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Fatigue, pain and faecal incontinence in adult inflammatory bowel disease patients and the unmet need: a national cross-sectional survey

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Abstract

Background and Aims The co-existence of fatigue, pain and faecal incontinence in people with Inflammatory Bowel Disease (IBD) is unknown. We aimed to determine the presence of and relationship between these symptoms and patients' desire for intervention.

Methods Adults with IBD in the UK, recruited from clinics, the national IBD-BioResource, a patient charity and social media sources, completed PROMIS validated patient-reported questionnaires to identify fatigue, pain and faecal incontinence, in addition to symptom severity and impact, disease activity, anxiety and depression questionnaires and questions about their desire for help with these symptoms. Statistical analysis used descriptive statistics to report presence of symptoms and Pearson correlation coefficients were calculated.

Results Of 8486 responses, 54% reported faecal incontinence, 24% reported fatigue, and 21% reported pain; 10% reported all three symptoms in the past 7 days. Only 29% reported none of these symptoms. Fatigue and pain were moderately correlated (Pearson correlation coefficient 0.57); both fatigue and pain had a lower correlation with faecal incontinence (0.43 and 0.46 respectively). On a 0–10 scale for severity, participants scored fatigue highest, followed by incontinence then pain. For impact, participants scored incontinence highest, followed by fatigue then pain. 56% reported depression (27% with clinically relevant levels) and 49% reported anxiety (20% with clinically relevant levels); 23% had previously medically diagnosed mental health disorders. 56% of respondents "definitely" wanted help for fatigue; 53% for incontinence; 42% for pain; 29% "definitely" wanted help with all three symptoms. Factors associated with all three symptoms were Crohn's disease (vs. ulcerative colitis), IBD activity, IBD Control score, anxiety, depression, and history of surgery (all $p \leq 0.0001$).

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Conclusions Fatigue, pain and incontinence are common in IBD and patients desire help for these symptoms, currently a substantial unmet need. Anxiety and depression are common, are underdiagnosed, and are independently associated with these symptoms.

Keywords Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Fatigue, Pain, Faecal incontinence

Background

It is known that many people with IBD experience fatigue, pain or faecal incontinence [1]. Much previous IBD research has, understandably, focused on controlling inflammation. However, resolving inflammation does not always alleviate these symptoms and many people report continuing fatigue, pain, and difficulty with continence when IBD is in remission [2–4].

Patients feel that these symptoms, which limit quality of life and ability to work and socialise, are not taken seriously by health professionals who seldom asked about fatigue, pain or incontinence; even if symptoms are discussed, little professional help is given [5, 6]. Health professionals often report feeling frustrated by patients' fatigue, pain and incontinence, especially if these symptoms do not respond to treatment for active disease [7]. Patients with IBD and clinicians have agreed that fatigue, pain, and incontinence are in the top 10 issues that they want to be addressed by research [8].

While previous studies have reported both prevalence and factors correlating with fatigue, pain and incontinence individually [2, 4, 9], we know little about the presence of multiple symptoms and any correlates, nor how these symptoms cluster together in the same individual or are associated with anxiety and depression. It is evident that having multiple symptoms increases symptom burden and consequent disability [10, 11]. Patients with IBD experience vicious circles of fatigue, pain and incontinence, which they find hard to disentangle, each symptom feeding on the other to perpetuate the symptoms [12, 13]. Previous studies on these symptoms have been small scale, explored a single symptom only, have not used validated measures to detect or measure symptoms, or have studied clinic attenders who are likely to represent a biased sample.

This study aimed to explore symptoms of fatigue, pain, and incontinence in IBD. The research questions were: how many people with IBD report fatigue, pain, and faecal incontinence in IBD?; the size of any associations between symptoms and who is most at risk of one or more symptoms?; do people with IBD want help for these symptoms?

Methods

A cross-sectional self-completed postal or online survey was conducted.

Ethics approval was received from North West - Greater Manchester West Research Ethics Committee (Reference no: 18/NW/0613) on 11th October 2018. The study consent form was incorporated into the postal and online survey. Informed consent to participate was obtained from all participants either in writing (postal) or online before accessing the online version of the survey. The study conformed to the requirements of the Helsinki declaration and the principles of Good Clinical Practice (GCP).

The survey was developed and tested with extensive patient and public involvement and engagement (PPIE) with a panel of 100 patients with IBD, who advised and completed multiple drafts to refine the content, instructions, layout, and readability, attempting to achieve a balance between comprehensiveness and participant burden. The survey was available in English and included the items in Table 1. We used validated measurement tools to define presence in the past seven days of the primary outcomes of fatigue (PROMIS fatigue T-score ≥ 60) [14], pain (PROMIS pain intensity T-score ≥ 60) [14], and faecal incontinence (PROMIS bowel incontinence raw score ≥ 5) [14, 15]. We used the GAD7 questionnaire [39] to measure anxiety and the PHQ9 [40] for depression. The full survey is available in additional file 1.

The target populations were:

- an unselected cohort of adults with IBD who attended one of 18 participating IBD clinics which had a register of all patients with IBD at that clinic recorded on a database, or.
- unselected patient members of the charity Crohn's & Colitis UK (CCUK), or.
- patients with IBD who had previously been recruited to the UK national IBD BioResource register.

Patients were invited to participate, consent and complete the survey remotely through a paper copy sent to their postal address (with return stamped addressed envelope) or through a link to the online version of the survey sent to their email address, or in a text to their phone.

Following the COVID-19 lockdown, as UK hospitals had stopped recruiting to non-COVID studies, additional ethical approval was obtained so that potential participants could also self-select by following an online survey link posted on social media (Twitter and Facebook accounts of CCUK, Bowel Research UK and the study team) and IBD-related websites (such as Crohn's & Colitis UK and the IBD BioResource) from 20 April 2021.

Table 1 Survey questionnaire items (the full survey is available as a PDF in additional file 1)

