Fatigue Article

Fatigue in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis of Pooled Frequency and Severity of Fatigue

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SUMMARY

Purpose: Fatigue is the third most common "extraintestinal" complaint of patients with irritable bowel syndrome (IBS), but it is still poorly understood. This study aimed to review characteristics of IBS-associated fatigue and to examine pooled frequency, severity of fatigue, and correlations of related factors with fatigue in IBS via meta-analyses.

Methods: Publications were searched in eight databases from 1995 to 2014. Random effects meta-analyses were applied with standard error, weighted effect size, and correlation-based measure of effect size.

Results: Twenty-four studies were included in systematic review. Seventeen studies were used for meta-analyses (2 studies were excluded in the frequency of fatigue analysis due to data unavailability). Using "tiredness" to define fatigue, and Fatigue Impact Scale to assess fatigue were the most frequently used across the studies. Gastrointestinal symptoms, psychological distress, and health-related quality of life were the most common correlates with fatigue. The pooled frequency of fatigue was 54.2% [95% confidence interval (38.5, 69.4)]. Meta-regression on the frequency of fatigue showed positive and significant relations with tertiary care settings, female sex, and younger age. There was a negatively moderate relationship between the severity of fatigue and health-related quality of life score (correlation-based measure of effect size: −0.378).

Conclusions: Fatigue is prevalent among patients with IBS and commonly co-occurs with other symptoms. This is the first study to fully examine fatigue in IBS, which shed light on the comprehensive management of fatigue in this patient group. Future research is warranted to further explore fatigue-related factors and underlying mechanisms of fatigue in IBS.

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Introduction

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disorder diagnosed by Rome III criteria, which was developed to classify IBS based on clinical symptoms [1]. The worldwide prevalence of IBS in adults is between 9.0% and 23.5% [2]. It affects about 22 million people in the United States, representing 14.0% of the U.S. population [3] and 2.9%–15.6% in Asian countries [4]. Low-grade mucosal inflammation, microbiome, and visceral hypersensitivity are commonly accepted mechanisms that alter gut function and generate symptoms of IBS [5,6]. Common GI symptoms are changes in bowel habits (e.g., constipation-dominant, diarrhea-dominant, & mixed), abdominal pain, bloating, intestinal gas, distension, flatulence, incomplete evacuation, and urgency [1]. Non-GI symptoms, such as depression, anxiety and fatigue, can co-occur with GI symptoms in IBS [7,8].

Symptoms of IBS could result in significant direct costs (e.g., physician visits, diagnostic tests, and prescription, or over-the-counter medication) and indirect costs [e.g., work absenteeism, diminished health-related quality of life (HRQOL)] to patients and health care industries. The biggest causes of health care costs of patients with IBS are non-GI symptoms and visit frequency of patients with IBS [8,9]. Among non-GI symptoms of IBS, Lackner and Gudleski [8] reported that 60.0% of patients with IBS (N = 176) experienced fatigue independent of other symptoms in IBS. In addition, fatigue ranks as the third most common [8] somatic complaint after abdominal pain and frequent bowel movements in patients with IBS. Fatigue in IBS...
was described with a wide range of definitions, such as tiredness, extreme weariness, and a state of exhaustion [8, 10]. Fatigue is likely to interfere with work productivity, HRQOL, cost effectiveness, and daily activity in this patient group [11]. Qualitative research has shown that patients with IBS experience fatigue as multidimensional, persistent symptoms with far-reaching consequences, and report low HRQOL [10].

It is challenging to provide effective fatigue management for patients with IBS because there is a lack of research and information about fatigue compared to other IBS symptoms, such as abdominal pain, diarrhea, constipation, and psychological distress [8]. The characteristics of fatigue (i.e., prevalence, severity, related factors) and overall health care burden of fatigue in IBS are unknown [8]. In addition, definition and assessment of fatigue used in IBS studies are not consistent. The underlying mechanisms remain unclear, although one study demonstrated that low-grade inflammation is related to fatigue in IBS [12].

Understanding the phenomenon of fatigue in IBS via systematic review and meta-analyses can guide health care providers toward having insight and knowledge for the consistent symptom diagnosis and fatigue-specific management. Therefore, the aims of this study are (a) to explore characteristics of fatigue in IBS via a systematic review, and (b) to examine pooled frequency and severity of fatigue as well as pooled correlations between related factors and fatigue in IBS via meta-analyses.

