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Exploring Brain Fog, Fatigue, Psychological Distress and the Impact on Quality of Life for Those Living with Gastroparesis

Grace Draper, Simon R. Knowles

Department of Psychological Sciences, Faculty of Health, Arts and Design, Swinburne University of Technology, Melbourne, Australia.

Address for correspondence:
Assoc. Prof. **Simon R. Knowles**
Swinburne University of Technology, John St, Hawthorn VIC 3122, Melbourne, Australia
sknowles@swin.edu.au
orcid.org/0000-0001-8000-1000

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ABSTRACT

Background & Aims: People living with gastroparesis often report experiencing brain fog yet despite this, this phenomenon is lacking research. This study aimed to address this gap by exploring the relationships between gastroparesis symptoms, brain fog, fatigue, psychological distress, and quality of life (QoL).

Methods: A cross-sectional online study was conducted. Gastroparesis symptoms were measured by the Upper Gastrointestinal Symptom Severity Index. Participants also completed specific questionnaires for brain fog, fatigue, psychological distress and QoL. Pearson's product-moment correlations and Hayes' process mediation macro were used.

Results: Of the total 114 participants (mean age 40.63 years, 87.7% female, 55.3% idiopathic diagnosis) diagnosed with gastroparesis, 97.3% participants reported experiencing brain fog. The majority of participants (46.8%) reported experiencing brain fog at least once a week, lasting 10.42 hours on average. Gastroparesis symptom severity had a significant positive relationship with brain fog, fatigue and psychological distress, and a significant negative relationship with QoL. Fatigue partially mediated the relationship between gastroparesis symptoms and QoL after controlling for psychological distress, such that symptom severity was associated with higher fatigue and lower QoL. Brain fog however was not a significant mediator in this relationship, suggesting that brain fog is not a pathway through which symptom severity decreases QoL.

Conclusions: This study provides evidence that brain fog is common in people living with gastroparesis. Contributing to the burden associated with the condition, gastroparesis adversely impacts experiences of fatigue, brain fog, psychological distress, and QoL, and informs the recommendation that these variables be screened for as part of gastroparesis management

Key words: gastroparesis – brain fog – fatigue – psychological distress – quality of life.

Abbreviations: BFASS: Brain Fog Assessment and Severity Scale (BFASS); DASS-21: Depression, Anxiety and Stress Scale; FSI: Fatigue Symptom Inventory; IBD: inflammatory bowel disease; PAGI-QOL: Quality of Life in Upper Gastrointestinal Disorders; PAGI-SYM: Upper Gastrointestinal Symptom Severity Index; QoL: quality of life.

INTRODUCTION

Affecting around 50.5 per 100,000 individuals, gastroparesis is a gastrointestinal disorder characterised by delayed gastric emptying in the absence of mechanical obstruction, such that ingested food in the stomach is not digested and emptied properly [1, 2]. This can cause symptoms of nausea, postprandial fullness, vomiting, early satiety, bloating, upper abdominal pain and heartburn [1, 3-5]. While this condition is fairly uncommon, the disease burden is high and is associated with significant morbidity and mortality. Jung et al. [6] found that of 222 individuals living with gastroparesis (69.4% female, average age of 51 years at onset), just over 30% required hospitalization, medications, or tube feeding, with another one third dying as a result of the disease or its complications (e.g., infection).

Reflecting the high disease burden of gastroparesis, individuals living with this disease commonly identify as having increased psychological distress and poor quality of life (QoL) [4, 7-15]. Related to psychological distress and QoL, fatigue has been identified as a common experience for those living with gastroparesis [12, 13, 16]. For example, Cherian et

al. [13] found that 93% of individuals living with gastroparesis reported experiencing fatigue, with more than half experiencing severe fatigue levels. Fatigue was also associated with increased symptom severity and depression, and lower QoL.