1. Demographic characteristics
2. IBD disease history, extra-intestinal manifestations of IBD, and lifestyle behaviours (smoking and alcohol use)
3. Co-morbidities (major physical and psychological medically diagnosed illnesses)
4. Current treatment for IBD: prespecified list of medications with an additional free text option
5. Patient Reported Outcomes Measurement Information System (PROMIS) Short Form v1.0 – Fatigue 7a; 7 item validated scale to measure fatigue (14). The score is based on responses to 7 questions: each question with 5 possible responses. The raw score is the sum of the 7 responses, ranges 7–35, and is converted to a T-score based on published tables. PROMIS T-Scores have a **mean of 50 and standard deviation (SD) of 10** in a referent USA general population. For this study, a score of ≥ 60 was the cut off for determining that fatigue was present.
6. PROMIS Scale v1.0 - Pain Intensity 3a; 3 item validated scale to measure pain [14]. The score is based on responses to 3 questions each with 5 possible responses. The raw score is the sum of the 3 responses, range 3–15, and is converted to a T-score based on published tables. The PROMIS T-Score for the average general population is 50 for pain. PROMIS Pain Intensity T-scores up to 55 are considered within normal limits, 55–59 is mild, 60–69 is moderate, and 70 + is severe. For this study a score of ≥ 60 was the cut off for determining that pain was present.
7. PROMIS Scale v1.0 – Gastrointestinal Bowel Incontinence 4a; a validated scale to measure bowel control [15]. The score is based on responses to 4 questions each with 5 possible responses. The raw score is the sum of the 5 responses, range 4–20. The scores are not based on item response theory models, therefore there is no T-score. The raw score is used for analysis. Higher scores indicate increased faecal incontinence.
8. Overall rating of each symptom of fatigue, pain, and faecal incontinence on a 0–10 scale for each of severity and impact (non-validated scale with no time span stipulated to enable comparison of respondents' evaluation of these three symptoms).
9. For each symptom the following question was asked: "If there was help available for IBD-related fatigue, pain or incontinence, would you be interested? There were three response options: definitely, possibly and no.
10. IBD-Control score; a validated 8-item self-reported score to measure disease control from the patient's perspective [34, 35]. The range of scores is 0–16, with 0 indicating worst control and 16 indicating best control.
11. Patient Reported Outcome-2 (PRO 2); 2-item disease activity measure for ulcerative colitis [36] also used for IBD-Unclassified or PRO2; 2-item disease activity measure for Crohn's Disease [37], depending on self-reported disease type.
12. EQ-5D-5 L (Quality of Life measurement); a 5-item standardised measure of health [38]. Possible scores range from 1 (i.e., best health state possible) to -0.594 (i.e., worst possible health state). The EQ-Visual Analogue Score is continuous and ranges from 1-100, with 100 indicating "the best health you can imagine" and 0 indicating "the worst health you can imagine". This score shows the patient's perceived overall health.
13. GAD-7; self-administered patient questionnaire used as a screening tool and severity measure for generalised anxiety disorder [39]. The score is derived from summing the responses to 7 questions, possible range 0–21. A score of 0–4 indicates no anxiety, 5–9 indicates mild anxiety, 10–14 indicates moderate anxiety, and 15–21 indicates severe anxiety. A score of 10 or more is recommended as a cut-off for clinically relevant anxiety [22].
14. PHQ-9; a 9-item measure of depression severity [40]. The total score is the sum of the 9 items and ranges from 0–27. A score of 0–4 indicates no depression, 5–9 indicates mild depression, 10–14 indicates moderate depression, 15–19 indicates moderately severe depression, and 20–27 indicates severe depression. A score of 10 or more is the usual cut-off for clinically relevant depression [23].

Inclusion criteria (self-reported):

- A diagnosis of Crohn's disease, ulcerative colitis, or another type of IBD.
- 18 years old and over.
- Living in England, Scotland or Wales.
- Able to give informed consent.

We planned to approach 12,500 people with IBD, anticipating completed surveys from at least 6,250 participants. This target sample size was based on a power calculation for the numbers needed (680 participants) for a planned Randomised Controlled Trial (RCT) of an online symptom management intervention, which was part of an overall programme of downstream research, which will be reported separately [16].We sent the survey out in batches, until we had recruited the required target of participants needed for the RCT. This resulted in 26,718 invitations being sent to the unselected cohort, more than double our original estimate (with additional recruits via social media posts which reached an unknown number of people with IBD) as we had overestimated both the survey response rate and the proportion which would translate into RCT participants.

Data were entered directly into a REDCap database by the participants via a secure online-based survey website. Paper copies were received by post and entered manually into the database by the study team; 10% of these were double-checked for accuracy. We used mobile phone numbers, age, post codes and surname to detect potential duplicates. In this case the first response was counted as definitive and other responses were deleted. Data were collected, transferred, and stored in accordance with UK Good Clinical Practice (GCP) guidelines, data protection requirements including the UK Data Protection Act (DPA) 2018, General Data Protection Regulation (GDPR) and Information Governance requirements.

Data analysis

The analysis was conducted in Stata version 17. *R* was used for data visualisation. Demographic and clinical characteristics of participants according to disease diagnosis and symptoms were summarised using mean (standard deviation), median (interquartile range) or

percentages as appropriate. Symptom presence was calculated individually and as multiple symptoms.

The relationships between the scores of the PROMIS Pain Intensity, PROMIS Fatigue and PROMIS bowel incontinence score were explored visually and via Pearson's correlation coefficients with confidence intervals (using Fisher's transformation).

We aimed to identify risk factors for presence of each symptom to enable targeting future interventions. Univariate and multiple linear regression analyses were performed to explore the associations between PROMIS symptom scores and (i) IBD Control score, (ii) depression, (iii) anxiety, (iv) history of IBD-related surgery, (v) presence of a stoma or pouch, (vi) biologic medication use, (vii) diagnosis type (CD vs. UC), and (vii) time since diagnosis. The disease activity index (PRO-2) we used for CD includes one of our symptoms (pain), so the relationship between symptoms and disease activity was not a primary analysis.

Linear regression was performed for continuous outcome variables and assumptions were assessed. If heteroskedasticity was observed quantile regression was performed at the 50th and 79th quantiles of the outcome variable's distribution. The 79th quantile was selected as this quantile corresponded to the PROMIS T-score of 60 that was the threshold pre-specified to indicate the presence of pain and fatigue symptoms. Unstandardised regression coefficients are reported. A confounding variable set comprising participant age, gender, physical and mental health condition, pregnancy, body mass index (BMI), employment status, and education level were included in adjusted analyses. The selection of confounding variables was informed by clinical experts in our team and pre-specified in the statistical analysis plan (SAP).

Sensitivity analyses were conducted to assess the effect of missing data on the analysis of PROMIS symptom scores and for the effect of excluding self-selected participants after social media recruitment commenced. Missing data were multiply imputed ($n=20$ iterations) at the item level by multivariate imputation using chained equations.

Results are reported in line with the guideline in The CROSS checklist for reporting survey studies [17]: the completed CROSS checklist is presented in Additional file 2. A detailed SAP was finalised prior to statistical analysis and data access. This SAP can be accessed at https://osf.io/8kdb3/.

Throughout the results, CD is presented compared to all other forms of IBD (i.e., UC and IBD-Unclassified and all other types of IBD), the latter labelled as "ulcerative colitis or UC" for brevity.

Results

The sample

We received 8486 replies (7716 online, 770 postal) after duplicates, incomplete consent and blank replies were excluded. Generally, missing data were low (<5%), except disease activity scores (PRO-2 scores: 15% missing for both CD and UC) and PROMIS incontinence score (10% missing). Full details on missing data are given in Additional file 3 Table S1.

Prior to the first COVID-19 lockdown (22.03.20), 26,718 unselected patients were approached from clinical sites, CCUK or the IBD BioResource, and 6,123 replies were received (23.39%). A further 2363 (self-selected) replies were received from social media recruitment following the onset of the COVID-19 pandemic (not possible to calculate response rate, as the denominator was unknown). Figure 1 illustrates the flow of responses.

