**Title:**

Systematic review: The Impact of Inflammatory Bowel Disease related fatigue on Health-related quality of life.

**Running Title:**

Systematic review: IBD fatigue and HRQoL

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**Funding:**

There is no specific funding awarded to undertake this research.

## Declarations:

None of the contributing authors have any declarations, personal or financial, to make.

There are no conflicts of interest to declare, for any of the contributing authors of this paper.

## Article Summary:

What is already known about this subject?

- Fatigue is frequently reported in IBD and has been identified as one of the most burdensome symptoms.
- IBD fatigue has been reported as multidimensional and complex, impacting individual's activities of daily living and reducing HRQoL.
- The subjective nature of fatigue and poor understanding means it is often underestimated by clinicians.

What are the new findings?

- This work identified the experiences of fatigue were significantly related to three HRQoL linked themes; Symptom acceptance and management, psychosocial wellbeing and management and physical activity.
- Psychosocial factors were strongly associated with both, fatigue and HRQoL.
- Physical activity was impaired by higher fatigue levels, lowering HRQoL, but it was also used as a means of reducing fatigue and improving HRQoL.

How might it impact on clinical practice in the foreseeable future?

- Better understanding of the Impact of IBD fatigue will help patients and clinicians better manage fatigue, for individuals with IBD this has the potential to improve HRQoL, reduce costs to the NHS and allow patients to feel a sense of control over their treatment through effective self-management.
- This review has identified areas for possible further research with use of validated fatigue and HRQoL measures and clearer characterisation of disease activity to define a diagnostic cut off for IBD fatigue.

**Authors Contribution:**

- Shellie J. Radford- Whole manuscript preparation, literature searching, data appraisal and extraction, analysis and write up.
- Jordan McGing – Literature searching, data appraisal and extraction and analysis.
- Dr Wladyslawa Czuber-Dochan – review of manuscript and supervision of data extraction and analysis.
- Dr Gordon W. Moran – Whole manuscript review, supervision of data extraction and analysis.

**Abstract:**

**Background:** Fatigue is frequently reported in inflammatory bowel disease (IBD) and impacts on Health-Related Quality of Life (HRQoL). HRQoL has not been systematically reviewed in IBD fatigue.

**Aim:** To investigate what impact IBD fatigue has on HRQoL in adults with IBD.

**Methods:** Systematic searches (CINAHL, EMBASE, PsychInfo, Medline) were conducted 25.09.2018, restricted to 'human', 'adult', 'primary research' and 'English language'. Search terms encompassed concepts of 'Fatigue', 'IBD' and 'HRQoL'. A 5 year time limit (2013-2018) was set to include the most relevant publications. Publications were screened, data extracted, and quality appraised by two authors. A narrative synthesis was conducted.

**Results:** Eleven studies were included, presenting data from 2823 participants. Fatigue experiences were significantly related to three HRQoL areas: symptom acceptance, psychosocial wellbeing, and physical activity. Patients reporting high fatigue levels had low symptom acceptance. Psychosocial factors were strongly associated with both, fatigue and HRQoL. Higher social support levels were associated with higher HRQoL. Physical activity was impaired by higher fatigue levels, lowering HRQoL, but it was also used as a means of reducing fatigue and improving HRQoL. Quality appraisal revealed methodological shortcomings in a number of studies. Notably use of multiple measures, comparison without statistical adjustment and fatigue and HRQoL assessment using the same tool.

**Conclusion:** Psychosocial factors, symptom management and acceptance and physical activity levels have significant impact on HRQoL. Results support application of psychosocial or exercise interventions for fatigue management. Further exploration of HRQoL factors in IBD fatigue is required, utilising validated fatigue and HRQoL measures.

