

Exploring the Role of Brain Fog, Fatigue, and Psychological Distress on Quality of Life in Individuals Living with Inflammatory Bowel Disease: A Cross-sectional Study

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ABSTRACT

Background & Aims: Despite reports of brain fog in patients with inflammatory bowel disease (IBD), empirical research into this phenomenon has been lacking. This study aimed to validate a brain fog scale and explore the relationships between IBD symptom activity, brain fog, fatigue, psychological distress, and quality of life (QoL).

Method: A cross-sectional online study.

Results: Of the 170 adults with IBD (mean age 38.75 years, 85.9% female, 62.35% Crohn's disease), 94.10% percent reported experiencing brain fog, with the majority (53.75%) experiencing brain fog at least 2 times a week, with each episode lasting around 2 hours. A confirmatory factor analysis supported the first hypothesis, demonstrating validity and stability of the brain fog scale in an IBD sample. Correlation analyses supported the second hypothesis, revealing positive relationships between IBD symptom activity and brain fog, fatigue and psychological distress, and a negative relationship between IBD symptom activity and QoL. A structural equation model with excellent fit (CMIN/df=1.84, $p=0.137$, TLI=0.98, CFI=0.99, SRMR=0.03, and RMSEA=0.07), provided support for the third hypothesis in that the relationship between IBD symptom activity and QoL was fully mediated by brain fog, fatigue, and psychological distress.

Conclusions: This is the first study to explore the lived experience of brain fog and to validate the brain fog scale in an IBD sample. The study provides evidence that like fatigue, brain fog is not only common in IBD cohorts but is also frequent and adversely impacts psychological distress and QoL.

Key words: IBD – inflammatory bowel disease – brain fog – fatigue – psychological distress – quality of life.

Abbreviations: BFASS: Brain Fog Assessment and Severity Scale; CD: Crohn's disease; CFA: confirmatory factor analysis; CFI: Comparative Fit Index; DASS-21: Depression Anxiety and Stress Scale-21; FSI: Fatigue Symptom Inventory; HTMT: High-Trait Mono Trait; IBD: inflammatory bowel disease; PRO3-CD: Patient-Reported Outcome for CD; PRO2-UC: Patient-Reported Outcome for ulcerative colitis; QoL: quality of life; RMSEA: Root Mean Squared Error of Approximation; SRMR: Standardised Root Mean Square Residual; TLI: Tucker-Lewis Index; UC: ulcerative colitis; WHOQOL-Bref: World Health Organisation brief QoL Questionnaire.

INTRODUCTION

Inflammatory bowel disease (IBD) refers to a chronic and progressive inflammatory disease of the gastrointestinal tract and includes both ulcerative colitis (UC) and Crohn's disease (CD). Although the causes of IBD are not known, IBD is thought to arise from a combination of environmental, microbial, immunological, and genetic factors [1]. Symptoms include

severe abdominal pain, frequent bloody diarrhea, weight loss and fatigue [2]. It is estimated that around 6.8 million individuals worldwide currently live with IBD [3], with prevalence rates predicted to almost double and reach 1.0% in Western regions by 2030 [4].

Due to the severity and relapsing/remitting nature of symptoms, IBD is associated with significant psychosocial impairment and requires consistent management and treatment [5]. Multiple systematic reviews have highlighted the high prevalence of psychological distress (e.g., anxiety, depression) in IBD cohorts [6-10], with a recent systematic review by Dubinsky et al. [7] reporting the pooled prevalence of anxiety and depression to be 32.1% and 25.2%, respectively, with rates significantly higher in active versus remission disease

states (anxiety: 57.6% versus 38.1%; depression: 38.9% versus 24.2%).

Research has also highlighted the significant impact of IBD on perceived quality of life (QoL). A systematic review and meta-analysis by Knowles et al. [11] found those living with IBD had reduced mental and physical QoL relative to healthy individuals, and rates of mental and physical QoL were significantly lower in those reporting active versus remission disease states. Reflecting the high physical and psychological burden of IBD, multiple studies have also provided evidence that greater IBD symptoms were associated with increased psychological distress (anxiety, depression, stress), and lower QoL [12, 13-16].