CD was reported by 4168 (49.12%) and UC by 4252 (50.11%); 66 (0.76%) did not respond to the question on disease type. Throughout the results where numbers do not add up to 8486, this is due to missing responses on either disease type or the specific question. Table 2 reports key demographic and clinical characteristics for the 8486 respondents by disease type. Further details are given in Additional file 3 Tables S2 and S3. Overall, 57.60% of the sample were female, mean age was 49.77 years, 91.34% were white, 52.70% were overweight or obese, 29.92% had undergone IBD surgery, 6.47% had a current stoma, 2.46% had a pouch and 5.20% had a fistula. 25.98% of CD and 20.37% of UC patients had medically diagnosed mental health diseases.

There were some differences observed between unselected patients recruited from clinical sites, CCUK or the IBD BioResource prior to the COVID19 lockdown, and those recruited from social media subsequently (Additional file 3, Tables S4 and S5). Specifically, participants recruited via social media were more likely to be female, slightly younger, less likely to be White, more likely to possess a higher education, and more likely to be in full-time employment compared with participants who were invited to participate by their clinical team, CCUK, or the IBD BioResource. However, results of sensitivity analyses excluding the self-selected social medial cohort were consistent with results for the overall cohort throughout. Therefore, the two groups are presented together in most analyses.

Presence of fatigue, pain, and faecal incontinence

Faecal incontinence, fatigue, and pain was reported in the past 7 days by 53.76%, 23.99%, and 20.85% of participants, respectively (Table 3; Fig. 2). All three symptoms were reported in the past week by 9.58%. Only 29.01% reported no fatigue, pain, or incontinence in the past seven days. Table 3 provides details of those reporting

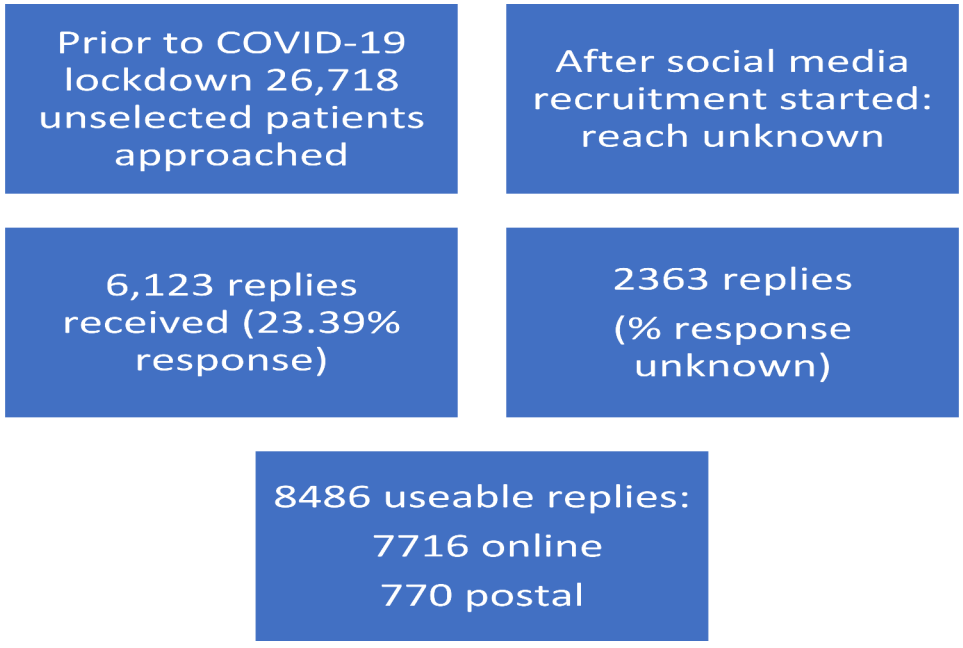

Fig. 1 flow chart of responses to the survey

Table 2 Demographic and clinical characteristics by diagnosis

Characteristic	Crohn's disease (*n* = 4168)		Ulcerative colitis (*n* = 4252)		Total[a] (*n* = 8486)	
Gender, *n* (%)						
Male	1479	(35.48)	1785	(41.98)	3285	(38.71)
Female	2550	(61.18)	2323	(54.63)	4888	(57.60)
Prefer to self-define	6	(0.14)	7	(0.16)	13	(0.15)
Age (years), mean (sd)	48.07	(15.08)	51.37	(15.56)	49.77	(15.43)
Ethnicity, *n* **(%)**						
White	3840	(92.13)	3876	(91.16)	7751	(91.34)
Mixed	60	(1.44)	58	(1.36)	118	(1.39)
Asian	78	(1.87)	130	(3.06)	209	(2.46)
Black	22	(0.53)	13	(0.31)	35	(0.41)
Other	24	(0.58)	27	(0.63)	51	(0.60)
Prefer not to say	7	(0.17)	13	(0.31)	20	(0.24)
BMI (kg/m^2) – mean (sd)	26.80	(5.99)	26.89	(5.79)	26.85	(5.89)
Underweight, *n*(%)	121	(2.90)	73	(1.72)	195	(2.30)
Healthy weight, *n*(%)	1625	(38.99)	1579	(37.14)	3215	(37.89)
Overweight or obese, *n*(%)	2142	(51.39)	2299	(54.07)	4472	(52.70)
Previous IBD surgery, *n***(%)**	2147	(51.40)	388	(9.12)	2539	(29.92)
Current stoma, *n***(%)**	382	(9.17)	166	(3.90)	549	(6.47)
Current pouch, *n***(%)**	73	(1.75)	136	(3.20)	209	(2.46)
Current fistula, *n***(%)**	386	(9.26)	54	(1.27)	443	(5.20)
Medically diagnosed mental health conditions, *n***(%)**	1083	(25.98)	866	(20.37)	1957	(23.06)
Medically diagnosed other physical health conditions, *n***(%)**	15,581	(37.21)	1671	(39.30)	3248	(38.27)
Pregnant, *n***(%)**	37	(0.89)	26	(0.61)	63	(0.74)

[a]Includes 66 further respondents who did not report their IBD disease type. Further details, including summary of missing data, are available in Additional file 3, Tables S2 & S3

Table 3 Symptom reporting presented as number (%) of total participants indicating presence of each symptom and each combination of symptoms in the past 7 days