**Key words:**
Inflammatory bowel disease; Crohn's disease; ulcerative colitis; fatigue; Health related quality of life

## Introduction:

Fatigue related to Inflammatory Bowel Disease (IBD) and other long term conditions is defined as an 'extreme and persistent sense of tiredness, weakness or exhaustion'[1] which can be physical, mental or both and is not easily resolved by sleep or rest.[2] Fatigue can be attributed to both physical and mental exertion[3,4] or as the outcome of pathological processes.[3,4] The international classification of diseases

code presents fatigue as an assortment of physical, cognitive and emotional symptoms affecting undertaking of daily tasks.[5] It is not known whether fatigue in a given disease is a result of being chronically ill or whether it represents a specific symptom of that disease.[6]

The prevalence of IBD fatigue is reported as 41-48% for patients in remission and 71-86% in patients with active disease.[7,8] The most frequently experienced symptoms of IBD are pain, urgency and fatigue.[9–15] IBD fatigue is one of the top 5 research priorities highlighted by the nurses European Crohn's and Colitis Organisation (N-ECCO) due to its pervasiveness and negative impact on Health Related Quality of Life (HRQOL).[12,16] The symptom of fatigue in long term conditions (LTCs) has received greater attention as part of overall HRQoL.[6] However, to date, there has been no thorough appraisal of the impact of IBD fatigue on an individual's HRQoL.

Increasing life expectancy has highlighted the need for other measures of health, capturing the quality of the years someone lives. Traditional markers for population health, such as life expectancy and causes of death, do not offer information regarding the quality of the physical, mental and social domains of life. The concept of quality of life (QoL) is not a new one, in 1995 the World Health Organisation (WHO) recognised the importance of improving peoples QoL.[17] When QoL in considered in the context of health and disease, it is commonly referred to as health-related quality of life (HRQoL) to differentiate from other aspects of QoL. Health is a multi-dimensional concept, HRQoL is also multidimensional and incorporates areas related to physical, mental and social functioning.[18] HRQoL goes beyond the direct measures of health and focuses on the QoL consequences of health status. HRQOL represents the functional effect of an illness and its consequent therapy upon a

patient, as perceived by the patient. It encompasses several dimensions of life, including physical functioning, psychosocial functioning, role functioning, mental health and general health perceptions. HRQOL is determined by socio-demographic, clinical and psychological and treatment-related determinants.[19,20]

Studies to date have rarely measured IBD fatigue as a primary outcome and there has been limited literature focused on the impact of IBD fatigueon HRQoL. The aim of this review is to synthesise the existing body of knowledge on IBD fatigue and its impact on HRQoL. This work is essential in order to better define the research streams needed to improve HRQoL in people with IBD fatigue.

**Methods:**

The review has been registered on the PROSPERO database for systematic reviews: CRD42018110005.

The review question *"What is the impact of IBD fatigue on the HRQoL of adults with IBD?"* was developed using the format: Population, Exposure, Outcome (PEO).

The final search of literature was performed on 25/09/2018. Databases searched were EMBASE, CINAHL, PsychINFO and MEDLINE. These databases were selected as they were likely to provide a broad combination of medical and healthcare allied papers related to the topic of interest.[21] To increase the reference retrieval, the medical subject headings (MeSH) and free text searching were employed, and each database was individually searched.[22] Grey literature searching was used to maximise the number of publications retrieved.[23,24] This was conducted by searching Google Scholar, reference lists of included publications and registered controlled trial registers.

193 Search terms were determined through consideration of previously reviewed
194 literature and scoping searches of Google Scholar (Table 1).[9,25–27]

| **Table 1:** Search Terms | | |
|---|---|---|
| **Fatigue** | **IBD** | **Quality of life** |
| Fatigue (MeSH) | Inflammatory Bowel Disease * | Quality of Life |
| Fatigue* | IBD | Health related quality of life* |
| Lethargy (MeSH) | Ulcerative Colitis* | Life Quality |
| Lethargy | UC | HRQoL |
| Low energy* | Crohn's Disease* | |
| Vigour* | CD | |
| Vitality* | | |
| Exhaustion* | | |
| Key=* free search term for truncation | | |

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196 Searches were performed with the 'suggested search terms' and 'explode' selection.
197 The Boolean operator 'OR' was used within each facet to maximise the searches,
198 with the operator 'AND' utilised between facets to combine terms. Searches were
199 restricted to 'human', 'adult', 'primary research' and 'English language' publications.
200 Studies of any design published in English were considered for the review if IBD
201 fatigue was mentioned in the abstract. Commentary papers and literature reviews
202 were excluded. A time limit of 5 years (2013-2018) was set to ensure inclusion of
203 only the most up to date information. Due to limited number of publications related to
204 IBD fatigue, no studies were excluded from the review based on study quality,
205 however quality wasconsidered when reviewing study findings. Studies that did not
206 meet the inclusion criteria were retained, if relevant, for background information.
207
208 ***Quality appraisal and data extraction***
209 Quality of studies was assessed and data was extracted by two independent
210 reviewers (SJR and JM), using forms specific to study design from the Joanna