In addition to the impact IBD has on psychological well-being and QoL, growing evidence indicates fatigue is common in IBD cohorts, and is also associated with adverse outcomes [17-19]. A recent systematic review and meta-analysis by D'Silva et al. [20], for example, found that the prevalence rate of fatigue in IBD cohorts was 47%, with fatigue significantly higher in active versus remission disease states (72% versus 47%). IBD related fatigue has also been linked to increased psychological distress and poorer QoL [21-23].

Along with fatigue, in recent years there has been growing recognition of the potential adverse impact of inflammatory conditions on cognitive functioning [24-29]. A recent systematic review and meta-analysis of 12 studies [25] found greater deficits in overall executive function (including working memory and attention) in those living with IBD compared to healthy controls. Attention-based deficits were also found to be more severe in complex tasks requiring a greater degree of executive function. These studies thus indicate a range of cognitive impairments in IBD cohorts that warrant further exploration.

One form of cognitive impairment anecdotally reported in IBD cohorts is brain fog, yet due to the absence of a dedicated brain fog scale, understanding of the phenomenology of brain fog, including its relationships to disease symptom severity, fatigue, psychological distress, and QoL in IBD cohorts is lacking. In recognition of the perceived and reported cognitive impairments associated with coeliac disease [28, 29], Knowles et al. [30] undertook a series of studies involving individuals living with coeliac disease to develop and validate a brain fog scale. The subsequent scale, the Brain Fog Assessment and Severity Scale (BFASS; referred to as the 'brain fog scale') consists of 12-items with two subscales, the first assessing perceived cognitive impairment (e.g., difficulty thinking, feeling mentally slow) and the second assessing Somatic and affective experiences (e.g., feeling lost, feeling detached). The brain fog scale demonstrated strong psychometric properties (including construct and test-retest reliability), and the authors have called on researchers to validate the scale in other inflammatory conditions including IBD. Further research is also needed to explore the potential overlap between brain fog and fatigue, and how they may influence psychological distress and QoL in those living with IBD.

Given this, the aims of the current study are to therefore: (1) explore the phenomenology of brain fog and conduct a confirmatory factor analysis (CFA) to validate the original coeliac-based factor structure of the brain fog scale in an IBD

cohort; (2) explore the relationships between IBD symptom activity, brain fog, fatigue, psychological distress, and QoL; and (3) explore the potential mediating roles of brain fog, fatigue and psychological distress on the relationship between IBD symptom activity and QoL. It was hypothesised that: (1) the brain fog scale will demonstrate a valid factor structure; (2) IBD symptom severity will be positively associated with brain fog, fatigue, psychological distress, and negatively related to QoL; and (3) brain fog, fatigue, and psychological distress will mediate the relationship between IBD symptom activity and QoL.

METHODS

Participants were recruited via online advertising circulated to members of Crohn's and Colitis Australia (CCA) and Australian social media (e.g., Australian IBD Facebook groups). The advertisement included a link to the online survey which was administered via Qualtrics. Inclusion criteria for the study were: (1) having a diagnosis of IBD by a medical professional, (2) being 18 years or older, and (3) not currently infected by COVID-19. After reviewing the participant information sheet and consent form, participants were asked to complete the anonymous online questionnaire which included the following measures. Ethical approval to conduct this study was obtained from the Human Research Ethics committee of Swinburne University of Technology (Ethics approval number: 20237107-14228).

Disease Activity Assessment

Crohn's disease symptom activity was measured using the Patient-Reported Outcome for CD (PRO3-CD) [31]. Derived from the Crohn's Disease Activity Index (CDAI), the PRO3-CD is based on summing 3 items (with score weighting in brackets): loose bowel movements (number of liquid or very soft stools; x2), abdominal pain (0=none, 1=mild, 2=moderate, 3=severe; x5), and general well-being (0=very well, 1=slightly below par, 2=3=very poor, 4=terrible; x7). Higher scores indicate greater disease symptom severity, with remission criteria defined as mean daily stool frequency ≤ 1.5 , abdominal pain score ≤ 1 , and general well-being score ≤ 1 .

