



## Extra-intestinal symptoms in patients with irritable bowel syndrome: related to high total IgE levels and atopic sensitization?

Ellen Johanne Vara, Jørgen Valeur, Trygve Hausken & Gülen Arslan Lied

To cite this article: Ellen Johanne Vara, Jørgen Valeur, Trygve Hausken & Gülen Arslan Lied (2016): Extra-intestinal symptoms in patients with irritable bowel syndrome: related to high total IgE levels and atopic sensitization?, *Scandinavian Journal of Gastroenterology*, DOI: [10.3109/00365521.2016.1157890](https://doi.org/10.3109/00365521.2016.1157890)

To link to this article: <http://dx.doi.org/10.3109/00365521.2016.1157890>



Published online: 10 May 2016.



Submit your article to this journal [↗](#)



Article views: 7



View related articles [↗](#)



View Crossmark data [↗](#)

RESEARCH ARTICLE

## Extra-intestinal symptoms in patients with irritable bowel syndrome: related to high total IgE levels and atopic sensitization?

Ellen Johanne Vara<sup>a</sup>, Jørgen Valeur<sup>b</sup>, Trygve Hausken<sup>a,c,d</sup> and Gülen Arslan Lied<sup>a,c,d</sup>

<sup>a</sup>Department of Clinical Medicine, University of Bergen (UiB), Bergen, Norway; <sup>b</sup>Unger-Vetlesen's Institute, Lovisenberg Diaconal Hospital, Oslo, Norway; <sup>c</sup>Section of Gastroenterology, Department of Medicine, Haukeland University Hospital (HUH), Bergen, Norway; <sup>d</sup>National Centre for Functional Gastrointestinal Disorders, HUH, Bergen, Norway

### ABSTRACT

**Objective** We have previously found that high levels of total IgE, but not atopic sensitization, was a significant predictor for functional gastrointestinal (GI) symptoms. In this study, we aimed to assess the prevalence of extra-intestinal symptoms in IBS patients, and explore their relation to total IgE levels and atopic sensitization. **Materials and methods** Seventy-one patients with functional GI complaints were included. Severity of GI symptoms, fatigue and musculoskeletal pain was evaluated using the following questionnaires: IBS-Severity Scoring System (IBS-SSS), Fatigue Impact Scale (FIS), FibroFatigue Scale (FFS), and Visual Analog Scales (VAS) for musculoskeletal pain. Levels of total IgE and specific IgE-antibodies were analyzed. **Results** Fatigue and musculoskeletal pain were demonstrated in 78.9 and 43.7% of the patients, respectively. IBS-SSS scores were significantly correlated with fatigue scores and musculoskeletal pain. Patients with fatigue and musculoskeletal pain had significantly higher IBS-SSS scores than patients without fatigue and musculoskeletal pain. Total IgE levels were significantly higher in IBS patients compared to a healthy control group from a previous study. However, neither total IgE nor atopic sensitization was significantly associated with extra-intestinal symptoms. **Conclusions** IBS, fatigue, and musculoskeletal pain were significantly associated. Total IgE levels were higher in IBS patients than healthy controls, but not related to intestinal or extra-intestinal symptom severity. Atopy was not associated with any of the co-morbidities. Thus, the clinical significance of high IgE levels in IBS remains unclear and further studies are warranted to explore a common underlying mechanism for the co-morbid triad of IBS, fatigue, and musculoskeletal pain.

### ARTICLE HISTORY

Received 21 December 2015  
Revised 19 February 2016  
Accepted 20 February 2016  
Published online 27 April 2016

### KEYWORDS

Atopic sensitization; fatigue; irritable bowel syndrome; musculoskeletal pain; total IgE