Briggs Institute to allow for comparison of quality across study types.[28] The data extracted includes specific details about populations, context, culture, geographical location, study methods and the phenomena of IBD fatigue relevant to the review question. Due to the time constraints all papers were read in full, but only data reflecting the aims of the review were extracted. For several of the studies, information and analysis regrading HRQoL was limited, but present, therefore deemed important to include given the comprehensive and systematic nature of the review.

### *Data analysis*

Thematic analysis was used to analyse data. The analysis included three phases: open coding, creating categories and abstraction. The open coding phase relies upon the research question driving the coding process so that only valid data is highlighted and further examined.[29–31] Open coding involved highlighting the text when reading, later the highlighted sections were grouped and categorised. During categorisation each category was named and combined into larger themes. The larger themes were analysed for sub-themes through analysis of the coding.
The abstraction phase involved conveying a general description of the topic being researched to the themes identified.

## Results

Searches yielded 76 publications overall, with 11 studies meeting inclusion criteria (Figure 1). A summary of the included papers and data extracted is shown in Table 2.

**Table 2: Summary of Data extracted from the reviewed literature** *(in ascending chronological order)*

| Author(s) | Year | Geographic location | study design | Sample size and characteristics, | Disease activity | Fatigue questionnaires and measurements | HRQoL questionnaires and measurements | Study findings | Quality |
|---|---|---|---|---|---|---|---|---|---|
| **Castillo-Cejas, M. D. Robles and V. Borruel, N. *et al*** | 2013 | Spain | Cross Sectional | Two-part study; Part 1/ 99 (55 CD, 44 UC) Part 2/ 137 (70 CD, 67 UC) | Active CD; 49%. Active UC; 46% | DFIS, FSS, MFI. | EQ-5D-5L, IBDQ-9 | High levels of disease activity related to high levels of fatigue. high levels of fatigue related to low HRQoL. | High |
| **Czuber-Dochan, W. Dibley, L.B. and Terry, H. *et al*** | 2013 | UK | Qualitative | 46 (28 CD, 18 UC) selected from online database | Not disclosed | No questionnaires used, focus group study | | Five themes identified: Experience, causes, management, consequences and seeking support. Participants described fatigue in terms of how it affected life. High levels of fatigue affected physical and cognitive abilities, impacting on everyday life. | High |
| **Viazis, N. Mantzaris, G. and Karmiris, K. *et al*** | 2013 | Greece | Qualitative | 1181 (827 online questionnaire, 354 outpatient clinic questionnaires) (642 CD, 539 UC) | Not disclosed | Survey of authors own design (unvalidated) | | 60% of patients felt depressed, 25% felt angry because of IBD fatigue. IBD fatigue interfered with social life in more than half of cases also affecting working capability. Respondents report good social support from family and friends. | Low |
| **Cohen, B. L. Zollga, H. and Shah, S. A. *et al*** | 2014 | USA | prevalence | 220 (125 CD, 95 UC) from Disease registry. | Active CD; fatigued 44%, non-fatigued 18%. Active UC; fatigued 38%, non fatigued 22%. | FACIT-F scale | SF-36, EuroQoL EQ-5D-5L, IBDQ-32 | Patients with fatigue reported having problems with their usual daily activities, except for self-care. The association of fatigue and impairment were strongest for usual activities. Patients with fatigue had worse valuations of current health status. | High |
| **Devlen, J. Beusterien, K. and Yen, L. *et al*** | 2014 | USA | Qualitative | 27 participants (4 focus groups), 10 1:1 interviews) (21 UC, 6 CD). | Active disease;22% (CD/UC not specified) | No questionnaires used, focus group study | | 21/27 participants were in disease remission. Patient reported key burdens of IBD fatigue were impact on lifestyle, impact on daily activities, impact on relationships and psychological impact. | Medium |