Colitis symptom severity was measured using the Patient-Reported Outcome for UC (PRO2-UC) [32]. The PRO2-UC is based on summing 2 items (with score weighting in brackets): stool frequency (normal [+0], 1-2 stools per day more than normal [+1], 3-4 stools per day more than normal [+2], >4 stools per day more than normal [+3]) and rectal bleeding none [+0], visible blood with stool less than half the time [+1], visible blood with stool half of the time or more [+2], passing blood alone [+3]). Higher scores indicate greater disease symptom severity, with remission criteria defined as rectal bleeding = 0 and absolute stool frequency ≤ 2 .

To allow direct comparison across the two different disease severity scales (PRO3-CD and PRO2-UC) and other study variables, a standardised disease severity score ("IBD symptom activity") was created. The IBD symptom activity score was attained by norming each of the PRO3-CD and PRO2-UC scores (e.g., for those with CD, individual PRO3-CD scores minus mean PRO3-CD score).

Fatigue

Fatigue was measured using the Fatigue Symptom Inventory (FSI)[33]. The FSI consists of 13 items assessing fatigue severity, frequency, and perceived interference in the past week. Fatigue severity was measured using 4 items on an 11-point scale (0 = *Not at all fatigued*; 10 = *As fatigued as I could be*; range 0-40). Frequency was measured based on number of days fatigued in the past week (0-7), as well as the extent they felt fatigued each day (0 = *None of the day*; 10 = *All of the day*). Perceived interference was measured using the remaining 7 items on separate 11-point scales (0 = *No interference*; 10 = *Extreme interference*; range 0-70), assessing the extent participants felt fatigue had interfered with normal daily functions. Scores were summed (range 0-127), with greater scores indicating greater fatigue.

Brain Fog

Brain Fog was measured using the newly developed BFASS [30]. Perceived brain fog severity over the past week was measured using 12 items on a 5-point scale (0 = *Not at all*; 4 = *Extremely*). For the two subscales, cognitive impairment was made up of the first 6 items, while the remaining were items represented somatic and affective experiences. Brain fog scores were based on summing items (total: 0-48; subscales: 0-24), with higher scores indicating greater brain fog symptoms.

Psychological Distress

Psychological distress was measured using the Depression Anxiety and Stress Scale-21(DASS-21)[34]. The DASS-21 consists of 21 items with 7 items assessing three subscales: Depression, Anxiety and Stress. Items are presented on a 4-point Likert scale (0 = *Does not apply*; 3 = *Does apply to me very much or most of the time*), with respondents asked to indicate their experience over the past week. Scores were multiplied by two and then summed for an overall score of mental health (range 0-126). Higher scores indicated a greater level of psychological distress.

Quality of Life

Quality of life was measured using the World Health Organisation brief QoL Questionnaire (WHOQOL-Bref) [35]. The WHOQOL-Bref contains 8 items on a 5-point Likert scale (0 = *very dissatisfied*, 4 = *very satisfied*), with each two items assessing four domains (physical, psychological, social, environmental). Scores were summed (range 0-32), with higher scores indicating better QoL.

Statistical Analyses

Data was analysed using IBM's SPSS and AMOS (version 29) software. Prior to conducting analyses, data was screened for errors, and assumptions relating to linearity, uncorrelatedness and multicollinearity of study variables were met. Descriptive statistics and frequencies were obtained for relevant socio-demographic data and brain fog characteristics. The final sample of 170 participants was sufficient to conduct the AMOS structural equation modelling analyses (ratio of items:participants was 1:14 ratio). A High-Trait Mono Trait (HTMT) [36] value of 0.75 of brain fog and fatigue items indicated that these two variables were related, whilst

importantly demonstrating discriminant validity (i.e., measure different constructs).