Methods

Search strategies

A systematic literature search was conducted in Medline, Web of Science, Scopus, EMBASE, PubMed, CINAHL, Cochrane Library, and PsychINFO. Key words were “symptoms”, “fatigue”, “prevalence”, and “frequency”, in combination with “irritable bowel syndrome” and “correlates”, “etiology” and “pathophysiology”. The lists of studies were published from January 1995 to July 2014. Other eligible studies were also identified by searching the cited references from obtained published studies. The screening procedure was based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses flow diagram [13] (Figure 1).
Inclusion/exclusion criteria and study selection

Studies were included if they met the following criteria: (a) the literature was published between 1995 and 2014; (b) the research report involved the frequency of fatigue; and (c) original and observational or experimental. By contrast, studies were excluded if they met the following criteria: (a) review papers or editorials, and not original research articles; (b) not published in English; (c) qualitative studies; (d) duplicated; and (e) no reported fatigue data. Next, 498 studies were present in the database. Finally, this procedure resulted in a preliminary set of 134 full-text studies.

On closer examination of the 134 abstract/full-text studies, a final 24 studies were selected for the systematic review. Among the 24 selected studies in this review, the data from 17 studies were eligible for each meta-analysis of the pooled frequency, severity of fatigue, and the pooled correlations between fatigue and related factors. Of these, fatigue data were not reported in two studies. Thus, two studies were excluded for the pooled frequency of fatigue meta-analysis (Figure 1).

Data extraction and quality assessment

Data were extracted based on numeric data, country, publication year, settings, sex, sample size, age, and study design. Sample size was obtained by subtracting the number of nonresponders from the total number of IBS participants recruited for the studies. Selected studies were evaluated using methodological criteria used in a previous study [14] (Table 1). This process resulted in quality scores ranging from 0 to 19 points, and the qualifying scores for applicable studies were 16 or above [14]. The two authors (C.J.H. & G.S.Y.) independently extracted data, reviewed selected studies, and evaluated the quality of studies. Disagreement was resolved through consensus by a third party, a nursing professor. The agreement rate to determine the reliability of the ratings was 97.6%, and disagreements were adjusted through discussions.

Meta-analytical and statistical methods

Meta-analysis is useful to get more precise estimates of disease frequencies, such as disease incidence rates, frequency proportions, overall mean, and 95% confidence interval (CI) [15,16]. Publication bias was tested by funnel plot (Figure 2), Begg’s test, and Egger’s test (Table 2). Heterogeneity was analyzed with Q statistics, in which p < .10 was considered statistically significant, and I² statistics (I² < 25.0%: no heterogeneity; I² > 75.0%: high or extreme heterogeneity). We primarily conducted meta-analysis for obtaining the pooled frequency of fatigue in IBS. Considering heterogeneity of study characteristics, we showed the pooled frequency of fatigue by subgroup analyses (e.g., age, settings, & study design) (Table 3). As well, metaregression was conducted for calculating the relation of study characteristics to the pooled frequency of fatigue. Independent variables for use in the logistic metaregression model were selected, if p (between-studies) < .05 was met in study characteristics listed in Table 3. Multicollinearity among independent variables were examined using the variance inflation factor (non multicollinearity: variance inflation factor < 10). Secondly,

Table 1 Criteria to Evaluate Quality of Prevalence Studies: Criteria and Scoring.

<table>
<thead>
<tr>
<th>Representativeness of the target population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• At least one of the following should apply for the study: an entire target population, randomly selected sample, or sample started to represent the target population with irritable bowel syndrome (2 points); reasons for nonresponse described &amp; nonresponders (2 points).</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Quality of data</td>
</tr>
<tr>
<td>• Were the data primarily from a prevalence study (2 points) or from a survey not specifically designed for that purpose (1 point)?</td>
</tr>
<tr>
<td>• The same mode of data collection should be the used for all subjects (2 points), if not (1 point).</td>
</tr>
<tr>
<td>• The data collected directly from the patient by means of validated tools (3 points), no validated tools (2 points), from proxies or retrospectively from the medical record (1 point).</td>
</tr>
<tr>
<td>General description of method &amp; inclusion of prevalence of fatigue in results</td>
</tr>
<tr>
<td>• Description of the target population &amp; setting where patients were found (2 points).</td>
</tr>
<tr>
<td>• Description of disease, sex, &amp; age. All (2 points), two or three (1-point).</td>
</tr>
<tr>
<td>• Final sample size (1 point).</td>
</tr>
<tr>
<td>• Prevalence recall periods should be stated (1 point).</td>
</tr>
</tbody>
</table>

Note. *Adopted from Deandrea et al [14]. Copyright 2014 by U.S. Cancer Pain Relief Committee.
we conducted a meta-analysis for the pooled severity of fatigue as measured by the most frequently used fatigue tools across studies. Lastly, a meta-analysis on correlation values was conducted to examine the pooled correlations of fatigue with its related factors.