| **Opheim, R. Fagermoen, M.S.and Bernklev, T. *et al*** | 2014 | Norway | Cross Sectional | 428 (238 CD, 190 UC) Adult IBD outpatients | Active CD; fatigued 73% non fatigued 45%. Active UC; fatigued 85%, non fatgued 58%. | FSS | Nil | 43% CD and 33% UC reported severe fatigue, 39% reported fatigue severely interfered with daily life. Those with higher education status, working and higher income were less likely to report high fatigue interference. 43% CD and 33% UC reported severe fatigue interference with everyday life. | Medium |
| **Van Langenberg, D.R. and Gibson, P.R.** | 2014 | Australia | Cross sectional | 379 (181 CD, 113 UC, 85 Control | Active disease: CD 51%, CD follow up group | FIS | Nil | Patients with IBD reported significantly higher scores on all global and dimensional fatigue indices compared with controls. Improved physical fatigue was | High |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | s) | 47%, UC 67%. | | | associated with establishing a regular exercise routine. Improvement was seen in cognitive fatigue when immunomodulator therapy ceased. | |
| **Artom, M. Czuber-Dochan, W. and Sturt, J. *et al*** | 2017 | UK | Cross Sectional | 182 (116 CD, 60 UC) from tertiary care | Those without stoma - Active disease 26%, remission 74% (CD/UC not specified) . | MFI, IBD-F | IBDQ-32 | There was a significant difference in fatigue and HRQoL according to employment, education, marital and smoking status. Negative fatigue perceptions, 'all-or-nothing' and avoidance behaviours were significantly associated with worse HRQol. | High |
| **Habibi, F. Habibi, M.E. and Gharavinia, A. *et al*** | 2017 | Iran | Cross sectional | 71 (46 UC, 25 CD) | Those with severe disese omitted. Further disease activity data not given. | Nil | IBDQ-32 | 44% of sample reported poor sleep quality, linked to daytime sleepiness and fatigue which decreases HRQoL. Higher fatigue level correlated with poorer HRQoL. | Medium |
| **Skrautvol, K. and Naden, D.** | 2017 | Norway | Qualitative | 13 (7 CD, 6 UC) | Not disclosed | No questionnaires used, face to face interview study | | Participants reported tolerance limits might be reflected in a lack of energy. Participants reported the importance of balancing regular physical activity with regular rest. | Medium |
| **Villoria, A. García, and V.Dosal *et al*** | 2017 | Spain | Prevalence. | 177 (127 CD, 50 UC) | Not disclosed | FACIT-F scale | IBDQ-9 | Patients with fatigue had higher scores for depression, sleep disturbance and anxiety than those without fatigue. A strong negative correlation was seen between HRQoL and fatigue. Those patients with more severe IBD fatigue had worse anxiety and depression and worse quality of life. | Medium |

**Key:** DFIS= *Daily Fatigue Impact Scale*., EQ-5D-5L= *EuroQual 5-dimension questionnaire (5 level),* FACIT-F scale = *Functional assessment of chronic illness therapy-Fatigue*. FSS= *Fatigue Severity Scale*, IBDQ-9/IBDQ-32= Inflammatory bowel disease Questionnaire 9(shortened)/32. IBD-F= Inflammatory bowel disease fatigue scale, MFI= *Multidimensional fatigue inventory*. SF-36 = *36 item short form survey*

## *Sample characteristics*

Eleven studies have been included in the review, four qualitative [7,32–34], two prevalance[35,36] and five cross sectional studies.[37–41] Geographical locations of the research studies included the UK [7,40], USA[33,42], Norway [34,38] and Spain[36,39] , with one study each from Australia[37], Iran[41] and Greece.[32] All are considered to be developed countries with good quality healthcare.

The current review presents data from a total of 2823 adults. Study sample sizes ranged from n=13 to n=1181, and 54% of the sample were female. Most settings were outpatient departments, however there was also use of online participation and

interview/focus group data collection. One study combined results from in- and outpatient areas. A total of 1550 participants studied had CD (54.9%), 1182 had UC (41.9%), 85 healthy volunteers (HV) (3%) and 6 with IBD-unclassified (IBD-U) (0.2%). Reported fatigue prevalence ranged between 26.4% and 54%. All studies reported data from mixed disease states (active or quiescent).