	Diagnosis				Selection route				Total[a] (*n* = 8486)	
	Crohn's disease (*n* = 4168)		UC (*n* = 4252)		Unselected prior to Covid-19 lockdown (*n* = 6133)		Self-selected after social media recruitment (*n* = 2353)			
Symptom	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
No symptoms	1041	24.98	1415	33.28	1949	31.78	513	21.80	2462	29.01
Pain	1041	24.98	717	16.86	1128	18.39	641	27.24	1769	20.85
Fatigue	1186	28.45	841	19.78	1272	20.74	764	32.47	2036	23.99
Incontinence	2323	55.73	2211	52.00	3198	52.14	1364	57.97	4562	53.76
Pain & fatigue	640	15.36	373	8.77	620	10.11	399	16.96	1019	12.01
Pain & incontinence	780	18.71	564	13.26	854	13.92	499	21.21	1353	15.94
Fatigue & incontinence	830	19.91	596	14.02	892	14.54	541	22.99	1433	16.89
Pain, fatigue, & incontinence	497	11.92	312	7.34	490	7.99	323	13.73	813	9.58
PROMIS Tscore: pain intensity, mean [median] (SD)	51.27 [51.40] (11.29)		48.40 [47.50] (10.86)		48.87 [47.50] (11.04)		52.45 [51.40] (11.08)		49.85 [51.40] (11.17)	
PROMIS Tscore: fatigue, mean [median] (SD)	54.84 [55.10] (8.82)		52.43 [52.20] (8.96)		52.69 [53.70] (8.90)		56.09 [56.40] (8.64)		53.63 [53.70] (8.96)	
PROMIS incontinence, mean [median] (SD)	6.85 [5.00] (3.47)		6.40 [5.00] (3.36)		6.45 [5.00] (3.31)		7.06 [6.00] (3.67)		6.62 [5.00] (3.42)	

[a]Includes 66 respondents who did not provide data on IBD disease type

each symptom and the combination of symptoms by diagnosis (CD vs. UC) and by recruitment route.

Clustering of fatigue, pain and faecal incontinence symptoms

For participants who reported PROMIS scores for all three symptoms (n=7324), overlap between symptoms is presented in Fig. 2; where 9.58% reported all three symptoms.

The correlation between each pair of symptoms is shown in Table 4. IBD-related symptoms were moderately correlated, with the strongest correlation between fatigue and pain.

Severity and impact of symptoms

Participants rated each symptom severity and impact on a 0–10 scale (Table 5). Fatigue was rated a mean of 4.77 (SD 2.67) for severity and 4.71 (SD 3.00) for impact; pain as 3.29 (SD 2.66) for severity and 3.34 (SD 2.91) for impact; faecal incontinence as 4.39 (SD 2.82) for severity and 4.78 (SD 3.22) for impact.

Anxiety and depression

Only 44% reported no depression on the PHQ-9 scale and 51% reported no anxiety on the GAD-7 (Table 6) in the last 2 weeks according to these well-validated measures. Taking the recommended cut-off of a score of 10 or more for clinically relevant scores, 27.17% reported above the threshold for depression and 20.43% above the threshold for clinically relevant anxiety.

Relationship between symptoms and other characteristics

Additional file 3, Table S6 shows the demographic characteristics by symptom. Females were more likely to report each symptom than males.

Additional file 3, Table S7 shows clinical characteristics and PROMIS symptom scores.

Who is at risk of symptoms?

There was very strong evidence of independent associations between PROMIS symptoms scores and several clinical measures while controlling for sociodemographic and medical confounders. After adjusting for age, gender, presence of medically diagnosed physical or mental health conditions, pregnancy, BMI, employment, and education level, PROMIS symptom scores for fatigue, pain intensity, and faecal incontinence were each independently associated with (i) IBD diagnosis (CD>UC), (ii) IBD activity (PRO-2 score), (iii) score on IBD Control, questionnaire (iv) GAD-7 measured anxiety, (v) PHQ-9 measured depression, and (vi) history of surgery (each p=0.0001 or p<0.0001). The only variable tested that was not independently associated with PROMIS symptom scores, after adjusting for the relevant confounders described above, was time since diagnosis for all three symptoms, and the presence of a stoma or fistula for pain (p=0.16).

Do people with IBD want help for symptoms of fatigue, pain and faecal incontinence?

Overall, 28.96% wanted help for all three symptoms and only 26.82% reported not wanting help for any of these three symptoms. Figure 3; Table 7 show the proportion