The frequency of fatigue in each study was expressed as the number of cases divided by the total number of participants in the original studies. The pooled frequency and severity of fatigue were calculated with weighted effect size and standard errors, along with 95% CI [15]. For the meta-analysis on correlation analysis, correlation-based measure of effect size (rES) was obtained using Fisher’s z transformation [17]. A two-sided p < .05 was considered statistically significant. The statistical analyses were conducted using Comprehensive Meta-Analysis 2.0 software (Biostat, Englewood, NJ, USA).

Results

This section consists of two parts. First, we provide a summary of the systematic review regarding characteristics of fatigue, and then we describe the results of meta-analysis of fatigue (pooled frequency, severity & correlations) in IBS.

Part 1. Systematic review

Characteristics of selected studies

A total of 24 studies were included for the systematic review (Table 4). The average quality score for the 24 studies was 16.7 (range: 16–19) out of 19. The majority were descriptive studies (n = 20) and four were case control studies. The most frequently used fatigue tools were Fatigue Impact Scale (FIS; n = 5) [12,18–21] and Short-Form 36 (SF-36; n = 3) [22–24] to assess fatigue in patients with IBS. Only 5 of the 24 studies used the FIS as a validated fatigue-specific tool [12,18–21]. In other studies, fatigue was evaluated using subitems of symptom diary or questionnaires. Half of the studies were conducted in the US from 2010 to 2014, and at both primary care and gastroenterology clinics. In most studies, the mean ages of participants ranged from 40 years to 50 years, and females accounted for 50.0%–70.0% of the participants.

Definitions of fatigue

There were various definitions of fatigue in IBS across the studies. Four definitions emerged from the IBS studies as follows: (a) tiredness, (b) loss of vitality, (c) cognitive, physical, psychological fatigue, and (d) disability (Table 4). “Tiredness” was the most frequently used term in six studies [11,25–29], where the fatigue was a state of exhaustion using a daily diary, a psychosomatic checklist, and general interview. In five studies [8,22–24,30], fatigue was defined as “loss of vitality or lack of energy”; and in four of the five studies, vitality scale of SF-36 [22–24] or SF-12 [8] were used. In another five studies [12,18–21], fatigue was described as a “cognitive, physical, and psychological fatigue” using FIS. Only Van Oudenhove et al. [31] defined fatigue as a disability. Fatigue was not specified, but described as mixed definitions in two studies that combined loss of vitality, tiredness and emotional worn out [32,33]. Fatigue was not defined in five studies [34–37]. In this review, it turned out that there were a wide range of definitions. Interestingly, definitions of fatigue in IBS seemed to be dependent on assessment tools used.

Fatigue-related factors

GI symptoms. GI symptom, which is measured by summing scores of abdominal pain, diarrhea, constipation, bloating, and other GI discomforts, was identified as a frequently appearing symptom associated with an increased level of fatigue in six studies [8,19–21,26,33]. Of these, four studies specified that the severity of abdominal pain was associated with fatigue [8,20,26,33]. Two studies [11,24] reported that the frequency of fatigue differed by IBS bowel pattern subtypes; however, the results were inconsistent between the two studies. Spiegel et al. [11] suggested fatigue was the most common IBS-related extraintestinal symptom, in which constipation-dominant IBS is 28.0%, diarrhea-dominant IBS is 15.0%, and mixed IBS is 9.0% (p < .05, N = 123). In contrast, Si, Wang, Chen, Sun, and Dai [24] reported the opposite; they found that the highest frequency of fatigue (78.3%) was reported in diarrhea-dominant IBS and the lowest frequency in constipation-dominant IBS (63.0%).