The first hypothesis, to confirm the construct validity (i.e., how well participant responses to the scale accurately reflect the proposed two-subscale structure) of the brain fog scale, was assessed by conducting a CFA using AMOS. Confirmation of a valid scale structure was based on the following recommended model fit criteria [37]: Comparative Fit Index (CFI) >0.950, Tucker-Lewis Index (TLI) >0.950, Root Mean Squared Error of Approximation (RMSEA) <0.05, and Standardised Root Mean Square Residual (SRMR) <0.05. For internal reliability, Cronbach's α > 0.70 was defined as acceptable. The second hypothesis was assessed using Pearson's correlations, with a two-tailed test of significance used. Strength of correlation was based on Dancy and Reidy [38]: 0.1-0.3 (weak), 0.4-0.6 (moderate), and 0.7-0.9 (strong). The third hypothesis was tested by developing a model derived using a stepwise approach of adding or removing paths based on theoretical and AMOS reported modification indices. Model fits was based on the previously identified recommended model fit criteria [37].

RESULTS

As shown in Table I, a total of 170 individuals (mean age 38.75 years) diagnosed with IBD by a medical doctor participated in this study. The majority were female (85.9%), diagnosed with CD (62.40%), married or in a defacto relationship (59.4%), worked full time (41.8%) and had either an undergraduate or postgraduate degree (54.4%). On average, participants had been diagnosed with IBD for 10.74 years and had 5.23 IBD-related operations. According to remission defined by the PRO2-UC and PRO3-CD, the majority of participants had an active disease state (58.8%).

Phenomenology of Brain Fog and CFA of the Brain Fog Scale (Hypothesis 1)

As shown in Table II below, 160 (94.1%) participants reported either experiencing brain fog 'right now' or that they do 'but not at this moment', whilst 10 (5.9%) reported not experiencing brain fog. In terms of IBD status, among participants who reported active IBD, 82 (48.2%) reported experiencing brain fog 'right now' and 78 (45.9%) experienced brain fog 'but not right now'. In terms of experiences relating to brain fog, the majority (53.75%) reported experiencing brain fog at least 2 times a week, just under half (49.40%) reported experiencing brain fog just after being diagnosed, 34.47% reported there was no pattern to when they experienced brain fog, and the majority (58.8%) reported that symptoms of brain fog did not reduce at the same time as their gastrointestinal symptoms. On average, the experience of brain fog lasted 2.08 hours, with those with active disease reporting a doubling of the time with brain fog compared to participants in remission (2.61 versus 1.33 hours).

Ninety seven participants (60.6%) reported experiencing chronic fatigue, and just under half (46.7%) reported that they could experience brain fog when not fatigued. Qualitative feedback by participants in relation to causes of brain fog included having IBD, medication side-effects, shiftwork, psychological distress (i.e., anxiety, depression, and/or stress),

Table I. Participant characteristics

	CD (n=106)	UC (n=64)	Total (n=170)
Age ^a mean (standard deviation)	38 (13.02)	40.2 (15.67)	38.75 (13.97)
Gender, n (%)			
Male	17 (16)	7 (10.9)	24 (14.1)
Female	89 (84)	57 (89.1)	146 (85.9)
Marital status, n (%)			
Married/defacto	62 (59.49)	39 (60.94)	101 (59.41)
Widowed	1 (0.9)	1 (1.6)	2 (1.2)
Divorced/separated	6 (5.66)	4 (6.25)	10 (5.88)
Single	32 (30.2)	19 (29.7)	51 (30)
Other	5 (4.7)	1 (1.6)	6 (3.5)
Highest Education Level, n (%)			
Secondary School	11 (10.4)	11 (17.5)	22 (13)
Certificate	12 (11.3)	9 (14.3)	21 (12.4)
Diploma	14 (13.2)	12 (19)	26 (15.4)
Undergraduate degree	35 (33)	11 (17.5)	46 (27.2)
Postgraduate degree	29 (27.4)	17 (27)	46 (27.2)
Other	5 (4.7)	3 (4.8)	89 (4.7)
Employment, n (%)			
Full-time employed	42 (39.6)	29 (45.3)	71 (41.8)
Part-time employed	33 (31.13)	18 (28.13)	51 (30)
Employed (Other)	21 (19.81)	8 (12.5)	29 (17.06)
Retired	6 (5.66)	6 (9.38)	12 (7.06)
Unemployed	4 (3.8)	3 (4.7)	7 (4.10)
IBD Years diagnosed, mean (standard deviation)	11.72 (13.02)	9.13 (8.12)	10.74 (9.41)
No history of surgical operations for IBD ^{+,**}	62 (59)	49 (80.3)	111 (66.9)
IBD disease state ⁺⁺⁺			
Active	76 (69.8)	26 (40.6)	100 (58.8)
Remission	32 (30.2)	38 (59.4)	70 (41.2)