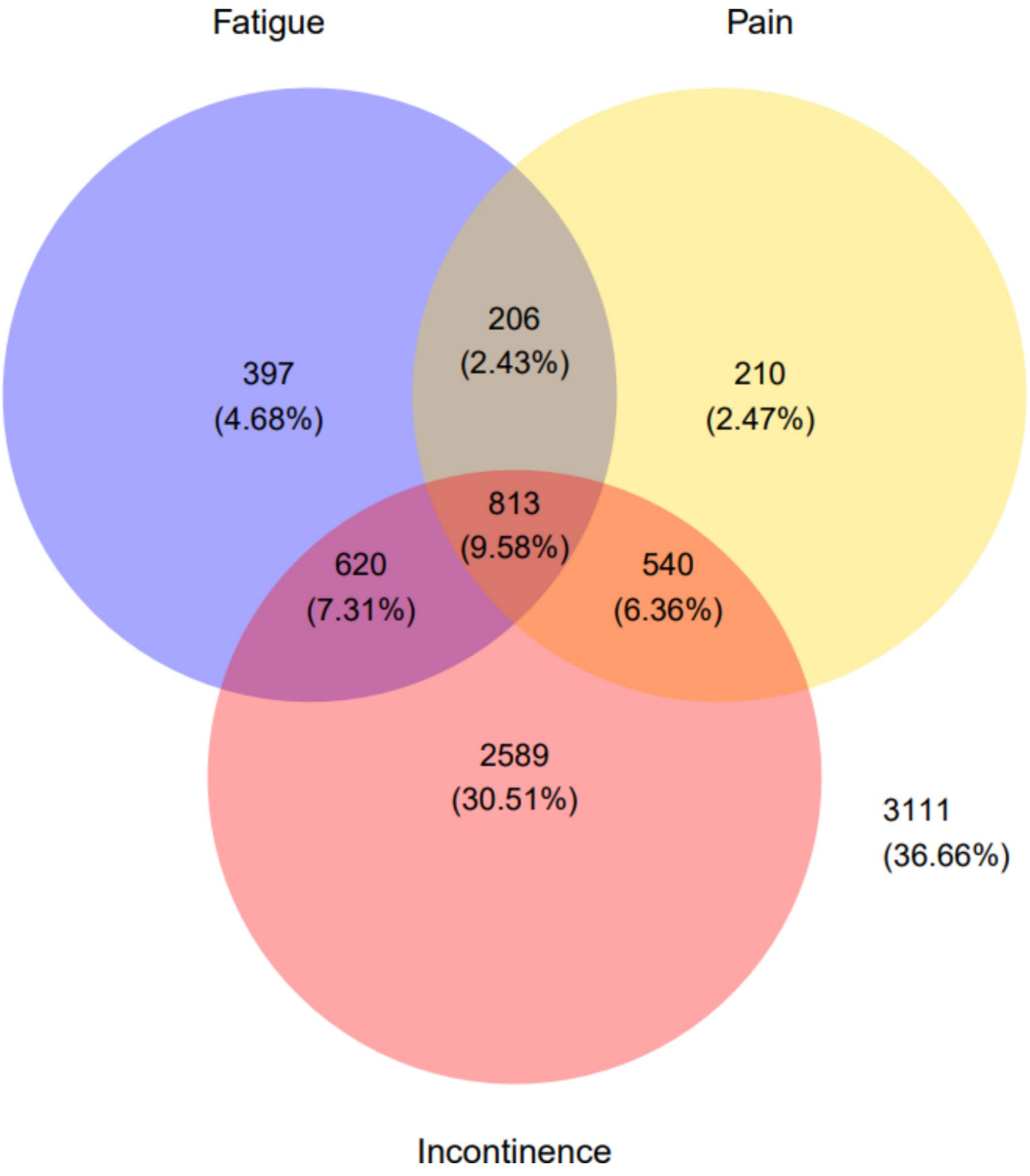

Fig. 2 Co-occurrence of IBD-related symptoms among survey respondents. Frequencies reported within each symptom "circle" of the Venn diagram sum to the frequencies reported in Additional file 3, Table S7 for IBD-related (i) pain ($n=1,769$), (ii) fatigue ($n=2,036$), and (iii) incontinence ($n=4,562$). The integer outside the Venn diagram ($n=3,111$) represents participants (i) reporting no IBD-related symptoms ($n=2,462$) OR (ii) with missing data for at least one IBD-related symptom AND reporting no for other IBD-related symptoms ($n=649$)

Table 4 Pearson's correlation coefficient for each pair of PROMIS symptom scores

Outcomes compared	*N* = 8486 *N* (%) who reported these symptoms	Pearson's correlation coefficient ρ	95% confidence interval
Pain & fatigue	7951 (93.70)	0.56	0.54–0.57
Fatigue & faecal incontinence	7388 (87.06)	0.42	0.40–0.44
Faecal incontinence & pain	7567 (89.17)	0.44	0.42–0.46

Kendall's tau-b correlation coefficient [95%CI] for each pair of PROMIS symptoms scores: Pain & fatigue (tau = 0.44 [0.43–0.45]), fatigue & incontinence (tau = 0.32 [0.31–0.34]), pain & incontinence (tau = 0.35 [0.33–0.37])

Table 5 Self defined symptom severity and impact of symptoms (0–10 scale: 0 = no problem or no impact, 10 = worst imaginable symptom or has a major impact on my life)

Symptom	Severity	Impact
Fatigue, mean (SD)	4.77 (2.67)	4.71 (3.00)
Pain, mean (SD)	3.29 (2.66)	3.34 (2.91)
Faecal incontinence, mean (SD)	4.39 (2.82)	4.78 (3.22)

of respondents reporting that they would be interested in help for each symptom if it was available.

Discussion

Over two thirds of people with IBD in this survey report at least one of the three symptoms of pain, incontinence or fatigue in the last week; over half report incontinence in the last week; and 10% report all three symptoms. This is the largest study to date of fatigue, pain and faecal incontinence in IBD and a particular strength is the use of validated questionnaires. Our survey confirms previous reports that fatigue, pain, and faecal incontinence are highly prevalent in people living with IBD, only 28% reported no symptoms, even when a time span as short as one week is specified. All of these symptoms are much more common than in the general population. This inevitably makes living with IBD difficult, especially alongside the direct effects of inflammation, disease flares, medication regimens and extra-intestinal manifestations.

People report a range of severity and impact of these symptoms, with fatigue and incontinence being particularly troublesome. There is a moderate correlation between fatigue, pain, and faecal incontinence, suggesting that these may be related in some way, possibly with some common underlying mechanisms. One mechanism is undoubtedly disease activity, but this alone may not explain all symptoms and many in apparent remission remain bothered. While in many patients there is clustering of symptoms, in others single symptoms predominate, suggesting that some symptoms may have specific underlying mechanisms and pathophysiologic pathways. In previous qualitative work, people with IBD have described the impact of these symptoms separately [6, 18, 19]. The cumulative impact of multiple symptoms is even greater, with patients describing them as a vicious circle, each making the other more likely [20]. New ways to measure IBD overall symptom burden are being developed [10]. Once multiple symptoms are present, these tend to be stable over time [21], suggesting that for many people symptoms are unlikely to resolve spontaneously.

Many people with IBD also have clinically relevant anxiety and depression. In the current survey the rates were 20.34% and 27.17% respectively. These rates are significantly higher than those in the general population. 5.6% in the general population report clinical depression [22, 23] 5% clinical anxiety [24]. Many more people in the

Table 6 Depression and anxiety reported by IBD diagnosis

Questionnaire responses	Crohn's disease (*n* = 4177)		Ulcerative colitis (*n* = 4255)		Total[a] (*n* = 8486)	
Depression (PHQ-9), *n*(%)	*n*	%	*n*	%	*n*	%
None	1663	39.90	2062	48.49	3741	44.08
Mild	1074	25.77	1047	24.62	2132	25.12
Moderate*	663	15.91	554	13.03	1223	14.41
Moderately severe*	376	9.02	275	6.47	652	7.68
Severe*	250	6.00	178	4.19	431	5.08
Missing	142	3.41	136	3.20	307	3.62
Anxiety (GAD-7), *n*(%)						
None	2032	48.75	2301	54.12	4353	51.30
Mild	1047	25.12	1040	24.46	2097	24.71
Moderate*	536	12.86	423	9.95	962	11.34
Severe*	416	9.98	351	8.25	771	9.09
Missing	137	3.29	137	3.22	303	3.57

*score compatible with a clinical diagnosis of depression or anxiety according to published norms