Psychological distress. Another most frequent factor related to fatigue were psychological distress in six studies [8,30–32,34,38],

Table 3 Heterogeneity Test for the Meta-Analysis: Pooled Frequency of Fatigue.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Sub-variables</th>
<th>Studies</th>
<th>n</th>
<th>Frequency of fatigue</th>
<th>Test for heterogeneity between &amp; within-studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Qd between</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>15</td>
<td></td>
<td>54.2 (38.5, 69.4)</td>
<td>266.42</td>
</tr>
<tr>
<td>Country</td>
<td>United States</td>
<td>7</td>
<td></td>
<td>54.4 (51.6, 57.1)</td>
<td>15.92</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>5</td>
<td></td>
<td>54.5 (52.2, 57.5)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Asia</td>
<td>3</td>
<td></td>
<td>63.2 (60.4, 65.6)</td>
<td>–</td>
</tr>
<tr>
<td>Publication year</td>
<td>1995–1999</td>
<td>1</td>
<td></td>
<td>57.8 (42.0, 72.0)</td>
<td>14.21</td>
</tr>
<tr>
<td></td>
<td>2000–2004</td>
<td>3</td>
<td></td>
<td>61.3 (58.6, 63.9)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2005–2009</td>
<td>4</td>
<td></td>
<td>53.9 (51.0, 56.5)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2010–2014</td>
<td>7</td>
<td></td>
<td>53.9 (51.0, 55.5)</td>
<td>–</td>
</tr>
<tr>
<td>Settings</td>
<td>Primary health</td>
<td>8</td>
<td></td>
<td>53.9 (50.6, 57.3)</td>
<td>21.83</td>
</tr>
<tr>
<td></td>
<td>care</td>
<td></td>
<td></td>
<td>58.5 (54.9, 60.9)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Tertiary health</td>
<td>7</td>
<td></td>
<td>53.9 (50.6, 57.3)</td>
<td>59.24</td>
</tr>
<tr>
<td>Female prevalence</td>
<td>≥ 50.0% &amp; &lt; 70.0%</td>
<td>11</td>
<td></td>
<td>53.9 (50.6, 57.3)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>70.0%</td>
<td>4</td>
<td></td>
<td>56.8 (53.8, 59.6)</td>
<td>–</td>
</tr>
<tr>
<td>Sample size of IBS</td>
<td>n &lt; 100</td>
<td>6</td>
<td></td>
<td>53.9 (50.6, 57.0)</td>
<td>8.71</td>
</tr>
<tr>
<td></td>
<td>n = 100</td>
<td>6</td>
<td></td>
<td>56.8 (53.8, 59.6)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>n &gt; 500</td>
<td>3</td>
<td></td>
<td>53.8 (50.2, 55.4)</td>
<td>–</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>&lt; 40</td>
<td>2</td>
<td></td>
<td>61.3 (58.6, 63.9)</td>
<td>42.42</td>
</tr>
<tr>
<td></td>
<td>≥ 40 &amp; &lt; 50</td>
<td>9</td>
<td></td>
<td>53.9 (51.2, 56.3)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>≥ 50</td>
<td>4</td>
<td></td>
<td>52.8 (50.2, 54.2)</td>
<td>–</td>
</tr>
<tr>
<td>Study design</td>
<td>Descriptive</td>
<td>12</td>
<td></td>
<td>53.9 (50.5, 57.1)</td>
<td>4.11</td>
</tr>
<tr>
<td></td>
<td>Case control</td>
<td>3</td>
<td></td>
<td>53.8 (51.2, 59.8)</td>
<td>–</td>
</tr>
</tbody>
</table>

Note. CI = confidence interval; df = degree of freedom; IBS = irritable bowel syndrome.

*p < .05.

* Weighted effect size and standard error were applied, resulting in pooled frequency and 95% CIs.
Table 4 Characteristics of Studies Included for Systematic Review and Meta-analyses (N = 24).