### Introduction

Irritable Bowel Syndrome (IBS), with an estimated worldwide prevalence of up to 20%, is a functional gastrointestinal (GI) disorder associated with several abdominal symptoms and significantly impaired quality of life.[1,2] The cause of functional GI diseases remains unknown, and the pathogenetic factors hypothetically involved are intestinal dysmotility, visceral hypersensitivity, and immunological and psychosocial factors. Dysregulation of the homeostatic relationship between gut bacteria and the host can lead to altered microbial metabolism and immune responses.[3] In addition, altered bacterial fermentation in the colon is considered as a major contributor of gas production, colonic distention, and subsequent bloating and discomfort symptoms in IBS patients.[4–6] Intriguingly, patients with IBS and chronic fatigue syndrome (CFS) are characterized by similar gut microbiota alterations and plasma profiles of the pro-inflammatory cytokines IL-6, IL-8, IL-1 $\beta$ , and TNF- $\alpha$ . [7–10] IBS and CFS may thus share common pathophysiological mechanisms.

Patients with IBS often present with co-morbid extra-intestinal symptoms.[11,12] Unfortunately, these extra-intestinal symptoms are often neglected by gastroenterologists. However, assessing extra-intestinal symptoms in IBS patients

is essential in order to establish potentially pathophysiological mechanisms of IBS and its extra-intestinal co-morbidities.

Interestingly, an association between atopy and GI complaints has been suggested,[7] possibly with a distinct role of colonic mast cells.[8] In a recent study, we found that functional GI symptoms were associated with higher total IgE levels, but less atopic sensitization, and demonstrated that a high total IgE level was a significant predictor of IBS symptoms.[9] Thus, it is also interesting to see if there is a such relationship when it comes to extra-intestinal co-morbidities comprising fatigue, and musculoskeletal pain and levels of total and/or specific IgE antibodies.

The aims of this study were to investigate the prevalence and severity of extra-intestinal complaints in patients with functional GI symptoms, and explore their association with serum total IgE levels and atopic sensitization.

### Materials and methods

#### Subjects

Seventy-one consecutive patients, referred to Section of Gastroenterology, Department of Medicine, Haukeland University Hospital for investigation of GI complaints, were examined

according the “Lovisenberg” model.[13] During consultations with their physician, the patients filled in validated patient-administered questionnaires to assess their GI symptoms, fatigue, and musculoskeletal pain.[8,14] Patients with organic diseases which could explain their abdominal symptoms, as well as pregnant or lactating women, were excluded.

### Questionnaires

The patients filled in four questionnaires, namely: (1) The short form of the Rome III criteria for diagnosing of IBS [15]; (2) the Irritable Bowel Syndrome-Severity Scoring System (IBS-SSS) to assess severity of IBS symptoms [16]; 3 the Fatigue Impact Scale (FIS) to grade the severity of chronic fatigue, and (4) two Visual Analog Scales (VAS), one for grading the severity of musculoskeletal pain and one for assessing joint pain.

The IBS-SSS contains five questions that were rated on a 100-point VAS: the severity of abdominal pain, the frequency of abdominal pain, the severity of abdominal distension, dissatisfaction with bowel habits, and interference with quality of life.[16] All the five components contributed to the score equally yielding a theoretical range of 0–500, with a higher score indicating a worse condition. Previous studies have established that scores below 75 represents no IBS (physiological levels of bowel symptoms), scores below 175 represent mild IBS symptoms, 175–300 represents moderate severity, and scores above 300 represent severe IBS.[16] The FIS questionnaire examines patient perceptions of the functional limitations that they attribute to fatigue during the past month. The scale is constructed to include three subscales assessing perceived fatigue impact on cognitive functioning (10 items), physical functioning (10 items), and psychosocial functioning (20 items). The statements are ranged on a five-level scale (0 = no problem to 4 = extreme problems), giving a maximum FIS score of 160. A FIS score >25 was considered as clinically significant fatigue. FIS is considered a reliable and valid tool to measure the influence of fatigue in patients.[17] The VAS for assessing musculoskeletal pain were 10 cm long lines with the following text at equal intervals along the lines: ‘no pain’, ‘mild’, ‘moderate’, ‘severe’, and ‘very severe pain’,[13] and a score of 25 or more was considered as clinically significant pain. Afterward, the physician also filled in the FibroFatigue Scale (FFS), a questionnaire based on communication with the patients.