Through the processes of data extraction and thematic analysis, three themes developed as aspects of IBD fatigue that have the greatest influence on HRQoL; Symptom acceptance and management, psychosocial wellbeing, and physical activity. Table 3 displays the distribution and frequency of the main themes throughout the reviewed studies.

**Table 3: Main themes from the reviewed literature**

| Reviewed studies | Year published | Main Themes | | |
|---|---|---|---|---|
| | | Symptom acceptance and management | Psycho-social well-being | Physical activity |
| Castillo-Cejas, M. D. Robles and V. Borruel, N. *et al* | 2013 | | | X |
| Czuber-Dochan, W. Dibley, L.B. and Terry, H. *et al* | 2013 | X | X | X |
| Viazis, N. Mantzaris, G. and Karmiris, K. *et al* | 2013 | X | X | |
| Cohen, B. L. Zollga, H. and Shah, S. A. *et al* | 2014 | X | X | X |
| Devlen, J. Beusterien, K. and Yen, L. *et al* | 2014 | X | X | X |
| Opheim, R. Fagermoen, M.S.and Bernklev, T. *et al* | 2014 | X | X | X |
| Van Langenberg, D.R. and Gibson, P.R. | 2014 | | | X |
| Artom, M. Czuber-Dochan, W. and Sturt, J. *et al* | 2017 | X | X | X |
| Habibi, F. Habibi, M.E. and Gharavinia, A. *et al* | 2017 | X | | X |
| Skrautvol, K. and Naden, D. | 2017 | X | X | X |
| Villoria, A. García, and V.Dosal *et al* | 2017 | | X | |

***Symptom acceptance and management***

Ability to accept diagnoses and IBD symptoms can depend on the care patients receive from healthcare professionals.This was particularly highlighted in those of a younger age.[33] One study reports 31% of participants were informed about disease advances, however only 30% of those obtained information from HCPs.[32] The same study reports 26% of participants do not discuss their treatment with healthcare professionals, with 40% feeling like HCPs are unsupportive of patients making decisions about their own healthcare.[7,32]

Participants who report feelings of not having control over IBD symptoms experience higher levels of fatigue than those who feel like they have good levels of control.[40,41] Altered self-image and fears about stigma caused participants to hold back sharing their diagnosis with friends, family, colleagues and employers.[7,32–34,40] Negative fatigue perceptions were associated with greater negative impact on daily activites.[40] 'Normalising behaviours' were described in terms of the participants incorporating their management techniques into their daily lives in order to reduce the negative impact that fatigue has on daily functioning. Those patients who utilised self-help techniques, such as complementary or herbal therapies , were more likely to report higher levels of fatigue than those who engaged in traditional healthcare.[38] Participants using poor methods of fatigue management, such as task avoidance and 'all or nothing' behaviours, experienced higher level of fatigue and worse HRQoL than those who did not.[40,41] Understanding one's own physical and cognitive tolerance limits and being able to adjust lifestyle to manage symptoms were highlighted as important steps for some participants.[34] Higher levels of IBD-related distress, namely a lack of symptom acceptance or ability to manage symptoms, have been shown to be associated with diminished HRQoL.[40]

***Psycho-social well-being***

Anxiety and depression were the factors most frequently associated with high levels of fatigue, [7,32,34–37,39–41] contributing to higher psychological distress.[36] Patients reported low mood (60%) or anger (25%) because of IBDand symptoms interfering with their social life.[32] Both, UC and CD patient populations affected by fatigue exhibit higher anxiety and depression and lower HRQoL than those without IBD.[41,42] Fatigue burden was frequently reported by study participants as a reason for limited or missed social interactions.[7,32,33] Family and friends have been presented as being supportive, however others , such as employers or colleagues,were reported as lacking in understanding of IBD fatigue.[34] Participants reported that they were mindful about depending heavily on family support whilst also recounting they would feel more supported if the people around them were better informed about IBD fatigue.[7] Support from family and friends may compensate for the gaps in support from healthcare professionalsas reported by participants.[32]

Interestingly, none of the studies considered the impact of fatigue on intimate relationships. Only one study touched on the subject of personal relationships, with participants feeling unable to disclose IBD to a new partner for the fear of stigma related to symptoms.[33] Two studies reported participants views regarding children; fatigue has impacted their decisions to delay having anychildren, having more children or not to have children at all.[7,33]