<table>
<thead>
<tr>
<th>First author, yr &amp; country</th>
<th>Design</th>
<th>Settings</th>
<th>Sample size, (% of female)</th>
<th>Fatigue scale</th>
<th>Frequency of fatigue (%)</th>
<th>Fatigue-related factors</th>
<th>Quality assessment (0–19 point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue as “tiredness”</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jarrett 2000 USA [27]</td>
<td>Descriptive</td>
<td>3°</td>
<td>N = 82 (100.0%)</td>
<td>SCL-90</td>
<td>NA</td>
<td>Female sex</td>
<td>16</td>
</tr>
<tr>
<td>Lustyk 2001 USA [29]</td>
<td>Descriptive</td>
<td>1°</td>
<td>N = 54 (100.0%)</td>
<td>BDQ</td>
<td>74.0%</td>
<td>Inactivity</td>
<td>16</td>
</tr>
<tr>
<td>Cain 2009 USA [25]</td>
<td>Descriptive</td>
<td>3°</td>
<td>N = 187 (83.2%)</td>
<td>Daily diary</td>
<td>NA</td>
<td>Menstruating or postmenopausal status</td>
<td>16</td>
</tr>
<tr>
<td>Kato 2010 USA [28]</td>
<td>Descriptive</td>
<td>1°</td>
<td>N = 1,105 (56.3%)</td>
<td>General interview</td>
<td>Idiopathic chronic fatigue (9.6%)</td>
<td>Comorbidity with chronic fatigue syndrome (2.9%)</td>
<td>16</td>
</tr>
<tr>
<td>Spiegel 2010 USA [11]</td>
<td>Descriptive</td>
<td>3°</td>
<td>N = 123 (73.2%)</td>
<td>IBS-Impact Scale</td>
<td>26.0%</td>
<td>Bowel pattern subtypes</td>
<td>17</td>
</tr>
<tr>
<td>Heitkemper 2011 USA [26]</td>
<td>Descriptive</td>
<td>3°</td>
<td>N = 166 (100.0%)</td>
<td>Daily diary</td>
<td>NA</td>
<td>IBS symptom severity, abdominal pain</td>
<td>17</td>
</tr>
<tr>
<td>Fatigue as “loss of vitality (lack of energy)”  Hahn 1999 USA [23]</td>
<td>Descriptive</td>
<td>1°</td>
<td>N = 500 (80.0%)</td>
<td>SF-36</td>
<td>40.0%</td>
<td>Sleep disturbance, low HRQOL</td>
<td>16</td>
</tr>
<tr>
<td>Anty 2011 France [18]</td>
<td>Descriptive</td>
<td>1°</td>
<td>N = 42 (75.1%)</td>
<td>FIS</td>
<td>55.0%</td>
<td>Leptin, female sex, low HRQOL</td>
<td>17</td>
</tr>
<tr>
<td>Fatigue as “disability”</td>
<td>Van Oudenhove 2011 Belgium [31]</td>
<td>Descriptive</td>
<td>3°</td>
<td>N = 142 (75.3%)</td>
<td>Chronic Fatigue-like Symptoms Questionnaire</td>
<td>56.0%</td>
<td>Depression</td>
</tr>
<tr>
<td>Fatigue as mixed-definition with “loss of vitality/tiredness/emotional tiredness” Longstreth 2005 USA [32]</td>
<td>Descriptive</td>
<td>1°</td>
<td>N = 155 (81.3%)</td>
<td>IBS-Impact Scale</td>
<td>NA</td>
<td>Emotional distress, sleep disturbance, low HRQOL</td>
<td>17</td>
</tr>
<tr>
<td>Fatigue not defined</td>
<td>Dunlop 2003 England [34]</td>
<td>Descriptive</td>
<td>3°</td>
<td>N = 28 (33.1%)</td>
<td>IBS-QOL Questionnaire</td>
<td>NA</td>
<td>Depression</td>
</tr>
<tr>
<td>Naliboff 2003 USA [36]</td>
<td>Descriptive</td>
<td>3°</td>
<td>N = 42 (50.2%)</td>
<td>Validated semantic differential scales: 23 items of current mood</td>
<td>98.7%</td>
<td>Stress, lower arousal ratings</td>
<td>16</td>
</tr>
<tr>
<td>Hamilton 2009 USA [35]</td>
<td>Case control</td>
<td>1°</td>
<td>N = 4,388 (76.3%)</td>
<td>General interview</td>
<td>13.3%</td>
<td>NA</td>
<td>19</td>
</tr>
<tr>
<td>Chang 2011 USA [37]</td>
<td>Descriptive</td>
<td>3°</td>
<td>N = 452 (57.1%)</td>
<td>Stress Symptom Ratings</td>
<td>47.5%</td>
<td>Depression</td>
<td>16</td>
</tr>
<tr>
<td>Tang 2012 China [38]</td>
<td>Case control</td>
<td>NA</td>
<td>NA</td>
<td>Stress Symptom Questionnaire</td>
<td>NA</td>
<td>Depression</td>
<td>17</td>
</tr>
</tbody>
</table>

Note: BDQ = bowel disease questionnaire; F = female; FIS = fatigue impact scale; HRQOL = health-related quality of life; IBS = irritable bowel syndrome; NA = not addressed; PHQ-15 = patient health questionnaire-15; SCL-90 = symptom checklist-90-revised; SF-36 = short-form 36; 1° = primary health care settings; 3° = tertiary health care settings.