Although similar to fatigue, brain fog differs in that it is the experience of neurocognitive impairment, often expressed by individuals reporting difficulty focusing, experiencing cloudy thinking and feeling confused [17]. Fatigue is defined more by the experience of tiredness or weariness which can be affected by physical, emotional, and cognitive variables [13]. Anecdotally, brain fog has been reported by individuals with gastroparesis [18]. However, research exploring the prevalence of cognitive symptoms, particularly brain fog in gastrointestinal disorders is limited, with the majority based on individuals living with coeliac and inflammatory bowel disease (IBD). Edwards et al. [19] found that 89% of a cohort of individuals living with coeliac disease reported experiencing neurocognitive impairment symptoms following gluten exposure. Similarly, a meta-analysis of 11 studies found that compared to healthy controls, individuals living with IBD experienced deficits in cognition on domains such as attention, executive functioning, and working memory [20]. In a recent study involving individuals living with a gastrointestinal condition, El Halabi et al. [21] found that 55% reported experiencing brain fog, rates being higher for those with gastroparesis and irritable bowel syndrome.

Until recently, researching brain fog in the context of gastrointestinal disorders has been challenging due to the lack of agreement on a brain fog definition that is distinct from other related constructs like cognitive impairment, depression or fatigue in these cohorts. To resolve this, a 12-item Brain Fog Assessment and Severity Scale (BFASS) was developed and validated in coeliac disease [17]. The BFASS demonstrated strong psychometric properties (including factor structure stability, internal consistency, and construct, temporal and discriminant validity) with brain fog severity being positively associated with increased mental fatigue, mental slowness, psychological distress, and lower QoL. Additionally, in this study, 53.9% of participants who had chronic fatigue reported experiencing brain fog even when they were not fatigued. In a related study, involving 170 participants living with IBD, Knowles and Dickinson [22] found that 53.7% of the participants experiencing brain fog at least twice a week for 2.08 hours on average. Increased IBD symptom severity was associated with more brain fog, fatigue and psychological distress, and poorer QoL. Evaluating these relationships, the effect of symptom severity on QoL was fully mediated via psychological distress, brain fog, and fatigue, where brain fog was observed to partially mediate the relationship between IBD symptoms and psychological distress, which consequently influenced QoL.

Despite the high burden of gastroparesis on individuals, little research has explored the complex inter-relationships among symptom severity, brain fog, fatigue, psychological distress, and QoL in this cohort. Given this, the current study aims to explore the: (1) phenomenology of brain fog in individuals living with gastroparesis, (2) relationships between gastroparesis symptoms, fatigue, brain fog, psychological distress, and QoL, and (3) potential mediating roles of fatigue, brain fog and psychological distress on the relationship between gastroparesis symptoms and QoL. It is hypothesised that: (1) gastroparesis symptoms will be positively associated with brain fog, fatigue, psychological distress, and negatively related to QoL, and that (2) fatigue and brain fog will mediate the relationship between gastroparesis symptoms and QoL after controlling for psychological distress, such that symptom severity will be associated with higher fatigue and brain fog which will in turn be associated with lower QoL.

METHODS

Participants

Participants were recruited through gastroparesis related social media groups (e.g., Facebook and Reddit support groups) and formal education and research organisations (e.g., the International Foundation for Gastrointestinal Disorders and Guts UK Charity). Some participants were also recruited through advertising to previous participants in Simon Knowles' research who consented to being contacted again. Participants were invited to complete a 25-minute online survey via Qualtrics. Inclusion criteria were people over the age of 18 years with a formal diagnosis of gastroparesis from a medical doctor. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The questionnaire and methodology for this study were approved by the Human Research Ethics committee of Swinburne University of Technology (Ethics approval number: 20247752-18414).

Gastroparesis Symptoms

Gastroparesis symptoms were measured by the Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) [23]. PAGI-SYM is a 20-item scale assessing the severity of symptoms (e.g., vomiting/ stomach fullness/ feeling excessively full after meals) in the past two weeks on a 6-point Likert scale (0 = none and 5 = very severe). Ratings were averaged to give a total score (range 0-5), where higher scores indicate increased symptom severity. The PAGI-SYM demonstrated excellent internal consistency ($\alpha = 0.91$).