### Allergologic examinations

In all participants, levels of total IgE and allergen specific IgE-antibodies were analyzed using the ImmunoCAP System (Thermo Fischer Scientific, Uppsala, Sweden), and IgE-antibodies to common inhalant and food allergens were measured using Phadiatop®, as described elsewhere.[8] All the participants were tested for seven common food items (egg white, cow’s milk, codfish, wheat, peanut, soy – and a native wheat flour suspension in saline) and eight inhalant allergens (birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, cat, dog, and horse). Atopic sensitization was defined as having increased levels of IgE-antibodies ( $\geq 0.35$  kUA/L) to at least one allergen. According to laboratory reference ranges,

**Table 1.** Demographic and clinical data in the study population.

|                                              | Patient group    |
|----------------------------------------------|------------------|
| Patients, total number                       | 71               |
| % Women                                      | 76.6% (n = 53)   |
| % Men                                        | 25.4% (n = 18)   |
| Age, mean years (range)                      | 36.15 (17–72)    |
| BMI, mean (range)                            | 22.5 (16.5–38.2) |
| IBS-Severity Scoring System (IBS-SSS) (mean) | 279.01           |
| IBS-SSS                                      |                  |
| >300 (severe)                                | 40.9% (n = 29)   |
| 175–300 (moderate)                           | 43.6% (n = 31)   |
| 75–175 (mild)                                | 11.3% (n = 8)    |
| <75 (no IBS)                                 | 4.2% (n = 3)     |
| IBS characteristics                          |                  |
| Diarrhea predominant                         | 42.3% (n = 30)   |
| Constipation predominant                     | 22.5% (n = 16)   |
| Constipation/diarrhea Mixed                  | 35.2% (n = 25)   |
| Musculoskeletal pains, mean                  | 43.7% (n = 31)   |
| Fatigue                                      | 19.01            |
| Fatigue Impact scale > 25                    | 78.9% (n = 56)   |
| Fibro Fatigue scale > 15                     | 67.6% (n = 48)   |
| Allergy                                      |                  |
| Total IgE (mean)                             | 205.61           |
| Atopic sensitized (%) <sup>a</sup>           | 49.3% (n = 35)   |

<sup>a</sup>% with elevated IgE-antibody levels ( $\geq 0.35$  kUA/L) to at least one allergen (Phadiatop and/or fx5).

patients with serum total IgE levels >120 kUA/L were considered as high total IgE responders. Detailed history about atopic diseases and duration of disease was also recorded.

### Statistical analyses

Statistical analyses were performed using the GraphPad Prism 6 statistical software package (GraphPad Software Inc, San Diego, CA). Data that were not normally distributed are reported as medians and Mann–Whitney *U*-tests were used for comparison of medians. Correlations between different parameters within the same group were evaluated by Spearman’s correlation coefficient. Kruskal–Wallis tests were performed for multiple comparisons between variables. All the tests were two-tailed and the level of significance was set to  $p < 0.05$ .

## Results

### Demographic and clinical data

Patients’ characteristics are presented in Table 1. Seventy-one patients were included, mean age 36 years, and 76.6% were women. Mean years of disease duration was 7.7. Mean Body Mass Index (BMI) was 22.5 (range 16.5–38.2). All but three patients had IBS according to IBS-SSS, where 40.9% of the patients had severe IBS, 43.6% had moderate IBS and 11.3% had mild IBS. Diarrhea was predominant among participants, affecting 30 (42.3%) patients. About 16 (22.5%) patients had constipation and 25 patients (35.2%) had mixed bowel habits. Defecation at night was seldom. IBS-SSS distribution among the different IBS subgroups is presented in Figure 1.