Denotes the studies excluded from meta-analyses (n = 7).
Of these, depression and anxiety were common psychological symptoms and comorbid with fatigue. Lackner and Gudleski [8] showed that 41.6% of the variance predicting fatigue included depression, anxiety and perceived stress in the regression model. In addition, stress was reported to be positively related to fatigue in four studies [8,30,36,37].

Sleep disturbance. The next frequently appearing factor related to fatigue in IBS was sleep disturbance as a co-occurring symptom [21,23,32,33]. In particular, Wittthoft et al [33] reported that fatigue was positively related to poor sleep quality (r = .29, p < .05, N = 414). Simren et al [21] found that IBS patients with high fatigue have more sleeping difficulties and “too little sleep”.

Biological factors. The severity of fatigue was greater in female patients than male patients in four studies [20,21,27,38]. In addition, one study [36] reported that the higher arousal of central processing of visceral stimuli was related to lower fatigue in IBS. Indicators of low-grade inflammation played a role as fatigue-related biomarkers [12,18,20]. Piche et al [12] demonstrated that mast cell count, a marker of intestinal inflammation, was correlated with fatigue (r = .64, p < .001, N = 50). Piche et al [20] and Anty et al [18] reported that the leptin levels related to inflammation were positively associated with fatigue in IBS. Other biomarkers of hemoglobin (r = -.19, p < .001, N = 80) and albumin (r = -.15, p < .01, N = 80), were negatively correlated with the severity of fatigue; however, no association was found between fatigue and C-reactive protein or platelets in IBS [21].

Impact of fatigue. The HRQOL was the most frequently reported factor in six studies as a possible consequence of fatigue in IBS. Many studies reported that fatigue was significantly inversely correlated with low HRQOL scores, and emphasized the negative impact of fatigue on HRQOL [8,18,22,24,32,38]. Two studies reported that fatigue was associated with interferences in daily life [23,32].

Others. Less frequently reported factors related to fatigue were menstruating or postmenopausal status [25], inactivity [29], unstable employment [21], comorbidity with chronic fatigue syndrome [28], and eating habits [32]. Cain et al [25] found that the level of fatigue was very high among women in menstruation and women postmenopause in IBS. Lustyk et al [29] reported that inactive patients with IBS had greater fatigue compared to active patients with IBS. With regard to social and environmental aspects, only Simren et al [21] reported that the employment status was associated with fatigue. Patients who were unemployed, retired, or on long-term sick leave had more severe fatigue than those who were employed (p < .001), but living conditions, educational level and marital status did not affect the severity of fatigue in IBS.

Part 2. Meta-analyses

Publication bias and test of heterogeneity

Begg’s funnel plot (Figure 2) and Egger’s test (Table 2) were performed for meta-analysis. The shape of funnel plot was symmetrical and the results of Egger’s test statistically supported the result of the funnel plot. As a result, no publication biases were present in any meta-analyses (Table 2). Q test and I² statistical analysis were tested to check for heterogeneity. High heterogeneities across studies were calculated for the pooled frequency of fatigue (Table 3 & Figure 3), the pooled severity of fatigue (Figure 4), and the pooled correlations between fatigue and related factors (Figure 5). Thus, random effect models were applied in each meta-analysis (Figures 3, 4, & 5).

Pooled frequency of fatigue

Overall pooled frequency. A total of 15 studies were included for meta-analysis of the pooled frequency of fatigue, with 2,096 cases reporting fatigue out of 7,954 participants with IBS. The results of the meta-analyses were reported in Table 3 and Figure 3. Table 3 showed the overall result and subgroup analyses (e.g., age, settings, design, & year) of pooled frequency of fatigue with 95% CI. The overall pooled frequency of fatigue in IBS was 54.2% [95% CI (38.5, 69.4)], and high heterogeneity was observed (I² = 98.4%). The frequency of fatigue ranged from 9.6% [28] to 98.7% [36].

![Figure 3. Forest plot of pooled frequency of fatigue in IBS. Note. CI — confidence interval; IBS — irritable bowel syndrome. *Total number of positive cases who reported fatigue in patients with irritable bowel syndrome. #Total number of patients with irritable bowel syndrome. Normal approximation of effect size with 95% CI.](image-url)
Subgroup pooled frequency and meta-regression. The pooled frequency of fatigue significantly differed by settings, female sex, and age (Table 3). The frequency of fatigue at the tertiary health care setting was 58.5% [95% CI (54.9, 60.9)], which was significantly higher than the frequency of fatigue at the primary health care settings [53.9%, 95% CI (50.6, 57.3), p = .042]. The frequency in the “female ≥ 70.0% group” [56.8%, 95% CI (53.8, 59.6)] was significantly higher than in the “female ranged from 50.0% to 70.0% group” [53.9%, 95% CI (50.6, 57.3), p = .004]. The frequency of fatigue in the “≤ 40 year-old group” was 61.3% [95% CI (58.6, 63.9)], which was higher than that in the “41–50 year-old group” [53.9%, 95% CI (51.2, 56.3)] and the “≥ 51-year-old group” [52.8%, 95% CI (50.2, 54.2), p = .039].

