JB, Sordi AO, Kessler FHP. «Pan-demic fear» and COVID-19: mental health burden and strategies. *Rev Bras Psiquiatr Sao Paulo Braz* 2020; 42: 232-235.
- 41) Shigemura J, Ursano RJ, Morganstein JC, Kuro-sawa M, Benedek DM. Public responses to the no-vel 2019 coronavirus (2019-nCoV) in Japan: Men-tal health consequences and target populations. *Psychiatry Clin Neurosci* 2020; 74: 281-282.
- 42) Fegert JM, Vitiello B, Plener PL, Clemens V. Challen-ges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to high-light clinical and research needs in the acute phase and the long return to normali-ty. *Child Adolesc Psychiatry Ment Health* 2020; 14.
- 43) Angus-Leppan H, Saatci D, Sutcliffe A, Guiloff RJ. Abdominal migraine. *BMJ* 2018; 360: 179-189
- 44) Raskov H, Burcharth J, Pommergaard H-C, Ro-senberg J. Irritable bowel syndrome, the microbio-ta and the gut-brain axis. *Gut Microbes* 2016; 7: 365-383.