### Extra-intestinal complaints

The majority of patients had extra-intestinal symptoms accompanying IBS. Symptoms indicative of chronic fatigue, according FIS questionnaire, were recorded in 56 (78.9%), whereas

musculoskeletal pain were present in 31 patients (43.7%). Symptoms of fatigue and musculoskeletal pain concomitant with IBS symptoms were reported in 32.4% ( $n=23$ ) of the patients. The patients' (FIS) and the doctor's (FFS) scoring of fatigue were strongly correlated ( $r=0.9$ ,  $p<0.001$ ). Moreover, we found that IBS-SSS scores were significantly correlated with fatigue scores, FIS ( $r=0.7$ ,  $p=0.02$ ) and FFS ( $r=0.3$ ,  $p=0.008$ ), and also with musculoskeletal pain ( $r=0.3$ ,  $p=0.02$ ). The distribution of FIS scores, FFS scores and scores of musculoskeletal pain among the different IBS subgroups are presented in Figure 2. Scores on fatigue (FFS and FIS) were neither related to bowel habits nor BMI.

Patients with symptoms of chronic fatigue indicated by FIS scale had significantly ( $p<0.0005$ ) higher IBS-SSS scores (median IBS-SSS: 300) compared to patients with no symptoms of fatigue (median IBS-SSS: 192) (Figure 3A). This was also same by doctor's FFS scheme, where patients with higher

scores of FFS had significantly ( $p=0.0038$ ) higher IBS-SSS scores (median: 307.5) compared to patients with lower FFS scores (median IBS-SSS: 215) (Figure 3B). In addition, patients with musculoskeletal pain had significantly higher IBS-SSS scores ( $p=0.03$ ) (median: 300) than patients without musculoskeletal pain (median: 265).

### Total IgE levels and atopy

Levels of total IgE were measured in all participants, and median value of total IgE was 75 kU<sub>A</sub>/L. No significant correlation was found between IBS symptoms and total IgE. Moreover, no significant associations were found between total IgE levels, fatigue scores, or musculoskeletal pain. According to IBS grading, total IgE levels were higher in patients with moderate IBS, compared to severe and mild IBS, but this was not significant (Figure 4). Interestingly, mean total IgE levels were also higher in IBS patients with symptoms of fatigue and musculoskeletal pain, compared to IBS patients without the mentioned co-morbidities, but the discrepancies did not reach statistical significance. In order to validate the levels of total IgE in all patients, a healthy control group was provided from a previous study,[18] and patients with IBS had significantly higher total IgE levels as compared to this control group (median: 29.5 kU<sub>A</sub>/L;  $p=0.04$ ).

In terms of serum inhalant and food antigen-specific IgE antibodies, 31 (43.7%) of the 71 included patients had detectable positive IgE levels to specific inhalant allergens as previously described,[9] and 14 (19.7%) of all participants had detectable IgE levels to specific food allergens. Together, 49.3% of the patients were atopic sensitized to one or more

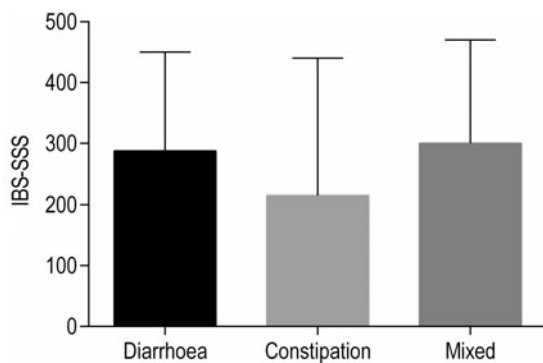


Figure 1. IBS-Severity Scoring System (IBS-SSS) distribution among the different IBS subgroups.