Female sex, age, and settings were included as independent variables in the multivariate meta-regression analysis (Table 3). The females were 3.3 times (β = 3.3, p = .023) more likely to report fatigue than males were. Younger patients were 3.2 times (β = 3.2, p = .012) more likely to report fatigue than older patients. The frequency of fatigue reported at the tertiary care setting was 4.7 times (p = .015; data not shown) greater compared to the frequency at the primary care settings.

Pooled severity of fatigue

Figure 4 showed the pooled severity of fatigue measured by FIS and SF-36-vitality scale, which were most frequently used tools across studies. Our pooled FIS score was 58.2 out of 160 (0 signifying “no problem”, 160 signifying “extreme problem”), indicating the higher the score the greater the impact of fatigue [95% CI (54.3, 86.7)]. Our pooled SF-36 score was 43.9 [95% CI (26.9, 64.9)]. The total score of the scale ranges from 0 which signifies “low vitality” to 100 which signifies “high vitality”. A lower score indicates a higher degree of fatigue, and a score less than 60.9 in SF-36 was interpreted as great severity of fatigue [39].

Meta-analysis on correlations

To conduct meta-analysis, at least three studies are required [15,16]. However, the available correlation values (r) of the majority of related factors with fatigue (except for HRQOL) were less than three from 17 studies. Thus, we were only able to obtain pooled correlation (rES) between the severity of fatigue and HRQOL in four studies [8,21,32,38]. The overall rES between the severity of fatigue and HRQOL was −.378 in random effects model (p < .001; Figure 5).

Discussion

This systematic review and meta-analysis provided an in-depth overview of the existing literature to understand fatigue in IBS. We reviewed characteristics of selected studies, fatigue instruments, definitions of fatigue and factors related to fatigue in IBS; we also conducted meta-analyses for the pooled frequency and severity of fatigue, and correlations between fatigue and related factors.

To our knowledge, there is no research that clearly defines fatigue in IBS; therefore, we could not specify the definition of fatigue in IBS in the current literature. However, our study showed that “tiredness” is the most commonly used term to describe fatigue in IBS. The patterns of fatigue in IBS were mixed-types of acute and chronic fatigue (duration > 6 months) [21,23]. Through this review, patients with IBS showed a tendency similar to central fatigue, such as mentally tired and physical fatigue (i.e., failure to initiate physical activity, lack of energy arising from central nervous system),...
not peripheral fatigue (i.e., muscle fatigue caused by disorders of neuromuscular junction transmission), which could be related to brain-gut axis interaction and cognitive psychological effect in IBS [40].

This review examined the possible correlates with fatigue in IBS, such as abdominal pain, psychological distress, and HRQOL. Fatigue was mentioned as a significant predictor of patients’ low HRQOL in many studies [8,18,22,24,32,38]. However, most of the studies did not provide the correlation values (i.e., Pearson r), and did not clearly state whether they adjusted confounders. In addition, there is a lack of studies that assess biological mechanisms, self-efficacy, self-coping, and social/environmental aspects of fatigue.

The pooled frequency of fatigue (54.2%) in IBS, which was acquired from our meta-analysis, was higher compared to the frequency of fatigue in the U.S. population (37.9%, N = 28,902 adults) [38,41], in cancer patients (30.0%, N = 6,125) [42], and in Parkinson’s disease (33.8%, N = 136) [43]. Hamilton et al [35] supported our findings. They examined the odds ratio (OR) of fatigue in IBS, and found that the odds of IBS patients with fatigue were 4.1 times greater than that of the healthy control group [OR = 4.1, 95% CI (3.6, 4.7)].

Meta-regression with subgroup variables on the frequency of fatigue showed significantly positive relationships with tertiary care settings, female sex, and younger age. The following reasons may be accountable for these results: Patients who visited tertiary health care settings are more likely to be ill and have severe diseases and other comorbidities, compared to the patients who visited primary health care settings. These comorbidities together with complex and severely ill conditions may contribute to the increased frequency of fatigue [44]. Also, females are more likely to report symptoms than males do, and the diagnosis of IBS is more likely to occur in young females (teens through their 40s) [45]. This tendency may also contribute to sex-related and age-related differences in the pooled frequency of fatigue in IBS across studies.