Data is presented as mean (SD) for continuous variables and as n (%) for categorical variables; ^a36 and 4 participants did not report their age or number of surgical operations, respectively; ^{**}9% had 1 operation, while 24.1% had 2 or more operations; ⁺⁺⁺IBD status active/remission was defined according to the PRO3-CD and the PRO2-UC criteria.

tiredness and lack of sleep, fatigue, pain, and diet. In terms of what helped, participants reported a range of strategies including sleep/napping, resting, caffeine, healthy diet, exercise, and keeping busy.

Confirmatory Factor Analysis

As this is the first time where the brain fog scale was used in a non-coeliac disease cohort, a CFA was conducted to confirm construct validity. A CFA using AMOS indicated that the brain fog scale two-factor model demonstrated an excellent fit ($\chi^2(46)=1.49$, $p < 0.02$, TLI= 0.97, CFI=0.98, SRMR=0.05 and RMSEA=0.06). CFA thus demonstrated a valid and stable factor structure of the brain fog scale, and that the scale items correctly allocated to the two-factor subscales, providing support for the first hypothesis.

Table II. Phenomenology and characteristics of brain fog

BF Characteristics	CD	UC	Total
Do you experience brain fog?			
Yes, right now	50 (47.2)	32 (50)	82 (48.2)
Yes, but not at this moment	51 (48.1)	27 (42.2)	78 (45.9)
No	5 (4.7)	5 (7.8)	10 (5.9)
Frequency of brain fog			
Once every 6 months or less	6 (3.75)	4 (2.5)	10 (6.25)
Once every few months	8 (5)	4 (2.5)	12 (7.5)
1-3 times a month	22 (13.75)	17 (10.63)	39 (24.38)
Once a week	8 (5)	5 (3.13)	13 (8.13)
2- 3 times a week	27 (16.88)	15 (9.38)	42 (26.25)
Once a day	30 (18.75)	14 (8.75)	44 (27.5)
Description of brain fog occurrence			
Only before being diagnosed with IBD	2 (2.00%)	1 (1.70%)	3 (1.90%)
Before and after being diagnosed with IBD	41 (40.60%)	26 (44.10%)	67 (41.90%)
Only after being diagnosed with IBD	54 (53.50%)	25 (42.40%)	79 (49.40%)
Other	4 (4.00%)	7 (11.90%)	11 (6.90%)
When experiencing brain fog, does it fluctuate throughout the day?			
Yes	90 (89.1)	48 (81.4)	138 (86.3)
No	11 (10.9)	11 (18.6)	22 (13.8)
When is brain fog most severe? (multiple options applicable)			
Morning	25 (12.14)	9 (4.37)	34 (16.5)
Afternoon	43 (20.87)	25 (12.14)	68 (33.01)
Evening	16 (7.78)	11 (5.34)	27 (13.11)
Night	2 (0.97)	4 (1.94)	6 (2.91)
No Pattern	45 (21.84)	26 (12.62)	71 (34.47)
Does brain fog reduce at the same time as gastrointestinal symptoms?			
Yes	35 (34.7)	19 (32.2)	54 (33.8)
No	60 (59.4)	34 (57.6)	94 (58.8)
Other	6 (5.9)	6 (10.2)	12 (7.5)
How long does brain fog last? (hours)	1.93 (SD=4.06)	2.33 (SD = 4.10)	2.08 (SD = 4.07)
Do you experience chronic fatigue?			
Yes	65 (64.4)	32 (54.2)	97 (60.6)
No	36 (35.6)	27 (45.8)	63 (39.4)
In relation to chronic fatigue and brain fog:			
I can experience brain fog when not fatigued	53 (29.12)	32 (17.58)	85 (46.7)
I only experience brain fog when I am fatigued/Brain fog is a symptom of fatigue	65 (35.71)	32 (17.58)	97 (53.3)
	Active	Remission	Total
Do you experience brain fog?			
Yes, right now	52 (52)	30 (42.9)	82 (48.2)
Yes, but not at this moment	42 (42)	36 (51.4)	78 (45.9)
No	6 (6)	4 (5.7)	10 (5.9)
How long does brain fog last? (hours)	2.61 (SD=4.93)	1.33 (SD=2.16)	2.08 (SD=4.07)