Brain Fog

Brain fog was measured by the BFASS [17], which is a 12-item scale assessing perceived experiences of brain fog over the past week (e.g., please rate the extent to which these symptoms are affecting you over the past week e.g., difficulty thinking). Items are scored on a five-point severity scale (0 = not at all and 4 = extremely)and the overall score is obtained by summing all individual ratings. Higher scores (range 0-48) indicate greater brain fog is experienced. The BFASS demonstrated excellent internal consistency ($\alpha = 0.90$).

Fatigue

Fatigue was measured by the Fatigue Symptom Inventory (FSI) [24]. FSI is a 14-item scale measuring perceived fatigue severity in the past week (e.g., rate your level of fatigue on the day you felt most fatigued during the past week; 0 = not

at all fatigued and 10 = as fatigued as I could be), along with interference with daily functioning (e.g., rate how much, in the past week, fatigue interfered with your general level of activity; 0 = no interference and 10 = extreme interference), fatigue frequency (e.g., indicate how many days, in the past week, you felt fatigued for any part of the day; 0 to 7 days) and duration (e.g., rate how much of the day, on average, you felt fatigued in the past week: 0 = none of the day and 10 = the entire day). A total score was calculated by summing the 13 items (range 0-127), where higher scores indicate increased fatigue. The FSI demonstrated excellent internal consistency (α = 0.95).

Psychological Distress

Psychological distress was measured by the Depression, Anxiety and Stress Scale (DASS-21) [25]. The DASS-21 is a 21-item scale which measures psychological distress in the last week by assessing symptoms of depression (e.g., I felt that I had nothing to look forward to), anxiety (e.g., I was aware of dryness of my mouth) and stress (e.g., I found it difficult to relax). Items are scored on a 4-point Likert scale (0 = did not apply to me at all and 3 = applied to me very much, or most of the time) and summed to produce a score which is then doubled. Total scores range from 0 to 126, where higher scores indicate higher levels of psychological distress. The DASS-21 demonstrated excellent internal consistency (α = 0.92).

Quality of Life

Quality of life was measured by the Quality of Life in Upper Gastrointestinal Disorders (PAGI-QOL) [26]. PAGI-QOL is a 20-item scale which assesses the impact of gastrointestinal problems on overall QoL and wellbeing in the past week (e.g., have you avoided performing your daily activities?). This scale is scored on a 6-point Likert scale (0 = none of the time and 5 = all of the time), where items were then reverse scored and averaged to give a total score (range 0-5) such that higher scores indicate higher QoL. The PAGI-QOL demonstrated excellent internal consistency (α = 0.92).

Statistical Analyses

Prior to performing the analysis using IBM's SPSS software version 29.0.2.0 (20), the data was screened for errors and missing values. Assumptions related to linearity, uncorrelatedness and multicollinearity for the study variables were met. Initial exploratory analyses to identify potential confounders indicated that age and psychological distress were significantly correlated with QoL and therefore needed to be controlled for. The first hypothesis was evaluated using Pearson's product-moment correlations. Correlation strengths were determined, such that 0.1 - 0.3 indicated a weak correlation, 0.4 – 0.6 moderate, and 0.7 – 0.9 strong [27]. The second hypothesis was assessed using Hayes' process mediation macro (Model 4) [28]. The independent variable (IV) was gastroparesis symptoms, and the dependent variable (DV) was QoL. The two mediators were fatigue (M1) and brain fog (M2).

RESULTS

As described in Table I, a total of 114 individuals (mean age 40.63 years) diagnosed with gastroparesis by a medical doctor participated in the study. The majority were female (87.7%), employed full-time (36%), had either an undergraduate or postgraduate degree (53.5%), and were either single (42.1%) or married (43%). Participants had been diagnosed with gastroparesis for an average of 4.66 years, and the majority of participants believed their gastroparesis was idiopathic (55.3%). Additionally, 105 participants (92.1%) disclosed having other physical and mental conditions that currently impacts their health.