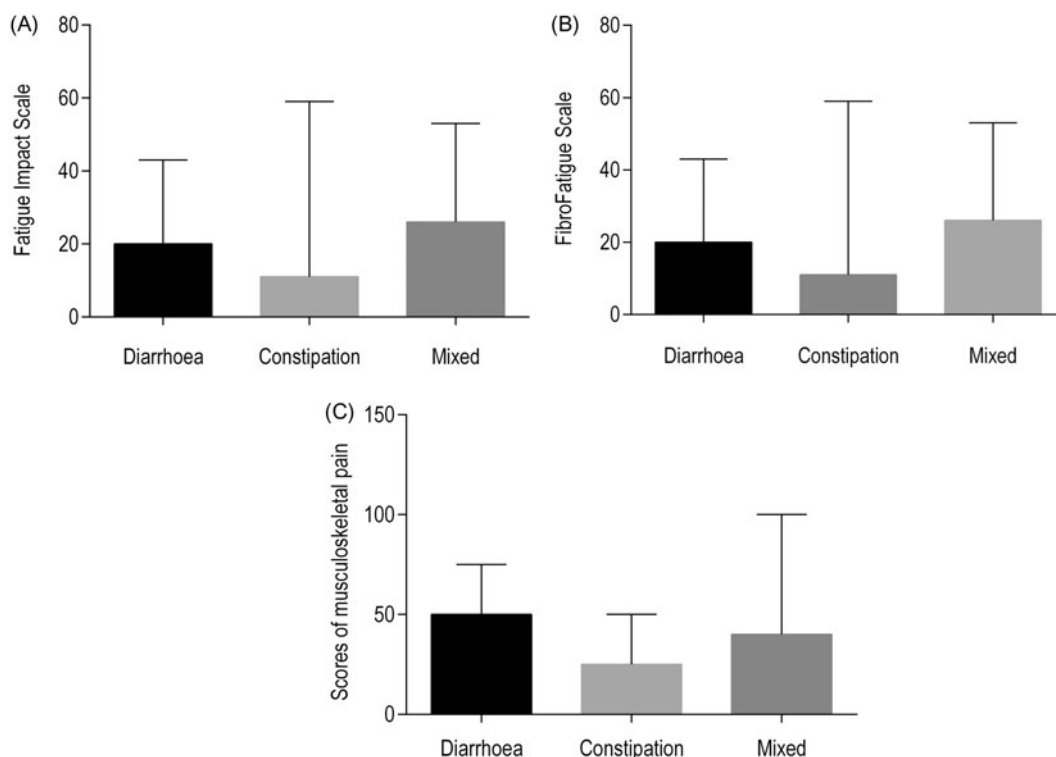


Figure 2. Distribution of (a) Fatigue Impact Scale (FIS) scores, (b) Fibro Fatigue Scale (FFS) scores, and (c) scores of musculoskeletal pain among IBS subgroups stratified according to bowel habits.

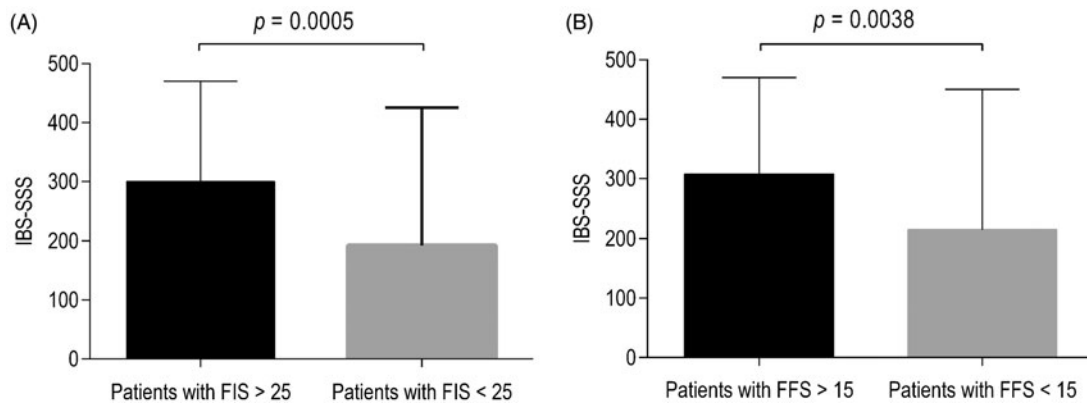


**Figure 3.** Comparison of IBS-Severity Scoring System (IBS-SSS) scores in patients with or without active symptoms of fatigue according to (A) Fatigue Impact Scale (FIS) questionnaire and (B) Fibro Fatigue Scale (FFS) questionnaire.