Data is presented as mean (SD) for continuous variables and as n (%) for categorical variables; % is represented as the portion of given answers.

Table III. Descriptive statistics and correlations for IBD symptom activity, QoL, psychological distress, fatigue severity and brain fog

Variable	1.	2.	3.	4.	M (SD)	α
1. IBD symptom activity	-				.30 (1.67)	-
2. Brain fog+	0.36***	-			19.06 (9.76)	.92
3. Fatigue	0.42***	.71***	-		67.32 (27.98)	.96
4. Psychological distress	0.40***	.62***	.48***	-	34.86 (24.09)	.93
5. QoL	-0.46***	-.61***	-.68***	-.60***	18.48 (6.11)	.86

* $p < 0.05$, * $p < 0.01$, *** $p < 0.001$; α = Cronbach's alpha. +Brain fog subscales: cognitive impairment (M=11.37, SD=5.47), somatic and affective experiences (M=7.69, SD=5.27).

Relationships between Study Variables (Hypothesis 2)

As shown in Table III, findings were consistent with the second hypothesis in that IBD symptoms had statistically significant, moderate to strong, positive correlations with brain fog, fatigue, and psychological distress. Also supporting the second hypothesis was the finding that IBD symptoms had statistically significant, moderate, negative correlations with QoL.

Mediation Analyses (Hypothesis 3)

To explore for potential mediation, a structural model was developed based on an iterative approach where nonsignificant paths were removed from a saturated mediation model. Overall, the final model (Fig. 1) had an excellent fit (CMIN/df=1.84, $p=0.137$, TLI=0.98, CFI=0.99, SRMR=0.03, and RMSEA=0.07). The total amount of variance accounted for in each of the variables was 14% of brain fog, 18% of fatigue, 43% of psychological distress, and 56% of QoL. As shown in Fig. 1, the influence of IBD symptoms on QoL was fully mediated via psychological distress, brain fog, and fatigue. Specifically, brain fog was found to partially mediate the relationship between IBD symptoms and psychological distress, which in turn influenced QoL. Fatigue was found to act as a mediator between IBD symptoms and QoL. Brain fog and fatigue were also shown to be highly interrelated.

DISCUSSION

Individuals living with IBD are at risk of psychological distress, fatigue, and poorer QoL [8, 11-16, 20]. Anecdotal evidence also points to the existence of brain fog in IBD;

however, research exploring the experience and severity of brain fog in IBD cohorts is lacking. This study therefore sought to explore the experience of brain fog and confirm the validity of a recently developed brain fog scale [30]. The study also sought to explore the potential overlap between brain fog and fatigue and how their influence psychological distress and QoL.