In our review, the findings showed that the severity of fatigue in IBS is higher compared to that of populations with GI disorders, cancer, or the general healthy population; however, it is lower compared to that of those with chronic fatigue syndrome. The pooled severity of fatigue in IBS (pooled FIS score = 58.2) is relatively high, when compared to non-IBS studies using FIS (M = 40.00 in 181 patients with Crohn’s disease [46], M = 54.5 in 108 patients with primary biliary cirrhosis [47]); but our pooled FIS score was lower than the score in 615 patients with chronic fatigue syndrome (M = 130.5) [48].

The pooled SF-36 vitality score in this review (M = 43.9) indicated high fatigue and low vitality (the lower the score, the higher the fatigue) [39]. Among the non-IBS studies using SF-36, our result was also relatively lower when compared to the fatigue in patients with Crohn’s disease (M = 51.0, N = 96) [49], with breast cancer (M = 46.0, N = 430) [50], and in the general population after adjusting for age, gender, and education (M = 60.0, N = 2,214) [49]. However, our pooled SF-36 score was higher than the score in the review paper of patients with chronic fatigue syndrome (M ≤ 35.0, N = 780 from 9 studies) [51].

The severity of fatigue was shown to have a negatively moderate linear relationship with HRQOL (rES = −0.378), indicating that there is a moderate effect of fatigue severity on HRQOL [17]. Because the high severity of fatigue in IBS patients and its impact on the HRQOL were presented in our analyses, a more comprehensive fatigue assessment is necessary for understanding fatigue to provide effective fatigue management in patients with IBS.

Although we obtained meaningful results regarding IBS-related fatigue, there are several limitations to be addressed in this study. First, this systematic review included all relevant studies of fatigue in IBS; however, nine studies were excluded because no frequency or prevalence of fatigue data was available for meta-analysis. If we have sufficient publications for this review, we might present results that can be generalized by obtaining true frequency and severity of fatigue. Second, this review only included published studies; therefore, publication bias may be a possible limitation, even though such a bias was not found in Begg’s test and Egger’s test in our meta-analyses. Third, high heterogeneity was found in study characteristics, such as gender, age, settings, and study design, across the selected studies. Fourth, the included studies in this review differed in the use of tools to measure fatigue. Sixteen of the 24 studies used multisymptom fatigue measurements, such as symptoms questionnaires and daily symptom diary. This inconsistency of fatigue measurements may lead to a biased estimation of fatigue in IBS. Taken together, the interpretations of our results should be made cautiously. Lastly, all of the studies measured variables at the same time, which does not allow the inference of causal relationships between fatigue and related factors.

Clinical implications

The findings from this systematic review and meta-analyses are important in translating research into education and clinical practice for health care professionals. This work will inform health care professionals (i.e., nurses, nurse practitioners, gastroenterologist) about understanding fatigue as one of the major symptoms of IBS, and have them be aware of comprehensive assessment and management of symptoms such as abdominal pain, psychological distress, sleep quality, and HRQOL. “Tiredness” can be suggested as a general definition of fatigue to assess fatigue in IBS. However, it may be hard to describe fatigue with one definition in chronic diseases such as IBS [8,21,52]. Thus, various definitions and tools of fatigue shown in this review can be used to assess fatigue for IBS patients. Qualitative data collection in clinical practice is needed for better understanding of and describing fatigue and associated symptom phenomena.

Furthermore, this study sheds light on future fatigue research in this population. Further IBS studies with large samples are needed to (a) test the psychometric properties of fatigue instruments, (b) further explore fatigue, and its related factors using validated tools, (c) examine causal relationships between fatigue and related factors, (d) identify underlying mechanisms of fatigue, and (e) develop further intervention study for managing fatigue.

Conclusion

This review is the first to fully examine fatigue in IBS via a systematic review and meta-analysis. This current review found that “tiredness” is the most commonly used term to define fatigue in IBS. GI symptom, psychological distress (depression & anxiety), and HRQOL are the most frequently related factors with fatigue in IBS. The pooled frequency and severity of fatigue in IBS via meta-analysis were high. Tertiary health care settings, female sex, and age were significantly and positively associated with the pooled frequency of fatigue in IBS. Among the fatigue-related factors, HRQOL was shown to have a negative moderate relationship with the severity of fatigue.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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