IBD fatigue was found to interfere with working capability in 40% of study participants, with more than half taking time off work for IBD related reasons.[32] Patients report not progressing in their careers at the same rate as collegues without IBD fatigue Participants report choosing not to take on more responsibility or reducing the working hours due to IBD fatigue.[7,33–35]

### *Physical activity*

Participants reported IBD fatigue impacted on their daily living by increasing absence from work or school, cancelling trips or events and avoiding undertaking certain activities such as sports or travelling.[33] Avoidance and 'all or nothing' behaviours associated with high levels of fatigue, such as decisions regarding not being in employment, were linked to the negative impact on HRQoL.[7,40]

High levels of physical fatigue impacted participants' ability to have a fulfilling life.[7] Patients with IBD fatigue reported having problems undertaking usual daily activities when compared to those without fatigue.[42] Very few participants reported issues with self-care regardless of fatigue level.[42] Patients who commenced a regular exercise program had greater improvement in the fatigue scores than those who did not.[37] Improvements in physical fatigue associated with the introduction of regular exercise were also associated with reduction of depression scores.[37] Establishing a regular routine between activity and rest helped some participants establish physical fatigue limits.[34] Introducing a healthy average amount of daily activity was important to participants.[34]

## Discussion

The symptom of fatigue across long term conditions all share characteristics; persistent, reduced energy and reduced muscle strength which is disproportionate to the level of activity, impacting daily physical and cognitive functioning and leading to impaired HRQoL.[1,43–49] IBD fatigue has been shown to have a predominantly negative impact on every aspect of an individual's life.[34,50–54]

The well-established link between increased disease activity and increased levels of fatigue is presented in many of the included studies.[7,32,34–37,39–41] However, disease

activity cannot independently explain the presence, or severity, of fatigue as IBD fatigue is also reported in disease remission.[55–57] This is also true in other Long term conditions. REF

*Symptom acceptance and management:*

IBD patients often feel it is important to remain 'in control' of their health.[34,52,58] Unpredictability and uncertainty concerning IBD relapses, treatment options and possible side effects contribute to low HRQoL.[52] On the contrary, a diagnosis of a long term condition can, after time, build an individual's resilience and can sometimes be a relief, such as eventually getting an answer to questions regarding symptoms.[59,60] Symptoms are reported more frequently when the patient has difficulty in coping with the demands of the disease.[26,61] Acceptance of IBD and using effective coping strategies, such as task management and pacing, seem to have positive impact on symptom activity and higher levels of HRQoL, whereas negative attitude and ineffective strategies, such as task avoidance, worsens HRQoL.[26,58,61,62]

*Psychosocial support:*

Stigma is found to be independent of level of disease activity and seems to affect the lives of IBD patients in multiple ways.[63] Stigma related to ill health has been shown to be connected with the perceived views of employers, co-workers and friends.[52,63] In the case of IBD fatigue, like in other long term conditions, stigma results from perceived physical weakness, cognitive limitations, reduced social activity and the inability to fulfil certain roles within an individuals personal and professional life.[64–68]

Lack of support from colleagues negatively impacts on an individualsHRQoL.[52,53] Often the steps taken to adjust the work environment to accommodate IBD symptoms can lead to feelings of loneliness, such as adjusting the working day to accommodate more frequent rest breaks.[52,62] Patients in full time work experience significantly higher HRQoL, than those in part time work, unemployed or absent due to sickness.[62,69] Sick leave and work absence was reported to reduce HRQoL [7,32,33,35,38,53,69] This could be attributed to enhanced interaction in those individuals who work or are in education, consequently improving HRQoL.[70]