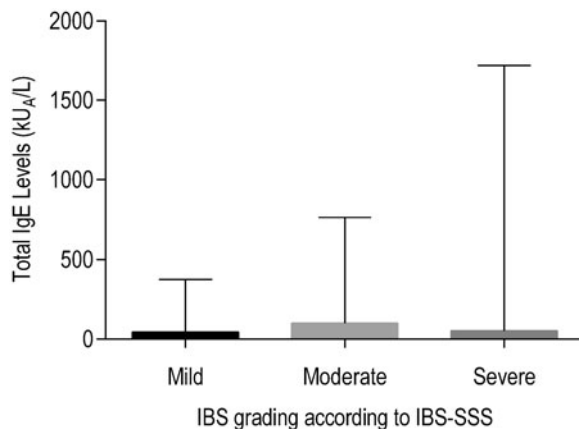


**Figure 4.** Relationship between total IgE and IBS-SSS (IBS-Severity Scoring System) grading.

allergens. Atopic sensitization was not significantly associated with fatigue scores or musculoskeletal pains. There were no significant differences in the distribution of atopy among the different IBS subgroups, where 15 with diarrhea, 11 with constipation, and 10 with mixed bowel habits was classified as having atopy.

## Discussion

To the best of our knowledge, this is the first study to investigate whether extra-intestinal complaints in IBS patients are related to total IgE levels and atopic sensitization. Recently, we found that functional GI complaints were significantly associated with higher levels of total IgE, but less atopic sensitization. Therefore, we wanted to go one step further in the current study with a different patient population, to see if there were any relationships between atopy and the co-morbid triad of IBS, chronic fatigue and musculoskeletal pain. In the included patients, all but three had IBS. Almost 80% of the IBS patients had fatigue and 44% had symptoms of musculoskeletal pain. Moreover, we found that one third of patients had all symptoms of IBS, fatigue and musculoskeletal pain, a relationship earlier described as a co-morbid 'triad'.<sup>[13]</sup> A significant correlation was found between IBS complaints and symptoms of fatigue and musculoskeletal pain in the included patients. Total IgE levels and IBS symptoms were

not significantly correlated. Moreover, no significant associations were found between total IgE levels and severity of extra-intestinal complaints (fatigue and musculoskeletal pains). In addition, no significant differences were found in serum total IgE levels in IBS patients with fatigue compared to IBS patients without fatigue. Atopic sensitization was not significantly associated with IBS, fatigue or musculoskeletal pains. However, the IBS patients had significantly higher serum total IgE levels compared to a healthy control group from a previous study concerning self-reported food hypersensitivity.<sup>[19]</sup>

This study indicates that the co-morbid triad of IBS, fatigue and musculoskeletal pains is prominent, as reported in some previous studies, supporting the notion that they may have a common underlying cause.<sup>[10,17,20–23]</sup> The co-existence of these conditions is not well understood, though a disturbed intestinal microflora has been postulated as a cause of both IBS and CFS.<sup>[10,24]</sup> Since plasma profiles of the pro-inflammatory cytokines (IL-6, IL-8, IL-1 $\beta$ , and TNF- $\alpha$ ) are also similar in both patients with IBS and CFS, a systemic inflammatory situation due to the translocation of commensal bacteria resulting from an increased intestinal permeability might be involved.<sup>[21]</sup> Thus, gut inflammation and loss of mucosal integrity may also contribute to the pathogenesis of this triad.