In relation to the experience of brain fog, this study found that almost all participants reported experiencing brain fog (either 'right now' or in the past), with the majority experiencing brain fog at least 2 times per week. The average length of brain fog episodes was found to be just over 2 hours, with duration increasing for those with active versus remission disease states. These findings are consistent with the original validation study conducted in coeliac disease [30], which found more than 40% of participants reported experiencing brain fog at least once per week, and that brain fog lasted on average, for over an hour.

In relation to chronic fatigue, the current study found around 60% reported experiencing fatigue, with just under half of this group (47%) reported experiencing brain fog when not fatigued. This findings is consistent with the original coeliac brain fog study which found around 54% could experience brain fog when not fatigued [30]. These findings suggest that, like coeliac disease, individuals living with IBD frequently experience brain fog and that it can be perceived as being different from fatigue. This finding is further supported by the HTMT analyses in the current study which demonstrated that while the brain fog and fatigue items were related, it also demonstrated they these scales measure different constructs. Together, these findings suggest that both brain fog and fatigue are related but also distinct phenomena.

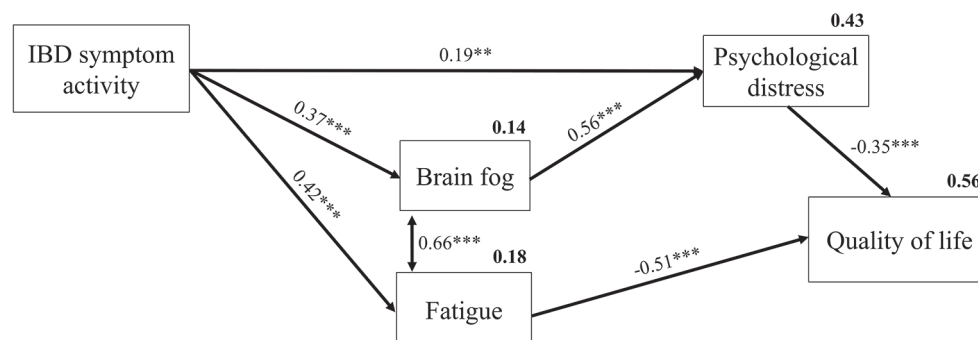


Fig. 1. Final mediation model (** $p < 0.01$, *** $p < 0.001$).

Supporting the first hypothesis was the finding that the CFA confirmed a valid two-factor structure for the brain fog scale in IBD. The brain fog scale was also found to have a strong internal reliability. These findings provide the first successful psychometric validation of the brain fog scale among individuals with IBD. Supporting the second hypothesis was the finding that IBD symptom activity had a significant positive relationship with fatigue, brain fog and psychological distress, and was also negatively related to QoL. These findings were consistent with the original brain fog study [30], and previous research demonstrating the adverse impact of IBD symptom activity on fatigue, psychological distress, and QoL [8, 11-16, 20].

Support was provided for the third hypothesis, in that the relationship between IBD symptoms and QoL was fully mediated by psychological distress, brain fog, and fatigue. Reflecting the likely physical aspects of QoL, fatigue was found to mediate the relationship between IBD symptoms and QoL. While in contrast, the influence of psychological distress on QoL was found to be partially mediated by brain fog. These findings suggest that brain fog has a stronger impact on psychological distress than QoL, while fatigue has a greater impact on QoL.

The potential mechanisms underlying the observed associations between brain fog, fatigue, psychological distress, and QoL are not well understood. As noted by Yelland et al [27], increased circulating cytokines are associated with systemic inflammation, which may contribute to increased brain fog in those living with coeliac disease. Similarly, research has indicated a relationship between IBD related inflammation and cognitive impairment and fatigue [39, 40]. To date, recent reviews IBD and fatigue [40, 41] have proposed multidimensional models of fatigue which highlight the role of inflammation, anemia, muscle mass and physical conditioning, psychological comorbidity and sleep disturbances. These reviews also recognise the growing evidence for the role of microbiome (e.g., changes in bacterial diversity, abundance of pro-inflammatory versus beneficial bacterial populations) and metabolomic processes and central nervous system changes (e.g., branched-chain amino acids, glutamate, dopamine and noradrenaline, grey matter atrophy, cerebral blood flow) in relation to fatigue in IBD [40, 41]. Given the overlap of brain fog and fatigue and their relationship with symptom severity in individuals living with IBD, it suggests that the underlying mechanisms may be similar. Further elucidation of these potential mechanisms, including how they may differ in relation to the underlying processes associated with brain fog and fatigue is an important area of future exploration.