Table I. Participant characteristics

	N = 114
Age, mean	40.63 (SD = 15.18)
Gender, n (%)	
Male	11 (9.6)
Female	100 (87.7)
Third gender (e.g., non-binary)	3 (2.7)
Marital status, n (%)	
Married	50 (43.9)
Defacto	5 (4.4)
Divorced	7 (6.1)
Single	48 (42.1)
Other	4 (3.5)
Highest education level, n (%)	
Primary school	1 (0.9)
Secondary school	13 (11.4)
Certificate	10 (8.8)
Diploma	21 (18.4)
Undergraduate degree	33 (28.9)
Postgraduate degree	28 (24.6)
Other	8 (7.0)
Employment, n (%)	
Full-time employed	41 (36.0)
Part-time/ casually employed	16 (14.0)
Self-employed	6 (5.3)
Pensioner	9 (7.9)
Unemployed	12 (10.5)
Home duties	6 (5.3)
Retired	7 (6.1)
Student	6 (5.3)
Other	11 (9.6)
Mean years diagnosed	4.66 (SD = 5.54)
Self-reported gastroparesis etiology*, n (%)	
Idiopathic	63 (55.3)
Post infection	18 (15.8)
Diabetes I	7 (6.1)
Diabetes II	7 (6.1)
Post-surgical	18 (15.8)
Neurological	6 (5.3)
Connective tissue	17 (14.9)
Medication	13 (11.4)
Comorbidity	26 (22.8)

Table I (continued)	
Food intolerance	9 (7.9)
Unhealthy diet	5 (4.4)
Genetics	3 (2.6)
Psychological	6 (5.3)
Psychological Distress (DASS-21), n (%)	
Normal	58 (50.9%)
Mild to moderate	47 (41.2%)
Severe to very severe	9 (7.9%)

DASS-21: Depression, Anxiety and Stress Scale; SD: standard deviation; *Multiple options can be selected by participants if relevant.

Phenomenology of Brain Fog

As shown in Table II, 111 (97.3%) participants reported either experiencing brain fog 'right now' or that they do 'but not at this moment'. In terms of frequency, half of the participants (46.8%) reported experiencing brain fog at least once a week.

Table II. Characteristics and phenomenology of brain fog

	N (%)
Do you experience brain fog?	
Yes, right now	64 (56.1)
Yes, but not at this moment	47 (41.2)
No	3 (2.6)
Frequency of brain fog	
Less than once every few or more years	22 (19.8)
Once every few or more years	5 (4.5)
Once every year	1 (0.9)
Once every 6 months	4 (3.6)
Once every few months	9 (8.1)
Once a month	4 (3.6)
2-3 times a month	14 (12.6)
Once a week	10 (9.0)
2-3 times a week	23 (20.7)
Once a day	19 (17.1)
Description of brain fog occurrence	
Only before being diagnosed with gastroparesis	1 (0.9)
Before and after being diagnosed with gastroparesis	69 (62.2)
Only after being diagnosed with gastroparesis	34 (30.6)
Other	7 (6.3)
When experiencing brain fog, does it fluctuate throughout the day?	
Yes	105 (94.6)
No	6 (5.4)
When is it most severe?	
Morning	18 (16.2)
Afternoon	22 (19.8)
Evening	9 (8.1)
Night	2 (1.8)
No pattern	60 (54.1)
Does brain fog reduce at the same time as gastrointestinal symptoms?	
Yes	28 (25.2)
No	66 (59.5)
Other	17 (15.3)
How long does brain fog last? (hours)	10.42 (SD = 28.38)
Do you experience chronic fatigue?	
Yes	95 (85.6)
No	16 (14.4)
In relation to chronic fatigue and brain fog:	
I can experience brain fog when not fatigued	65 (68.4)
I only experience brain fog when I am fatigued	30 (31.6)

The majority (85.6%) expressed that their brain fog fluctuates throughout the day, where over half of participants (62.2%) described that their brain fog occurred before and after being diagnosed with gastroparesis. 54.1% reported there was no pattern to when they experienced brain fog and 59.5% of participants reported that brain fog does not reduce at the same time as gastroparesis symptoms. On average, participants experience brain fog episodes lasting for 10.42 hours. A large proportion of participants (85.6%) experience chronic fatigue and more than half (68.4%) can experience brain fog when not fatigued.

Relationships between Study Variables (Hypothesis 1)

The results support the first hypothesis (Table III). Specifically, gastroparesis symptoms had significant positive correlations with brain fog (moderate strength), fatigue (weak strength), and psychological distress (weak strength). Additionally, gastroparesis symptoms had a significant moderate negative correlation with QoL.