A study in multiple sclerosis showed a cycle of depression; social isolation leading to a reduction in social support, contributing to increased depression.[71] Similar cycle has been also observed in IBD fatigue.[26,57] Social support has been found to be important to individuals and helps encourage good coping strategies, whilst disengagement from social activity had negative affect on HRQoL.[26,52,54,62] It is reported that 68% of IBD patients have experienced social constraint in some way, such as an inability to undertake hobbies or leisure activites.[52–54,62] Patients worry that their fatigue restricts not only their own, but also their families social activites.[52] Close relationships with friends and social support groups are evidenced to positively impact on HRQoL by improving fatigue managment.[54,58] IBD fatigue has been reported to be a daily concern of 66% of patients, however only 44% of family and friends and 36% of healthcare professionals demonstrated agreement with the patients perceived fatigue levels.[72] This kind of discrepancy may result in patients feeling misunderstood and isolated, leading to under reporting of symptoms. Family and friends occasionally express disbelief that symptoms of IBD are real, causing feelings of hurt and anger in patients.[52,62] Some healthcare professionalsconsider

some IBD symptoms as psychological in nature, causing emotional distress amongst patients due to feelings of lack of support and understanding.[62] This is echoed in other long term conditions, such as cronic fatigue syndrome, where there has been converse viewpoints regarding the origins of fatigue from healthcare professionals and patients.[73]

*Physical Activity:*

There is very little evidence regarding exercise or physical activity in IBD fatigue. The benefit of exercise on an individual's levels of fatigue was identified in a recent RCT.[74] The pilot study compared exercise advice, dietary advice, dietary supplementation of Omega-3 fatty acids and placebo. It was found that fatigue was considerably reduced in the exercise group.[74] Evidence from the review demonstrates that those who commenced a regular exercise program generally had greater improvement in fatigue scores than those who did not undertake regular exercise.[37] This is supported in the wider literature, were introducing regular exercise was associated with more positive feelings, Improved HRQoL and better functioning by patients with long term conditions, such as cancer or multiple sclerosis.[75–77]

**Limitations:**

There are potential limitations to this work. The use of thematic analysis may be limited by the subjective nature of the reviewer, influencing the repeatability of data analysis. This may introduce an element of inter-observer variability which might limit the reliability of the themes chosen. Thematic analysis may as well be overly reductive and emphasise less important themes. To increase reliability of this work,

the categories and subcategories were reached through discussion with multiple authors.

Multiple databases were searched, and only relevant publications considered. Each publication was discussed by at least two researchers, with a third or fourth being consulted if there were any discrepancies. The outcomes represent an accurate response to the research question. Continuous conversations between authors occurred throughout to ensure a unanimous decision regarding article searches and quality appraisal criteria, thus limiting any potential bias.

The scope of background information collected, disease activity levels, depth of data relating to types and magnitude of fatigue and its effects appears to vary vastly between studies.

**Contribution to knowledge:**

This is the first systematic review considering the impact of IBD fatigue on HRQoL. This review has highlighted the areas of HRQoL identified by individuals with IBD, to be most impacted by IBD fatigue. Uncovering these compounding factors of HRQoL has identified areas for further research and has begun a pathway to better understanding of the patient experience of living with IBD fatigue.

**Clinical Implications:**

The clinical implications of this work include permitting healthcare professionals to better understand the lived patient experience of IBD fatigue. Healthcare professionals will be better able to consider IBD fatigue holistically taking into consideration factors that have be raised throughout this review. Researchers will be

more efficient in designing and conducting targeted research for interventions for both IBD fatigue and IBD related HRQoL.

**Conclusion:**

This work identified the experiences of fatigue were significantly related to three HRQoL linked themes; Symptom acceptance and management, psychosocial wellbeing and management and physical activity. Individuals with IBD fatigue who exhibit better coping and management mechanisms were shown to have higher levels of HRQoL than those with IBD fatigue who adopted maladaptive behaviours. Good social support from friends, family and colleague was found to be important to individuals with IBD fatigue and was shown to meaningfully impact on HRQoL. Findings from the review suggest that patients who are more physical active have higher levels of HRQoL than those who are comparatively sedentary.

This would suggest that a psychosocial and/or exercise intervention for fatigue management would be beneficial. Further exploration of the impact of IBD fatigue on HRQoL is warranted in order to better understand patient experiences. There is a need for prospective long-term studies with serial measures of IBD fatigue alongside other key measures, such as HRQoL, anxiety and depression, physical activity, disease activity and measures of disease burden. Exploring this information would allow better understanding of IBD fatigue. Further work with use of validated fatigue and HRQoL measures, and clearer characterisation of disease activity is needed to define a diagnostic cut off for IBD fatigue that requires an intervention.

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