While this was the first study to explore brain fog in an IBD cohort, it is not without limitations. The study's cohort was largely homogenous (e.g., consisting of primarily female participants with Crohn's disease) and therefore limiting generalisability. The use of a cross-sectional design makes it difficult to infer prevalence of brain fog and provide evidence for causal processes and limits the assessment of the temporal dynamics of brain fog in relation to disease activity. Another limitation of this study was the self-reported diagnosis of IBD by a medical professional, as well as the failure to attain biological markers of disease activity. The lack of confirmed diagnosis and biological markers meant that the accuracy of

disease classification and activity in this study could not be ascertained. While disturbed sleep has been found to predict fatigue over time in IBD cohorts [42-44], this was not explored or controlled for in the current study, potentially confounding results. Given its overlap with fatigue, sleep disturbance (in addition to psychological distress) should be controlled for in future studies to enhance the robustness of findings and provide a more comprehensive understanding of the complex interplay between sleep, psychological factors, and fatigue in IBD.

As IBD is both chronic and unpredictable, future research should utilise a longitudinal design to explore the phenomenology of brain fog over time in relation to IBD symptoms. Future studies would benefit from investigating the link between brain fog, fatigue, inflammatory biomarkers of IBD and cognitive impairment. Consistent with the proposed multidimensional mechanisms that may underpin fatigue in IBD [40, 41], future research should seek to assess brain fog and fatigue in relation to biological disease activity in addition to other potential processes, including inflammatory (e.g., cytokine activity), biological (e.g., anaemia, malnutrition), microbiome (e.g., bacterial diversity, abundance of pro-inflammatory versus beneficial bacterial populations), metabolomic processes and central nervous system changes (e.g., branched-chain amino acids, glutamate, dopamine and noradrenaline, grey matter atrophy, cerebral blood flow), muscle mass and physical conditioning, and psychosocial (e.g., psychological distress, coping styles). Finally, further research is needed to explore the performance of the brain fog scale in relation objective cognitive tests, such as Stroop and/or trail making task.

There are several clinical implications of this study. While proven interventions for brain fog are lacking, the importance of identifying and screening for brain fog in individuals living with IBD is recommended. Screening should occur alongside assessments of pain, mental health, perceived disability and control of one's illness and overall QoL [6, 8, 11, 14, 45]. Use of the validated brain fog scale holds promise for improving clinical care by enabling more targeted assessments and interventions aimed at mitigating the impact of brain fog. Understanding the presence and persistence of brain fog should help guide healthcare professionals in providing appropriate support and management strategies to improve patient care and QoL.

CONCLUSION

This is the first study to explore the lived experience of brain fog and to validate the brain fog scale in an IBD sample. The study provides evidence that like fatigue, brain fog is not only common, but also frequently experienced by individuals with IBD. The study also provided evidence that brain fog and fatigue are related but also distinct phenomena. Along with increased disease activity, brain fog and fatigue were adversely related to psychological distress and QoL. Notably, results also reveal the complex interplay among these factors, with brain fog mediating the relationship between IBD symptom activity and psychological distress, and fatigue mediating the relationship between IBD symptom activity and QoL. These

insights highlight the multifaceted nature of IBD management, emphasising the need for holistic care which addresses both physical and psychological aspects of the disease. Finally, further research is required to explore the inflammatory, biological, and psychosocial processes that underpin brain fog and fatigue in order to develop targeted interventions aimed at addressing these common and frequent symptoms experienced by those living with IBD.

Conflicts of interest: None to declare.

Authors' contributions: Both authors contributed to the study conception, design, analyses and drafting, revision and final approval.

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