[a]Includes 66 respondents who did not provide data on IBD disease type

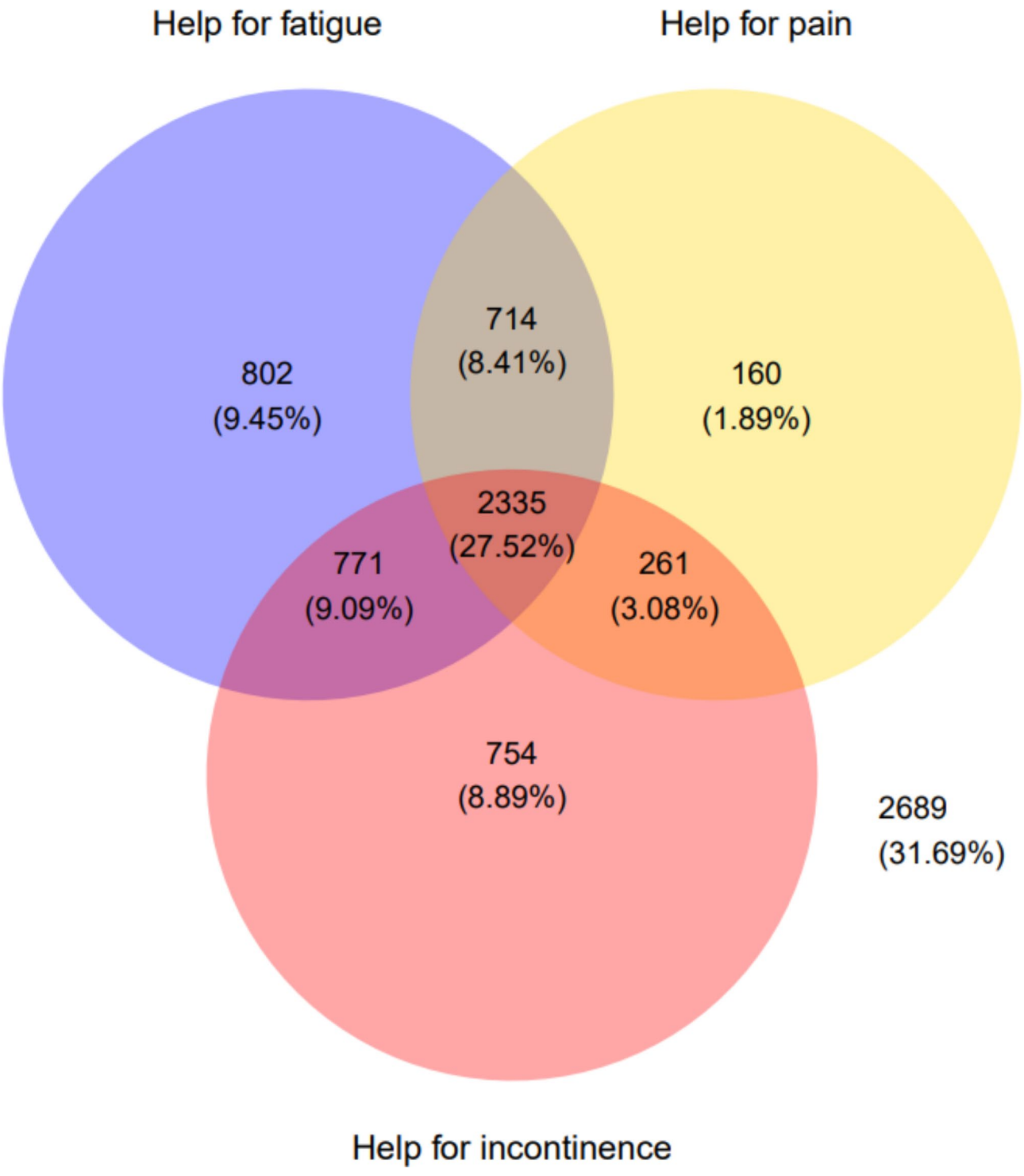

Fig. 3 People reporting wanting help for symptoms. Frequencies reported within each symptom "circle" of the Venn diagram sum to the frequencies reported in Additional file 3, Table S8 for IBD-related (i) pain ($n=3,470$), (ii) fatigue ($n=4,622$), and (iii) incontinence ($n=4,121$). Percentages reported in the Venn diagram do not agree with percentages reported in Additional file 3, Table S8 because a different denominator value is used for each (combination of) IBD-related symptom(s) in Additional file 3, Table S8 whereas the same denominator ($N=8,486$) is used for the Venn diagram. The integer outside the Venn diagram ($n=2,689$) represents participants (i) not wanting help for IBD-related symptoms ($n=2,276$) *OR* (ii) with missing data on wanting help for at least one IBD-related symptom reporting not wanting help for other IBD-related symptoms ($n=413$)

Table 7 Proportion of all respondents desiring help for each symptom or combination of symptoms

	Wants help with symptoms					
	Definitely		Possibly		No	
Symptoms	***n***	**%**	***n***	**%**	***n***	**%**
Fatigue (*n* = 8316)	4622	55.58	2809	33.78	885	10.64
Pain (*n* = 8255)	3470	42.04	3396	41.14	1389	16.83
Incontinence (*n* = 7711)	4121	53.44	2642	34.26	948	12.29
Fatigue & pain * (*n* = 8282)	3049	36.81				
Fatigue & incontinence * (*n* = 7962)	3106	39.01				
Pain & incontinence * (*n* = 8027)	2596	32.34				
Fatigue & pain & incontinence * (*n* = 8062)	2335	28.96				

*answered "definitely" to each of these symptoms

survey reported some degree of distress, with 48.70% reporting above the threshold for mild anxiety and 55.92% for mild depression.

Fatigue, pain and faecal incontinence were all associated with anxiety and depression and while direction of causation is unclear and may well be bi-directional, this represents a considerable total burden of IBD and associated symptoms. While for some the anxiety and depression were mild, this is likely also to represent an unmet need. A systematic review has reported a pooled prevalence of 35% for anxiety symptoms and 21% for anxiety disorders, and 22% for depressive symptoms and 15% for depression disorders in patients with IBD [25]. Depression has been found to be associated with a worse disease course in CD. A recent meta-analysis showed that treating depression significantly reduces inflammation in IBD [26]. Anxiety and depression are also independently associated with clinical recurrence in both CD and UC [27] and they warrant treatment in the interests of tight control of inflammation, as well as in their own right.

Most people were interested in intervention for these symptoms. More respondents reported wanting help for symptoms than reported current symptoms, with nearly one third (29%) definitely wanting help for all three symptoms. This represents a huge unmet need. It also suggests that many more may have experience of these symptoms than report them in the past 7 days, or perhaps anticipate that they may have symptoms for which they will need help in future. This desire for interventions for these symptoms is at present largely unmet by health professionals and health services. However, having a symptom does not always imply that a patient wants something done about it. People have clearly told us that they want options to be available remotely and to try self-management [28]. It is important not just to screen for symptoms but also to determine if the patient wants something done at this point in time and what interventions would be acceptable.

It has been recognised that "treating to target" for psychological wellness, as well as for inflammatory disease control, is an important goal of IBD care [29], but most IBD care remains focused on managing inflammation and active disease. There is a need to develop interventions for psychological wellness and the symptoms of fatigue, pain and incontinence that can be delivered at scale. So far, interventions for IBD-related fatigue, pain and faecal incontinence are limited and many interventions successfully used for these symptoms in other conditions have yet to be tested in people living with IBD. For IBD fatigue, Cochrane reviewers have concluded that the results of interventions are uncertain (14 studies) [30]. For IBD abdominal pain, from a total of 16 RCT studies, Cochrane reviewers were unable to draw firm conclusions or recommendations for clinical practice [31, 32]. For faecal incontinence, almost no interventions are reported (four uncontrolled studies with a total of 34 participants) [2]. Even where interventions for these three symptoms have been reported, access to interventions and success of treatment are highly variable, with particular difficulty accessing psychology-based interventions [29] or specialist dietetic advice in many settings. There are no reports of interventions for multiple symptoms in IBD.