Modifications of the microflora might affect inflammatory and metabolic responses in the host, and studies have indicated that dysbiosis of the gut microbiota could influence several organ systems, such as the nervous, endocrine, and immune system.<sup>[17]</sup> Moreover, alterations in the composition of intestinal microflora have been suggested to play a role in mediating some of the symptoms in patients with chronic fatigue.<sup>[10,25]</sup> Also, studies in patients with unexplained food-hypersensitivity have suggested that abdominal symptoms are often generated, at least partially, by delayed microbial fermentation of malabsorbed carbohydrates,<sup>[24,26]</sup> and assessment of intestinal fermentation in IBS patients have revealed significantly different colonic pH profiles in IBS patients compared to controls, suggestive of altered bacterial fermentation.<sup>[4,27]</sup> Alterations in bacterial fermentation in colon might lead to increased gas production, and thus it is considered as an important factor in generating IBS symptoms.<sup>[4,28]</sup> Studies in patients exposed to *Giardia lamblia* infection have demonstrated a high risk of developing fatigue

and post-infectious IBS. Furthermore, significantly higher prevalence of IBS and fatigue were reported in exposed patients compared to controls.[29–31] The mechanisms of post-infectious IBS and fatigue are probably multifactorial, but intestinal microbiota disturbances are consistent with the fact that many of the IBS patients often report long history of GI complaints before appearance of fatigue,[13] and observations from previous studies suggest that post-infectious IBS possibly could precede the development of fatigue.[14,32] Thus, it is conceivable to suggest that fatigue symptoms are not primary, but secondary to IBS, however the pathophysiology warrants further studies.

A link between atopy, total IgE levels and GI complaints has been suggested as a common underlying cause in an atopic IBS subgroup.[7] In a previous study, we have shown that levels of serum total IgE were significantly associated with less severe functional GI symptoms.[9] In the current study, no significant associations were found between total IgE levels, or atopic sensitization, and the extra-intestinal complaints in the included patients.

The patients in this study were a homogeneous group, with a high prevalence of severe and moderate IBS symptoms. Moreover, the small size of the patient sample is a weakness of this study, and it is suggested that this complies especially when comparing total IgE levels in patient groups with and without fatigue according to FIS ( $n = 55$  and  $n = 13$ , respectively). Further analyses with larger and more diverse patient and control groups are therefore of interest, in order to further elucidate the association between atopy and IBS-related complaints.

In conclusion, this study showed that functional GI complaints compatible with IBS are significantly associated with fatigue and musculoskeletal pain. Chronic fatigue and musculoskeletal pain were not significantly associated with total IgE levels or atopic sensitization. High serum total IgE levels in IBS patients is yet of unclear clinical significance, and further studies with larger patients groups are warranted to explore possible common underlying mechanisms behind the co-morbid triad of IBS, chronic fatigue and musculoskeletal pain.

## Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

## References

- Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014;6:71–80.
- Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107:1474–1482.
- Jandhyala SM, Talukdar R, Subramanyam C, et al. Role of the normal gut microbiota. *World J Gastroenterol*. 2015;21:8787–8803.
- Ringel-Kulka T, Choi CH, Tamas D, et al. Altered colonic bacterial fermentation as a potential pathophysiological factor in irritable bowel syndrome. *Am J Gastroenterol*. 2015;110:1339–1346.
- Collins SM. A role for the gut microbiota in IBS. *Nat Rev Gastroenterol Hepatol*. 2014;11:497–505.
- Ringel Y, Maharshak N. Intestinal microbiota and immune function in the pathogenesis of irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol*. 2013;305:G529–G541.
- Tobin MC, Moparty B, Farhadi A, et al. Atopic irritable bowel syndrome: a novel subgroup of irritable bowel syndrome with allergic manifestations. *Ann Allergy Asthma Immunol*. 2008;100:49–53.
- Lillestol K, Helgeland L, Arslan Lied G, et al. Indications of 'atopic bowel' in patients with self-reported food hypersensitivity. *Aliment Pharmacol Ther*. 2010;31:1112–1122.
- Vara EJ, Svanes C, Skorge TD, et al. Functional gastrointestinal symptoms are associated with higher serum total IgE levels, but less atopic sensitization. *Dig Dis Sci*. 2016;61:189–197.
- Fremont M, Coomans D, Massart S, et al. High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. *Anaerobe*. 2013;22:50–56.
- Sperber AD, Dekel R. Irritable bowel syndrome and co-morbid gastrointestinal and extra-gastrointestinal functional syndromes. *J Neurogastroenterol Motil*. 2010;16:113–119.
- Kim SE, Chang L. Overlap between functional GI disorders and other functional syndromes: what are the underlying mechanisms? *Neurogastroenterol Motil*. 2012;24:895–913.
- Berstad A, Undseth R, Lind R, et al. Functional bowel symptoms, fibromyalgia and fatigue: a food-induced triad? *Scand J Gastroenterol*. 2012;47:914–919.
- Lied GA, Lillestol K, Lind R, et al. Perceived food hypersensitivity: a review of 10 years of interdisciplinary research at a reference center. *Scand J Gastroenterol*. 2011;46:1169–1178.
- Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology*. 2006;130:1480–1491.
- Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther*. 1997;11:395–402.
- Lind R, Berstad A, Hatlebakk J, et al. Chronic fatigue in patients with unexplained self-reported food hypersensitivity and irritable bowel syndrome: validation of a Norwegian translation of the Fatigue Impact Scale. *Clin Exp Gastroenterol*. 2013;6:101–107.
- Lied GA, Lillestol K, Valeur J, et al. Intestinal B cell-activating factor: an indicator of non-IgE-mediated hypersensitivity reactions to food? *Aliment Pharmacol Ther*. 2010;32:66–73.
- Lied GA. Indication of immune activation in patients with perceived food hypersensitivity. *Dig Dis Sci*. 2014;59:259–266.
- Berstad A, Arslan G, Folvik G. Relationship between intestinal permeability and calprotectin concentration in gut lavage fluid. *Scand J Gastroenterol*. 2000;35:64–69.
- Scully P, McKernan DP, Keoghane J, et al. Plasma cytokine profiles in females with irritable bowel syndrome and extra-intestinal comorbidity. *Am J Gastroenterol*. 2010;105:2235–2243.
- Lind R, Arslan G, Eriksen HR, et al. Subjective health complaints and modern health worries in patients with subjective food hypersensitivity. *Dig Dis Sci*. 2005;50:1245–1251.
- Lillestol K, Berstad A, Lind R, et al. Anxiety and depression in patients with self-reported food hypersensitivity. *Gen Hosp Psychiatry*. 2010;32:42–48.
- Valeur J, Morken MH, Norin E, et al. Carbohydrate intolerance in patients with self-reported food hypersensitivity: comparison of lactulose and glucose. *Scand J Gastroenterol*. 2009;44:1416–1423.
- Rao AV, Bested AC, Beaulieu TM, et al. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog*. 2009;1:6.
- Undseth R, Jakobsdottir G, Nyman M, et al. Low serum levels of short-chain fatty acids after lactulose ingestion may indicate impaired colonic fermentation in patients with irritable bowel syndrome. *Clin Exp Gastroenterol*. 2015;8:303–308.
- Farmer AD, Mohammed SD, Dukes GE, et al. Caecal pH is a biomarker of excessive colonic fermentation. *World J Gastroenterol*. 2014;20:5000–5007.

- [28] Dapoigny M, Stockbrugger RW, Azpiroz F, et al. Role of alimentacion in irritable bowel syndrome. *Digestion*. 2003;67:225–233.
- [29] Wensaas KA, Langeland N, Hanevik K, et al. Irritable bowel syndrome and chronic fatigue 3 years after acute giardiasis: historic cohort study. *Gut*. 2012;61:214–219.
- [30] Wensaas KA, Langeland N, Rortveit G. Prevalence of recurring symptoms after infection with *Giardia lamblia* in a non-endemic area. *Scand J Prim Health Care*. 2009;27:12–17.
- [31] Wensaas KA, Langeland N, Rortveit G. Post-infectious gastrointestinal symptoms after acute Giardiasis. A 1-year follow-up in general practice. *Fam Pract*. 2010;27:255–259.
- [32] Morken MH, Lind RA, Valeur J, et al. Subjective health complaints and quality of life in patients with irritable bowel syndrome following *Giardia lamblia* infection: a case control study. *Scand J Gastroenterol*. 2009;44:308–313.