Our findings demonstrate a lower reporting of fatigue, pain and incontinence than reported in some other studies [33]. This is likely to be as a result of specifying a short time frame (past 7 days) and using the validated PROMIS scores, with recognised cut-off points for defining symptoms. However, many of our respondents also had symptoms which did not reach these thresholds and many more are likely to have experienced these symptoms at some point, just not in the past 7 days. Many previous studies on IBD pain or fatigue did not use a validated pain or fatigue score, but have measured fatigue or pain using a single question, often as part of a disease activity score, with no specified time frame.

Strengths and limitations

A major strength of this study is the large sample size and the use of validated measures and a specified time frame to measure symptoms. Previous studies of fatigue, pain, and incontinence in IBD have often been small scale

and many are in clinic populations only, which might be biased towards more severe disease. Many have used single non-validated questions to detect symptoms.

There is no escaping bias in response to a self-completed survey. We recognise that people with symptoms might be more likely to respond to the survey. However, in the unselected group with a 23% response rate, even in the unlikely scenario of all non-responders having no symptoms, there is still a huge unmet need in the IBD population globally.

Participants self-reported their IBD diagnosis, disease activity and their clinical details. It can be assumed that people recruited via clinical sites or the IBD BioResource have confirmed IBD, but those recruited via patient charities and social media may not have verified IBD. Our remote survey did not allow objective assessment of disease activity (faecal calprotectin tests would have been prohibitively expensive in a sample of this size), so data assessing interactions with objective disease activity were not possible. It was not therefore feasible to assess the burden of these symptoms in patients in remission compared with active disease. Arguably, defining remission requires more than markers such as faecal calprotectin (such as endoscopy and histology) and would not be possible in a survey on this scale.

We conducted sensitivity analyses using multiple imputation to assess the effect of missing data on results for PROMIS symptom scores, participants wanting support for each symptom and for effect of imputed data on correlation coefficients between pairs of symptoms. Results for imputed and non-imputed analyses were very similar, demonstrating robustness of primary analysis results to the presence of missing data.

Our questionnaire asked about a snapshot of symptoms experienced in the past 7 days only. It is possible that more people had experienced these symptoms in a longer timeframe. Some of our survey responses were received during the COVID-19 pandemic and lockdowns. This may have had an influence on response rate and responses, for instance increasing or decreasing symptoms. People with IBD were advised to "shield" in the UK and anxiety about the pandemic may have affected some responses, for instance anxiety may influence pain perception. Conversely, proximity to a toilet at home and not needing to commute to work may have influenced faecal incontinence rates.

Conclusions

Symptoms of fatigue, pain and incontinence are common in IBD, impact highly on quality of life, and patients desire help with managing these symptoms. Anxiety and depression are reported commonly according to validated questionnaires, much more so than patients reporting medically diagnosed mental health conditions, suggesting that depression and anxiety are underdiagnosed and undertreated in the IBD population. The symptoms of fatigue, pain and incontinence were independently associated with anxiety and depression, again suggesting the importance of identifying and treating these mental health disorders. Clustering of these symptoms occurs, but also some patients are troubled by single symptoms, highlighting the need for bespoke strategies to identify and address symptoms.

Abbreviations

CD	Crohn's disease
GAD	Generalised Anxiety Disorder
IBD	Inflammatory Bowel Disease
PHQ	Patient Health Questionnaire
PROMIS	Patient Reported Outcomes Measurement Information System
UC	Ulcerative colitis

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Author contributions

AH, CN, SS, RP, QA, WCD, LD and RMM: conception and design of the study and obtained funding. LM, VW, IS and CN acquired the data.FCB, TH, BM and CR contributed to the analysis of data. All authors contributed to interpretation of the data. CN, AH, FCB and TH drafted the article.All authors critically revised the article for important intellectual content and approved the final version submitted.

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Data availability

Access to data is available on reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate

Ethics approval was received from North West - Greater Manchester West Research Ethics Committee (Reference no: 18/NW/0613) on 11th October 2018. Informed consent to participate was obtained from all participants either in writing (postal) or online before accessing the online version of the survey. The study conformed to the requirements of the Helsinki declaration and the principles of Good Clinical Practice (GCP).

Consent for publication

Not applicable.

Competing interests

Ailsa Hart: has served as consultant, advisory board member or speaker for AbbVie, Arena, Atlantic, Bristol-Myers Squibb, Celgene, Celltrion, Falk, Galapogos, Lilly, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. She also serves on the Global Steering Committee for Genentech.Laura Miller: NoneFionn Cléirigh Büttner: None.Thomas Hamborg:

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References

1. Wilson BS, Lonnfors S, Vermeire S, Greco M, Hommes DW, Bell C et al. The true impact of IBD: a European Crohn's and Ulcerative Colitis patient life impact survey 2010-11. 2012 2012.
2. Proudfoot H, Norton C, Artom M, Didymus E, Kubasiewicz S, Khoshaba K. Systematic review: targets for health interventions for faecal incontinence in inflammatory bowel disease. Scand J Gastroenterol. 2018;53(12):1476–83.
3. Artom M, Czuber-Dochan W, Sturt J, Norton C. Targets for health interventions for inflammatory bowel disease-fatigue. J Crohn's Colitis. 2016;10(7):860–9.
4. Sweeney L, Moss-Morris R, Czuber-Dochan W, Meade L, Chumbley G, Norton C. Systematic review: psychosocial factors associated with pain in inflammatory bowel disease. Aliment Pharmacol Ther. 2018;47:715–29.
5. Norton C, Dibley L. Help-seeking for fecal incontinence in people with inflammatory bowel disease. J Wound Ostomy Cont Nurs. 2013;40(6):631–8.
6. Sweeney LH, Moss-Morris R, Czuber-Dochan W, Belotti L, Kabeli Z, Norton C. It's about willpower in the end. You've got to keep going: a qualitative study exploring the experience of pain in inflammatory bowel disease. Br J Pain. 2019;13(4):201–13. https://doi.org/10.1177/2049463719844539.
7. Czuber-Dochan W, Norton C, Bredin F, Darvell M, Nathan I, Terry H. Healthcare professionals' perceptions of fatigue experienced by people with IBD. J Crohn's Colitis. 2014. https://doi.org/10.1016/j.crohns.2014.01.004.
8. Hart A, Lomer MC, Verjee A, Kemp K, Faiz O, Daly A, et al. What are the top 10 research priorities in the treatment of inflammatory bowel disease? A priority setting partnership with the James Lind Alliance? J Crohn's Colitis. 2017;11(2):204–11. https://doi.org/10.1093/ecco-jcc/jjw144.
9. Artom M, Czuber-Dochan W, Sturt J, Murrells T, Norton C. The contribution of clinical and psychosocial factors in inflammatory bowel disease-fatigue: a cross-sectional study. Aliment Pharmacol Ther. 2016. https://doi.org/10.1111/apt.13870.
10. Tadbiri S, Nachury M, Bouhnik Y, Serrero M, Hebuterne X, Roblin X, et al. The IBD-disk is a reliable tool to assess the daily-life burden of patinets with inflammatory bowel disease. J Crohn's Colitis. 2021. https://doi.org/10.1093/ecco-jcc/jjaa244.
11. Farrell D, McCarthy G, Savage E. Self-reported symptom burden in individiuals with inflammatory bowel disease. J Crohn's Colitis. 2016. https://doi.org/10.1093/eeco-jcc/jjv218.
12. Dibley L, Khoshaba B, Artom M, Van Loo V, Sweeney L, Syred J, et al. Patient strategies for managing the vicious cycle of fatigue, pain and urgency in inflammatory bowel disease: impact, planning and support. Dig Dis Sci. 2021;3330–42. https://doi.org/10.1007/s10620-020-06698-1.
13. Fawson S, Dibley L, Smith K, Batista J, Artom M, Windgassen S, et al. Developing an online programme for self-management of fatigue, pain and urgency in inflammatory bowel disease: patients' needs and wants Digestive. Dis Sci. 2021. https://doi.org/10.1007/s10620-021-07109-9.
14. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The patient-reported outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol. 2010;63(11):1179–94.
15. Spiegel BM, Hays RD, Bolus R et al. Development of the NIH patient-reported outcomes measurement information system (PROMIS) gastrointestinal symptom scales. Am J Gastroenterol. 2014;109:1804-14.
16. Norton C, Syred J, Kerry S, Artom M, Sweeney L, Hart A, et al. Supported online self-management versus care as usual for symptoms of fatigue, pain and urgency/incontinence in adults with inflammatory bowel disease (IBD-BOOST): study protocol for a randomised controlled trial. Trials. 2021;22. https://doi.org/10.1186/s13063-021-05466-4).
17. Sharma A, Duc N, Thang T, Nam N, Ng SC, Abbbs K, et al. A consensus-based checklist for reporting of survey studies (CROSS). J Gen Intern Med. 2021;36(10):3179–87.
18. Czuber-Dochan W, Dibley L, Terry H, Ream E, Norton C. The experience of fatigue in people with inflammatory bowel disease: an exploratory study. J Adv Nurs. 2012. https://doi.org/10.1111/jan.12060.
19. Dibley L, Norton C. Experience of fecal incontinence in people with inflammatory bowel disease: self-reported experiences among a community sample. Inflamm Bowel Dis. 2013;19(7):1450–62.
20. Dibley L, Khoshaba B, Artom M, Van Loo V, Sweeney L, Syred J, et al. Patient strategies for managing the vicious cycle of fatigue, Pain and Urgency in Inflammatory Bowel Disease: Impact, Planning and Support. Dig Dis Sci. 2021;66(10):3330–42.
21. Conley S, Jeon S, Procter D, Sandler RS, Redeker NS. Longitudinal changes in symptom cluster membership in inflammatory bowel disease. J Nurs Scholarsh. 2018;50(5):473–81.
22. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. Can Med Assoc J. 2012;184(3):E191–6.
23. Kocalevent R-D, Hinz A, Brähler E. Standardization of the depression screener Patient Health Questionnaire (PHQ-9) in the general population. Gen Hosp Psychiatry. 2013;35:551–5.
24. Lowe B, Decker O, Muller S, Brahler E, Schellberg D, Herzog W, et al. Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the General Population. Med Care. 2008;46(3):266–74.
25. Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with inflammatory bowel disease: a systematic review. J Psychosom Res. 2016;87:70–80.
26. Seaton N, Hudson J, Harding S, Norton S, Mondelli V, Jones ASK et al. Do interventions for mood improve inflammatory biomarkers in inflammatory bowel disease? a systematic review and meta-analysis. EBioMedicine. 2024;100:104910. https://doi.org/10.1016/j.ebiom.2023.104910.
27. Mikocka-Walus A, Pittet V, Rossel J-B, von Kanel R. Symptoms of depression and anxiety are independently associated with clinial recurrence of inflammatory bowel diesase. Clin Gastrenterology Hepatol. 2016;14:829–35.
28. Fawson S, Dibley L, Smith K, Batista J, Artom M, Windgassen S, et al. Developing an online program for self-management of fatigue, Pain, and urgency in inflammatory bowel disease: patients' needs and wants. Dig Dis Sci. 2022;67(7):2813–26.

29. Keefer L, Bedell A, Norton C, Hart A. How should pain, fatigue and emotional wellness be incorporated into treatment goals for optimal managment of inflammatory bowel disease? Gastroenterology. 2022;162:1439–51.
30. Farrell D, Artom M, Czuber-Dochan W, Jelsness-Jorgensen L-P, Norton C, Savage E. Interventions for fatigue in inflammatory bowel disease (Cochrane review). Cochrane Database of Systematic Reviews. 2020(issue 4. Art CD012005):https://doi.org/10.1002/14651858.CD012005.pub2
31. Sinopoulou V, Gordon M, Akobeng AK, Gasparetto M, Sammaan M, Vasiliou J, et al. Interventions for the management of abdominal pain in Crohn's disease and inflammatory bowel disease (Review). Cochrane Database Syst Reviews. 2021;CD13531(11). https://doi.org/10.1002/14651848.
32. Sinopoulou V, Gordon M, Dovey TM, Akobeng AK. Interventions for the management of abdominal pain in ulcerative colitis (review). Cochrane Database Syst Reviews. 2021;CD013589(7). https://doi.org/10.1002/14651858.CD013589.pub2.
33. Blackwell J, Saxena S, Jayasooriya N, Bottle A, Petersen I, Hotopf M et al. Prevalence and duration of gastrointestinal symptoms before diagnosis of inflammatory bowel Disease and predictors of timely specialist review: a population-based study. J Crohns Colitis. 2020.
34. Bodger K, Ormerod C, Shackcloth D, Harrison M, IBD Control Collaborative. Development and validation of a rapid, generic measure of disease control from the patient's perspective: the IBD-control questionnaire. Gut. 2014;63:1092–102.
35. de Jong ME, Taal E, Thomas PWA, Römkens TEH, Jansen JM, West RL, et al. Cross-cultural translation and validation of the IBD-control questionnaire in the Netherlands: a patient-reported outcome measure in inflammatory bowel disease. Scand J Gastroenterol. 2021;56(2):155–61. https://doi.org/10.1080/00365521.2020.1857430.
36. Jairath V, Khanna R, Zou GY et al. Development of interim patient-reported outcome measures for the assessment of ulcerative colitis disease activity in clinical trials. Aliment Pharmacol Ther. 2015;42:1200–10.
37. Khanna R, Zou G, D'Haens G et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Aliment Pharmacol Ther. 2015;41:77–86.
38. Herdman M, Gudex C, Lloyd A, et al, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727–36.
39. Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–7.
40. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9 - validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.

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