Mediation Analyses (Hypothesis 2)

To test the hypothesis that brain fog and fatigue mediate the relationship between gastroparesis symptoms and quality of life, a non-parametric mediation analysis was conducted using the PROCESS v3.3 (Model 4) macro for SPSS [28]. This model used 5,000 bootstrapped samples and percentile-based 95% confidence intervals, where psychological distress was entered as a covariate. Symptom severity was a significant predictor of fatigue ($b = 6.90$, $SE = 2.70$, $p < 0.05$) and brain fog ($b = 4.02$, $SE = 0.78$, $p < 0.05$). Quality of life was significantly predicted by fatigue ($b = -0.01$, $SE = 0.00$, $p < 0.05$) but was not predicted by brain fog ($b = 0.00$, $SE = 0.01$, *ns*). The direct effect of symptom severity on quality of life was significant after including fatigue and brain fog into the model ($b = -0.27$, $SE = 0.07$, $p < 0.05$). There was a significant indirect effect of symptom severity on QoL via fatigue ($b = -0.09$, Boot $SE = 0.04$, 95%CI: -.19, -.03). Together, these analyses suggest that the relationship between symptom severity and QoL is partially mediated by fatigue (Fig. 1).

As shown in Table IV, the indirect effect of symptom severity on QoL via brain fog was not significant, suggesting that brain fog is not a pathway through which symptom severity decreases QoL. An additional mediation analysis was conducted where psychological distress was not included in the model as a covariate to determine if brain fog would then be a significant mediator. In this analysis, brain fog remained as a non-significant mediator, suggesting that it does not work through a similar pathway to fatigue.

Table III. Descriptive statistics and correlations for gastroparesis symptoms, quality of life, psychological distress, fatigue severity and brain fog

Variable		1.	2.	3.	4.	M (SD)
1.	Gastroparesis symptoms	-				2.71 (0.86)
2.	Brain fog	0.55***	-			24.00 (9.32)
3.	Fatigue	0.37***	0.64***	-		77.35 (26.39)
4.	Psychological distress	0.37***	0.62***	0.46***	-	49.56 (25.66)
5.	Quality of life	-0.46***	-0.56***	-0.66***	-0.51***	2.51 (0.73)

SD: standard deviation; ***p < 0.001.

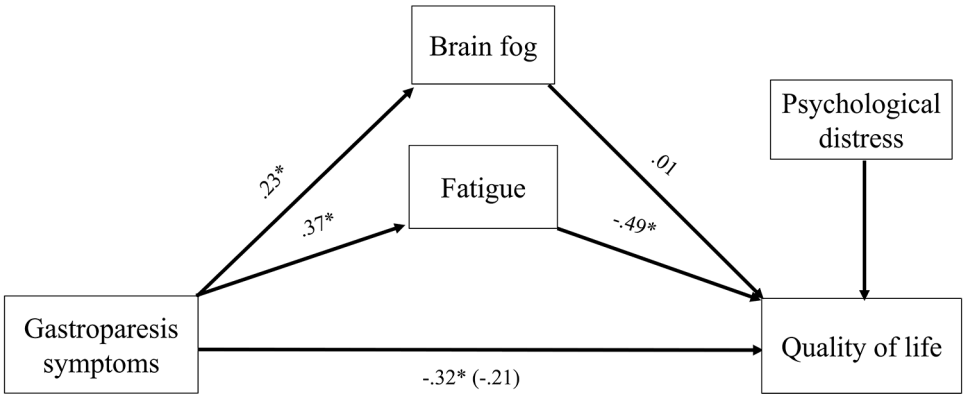

Fig. 1. Standardised regression coefficients for the symptom severity-quality of life mediation model with psychological distress entered as a covariate. * = p < .05. N = 114.

Table IV. Total, direct, and indirect effects in the gastroparesis symptoms-quality of life mediation model after controlling for psychological distress

Path/effect	b	95% CI	SE	β	t	p
Total effect (c): Gastroparesis symptoms → QoL	-0.27	[-0.41, -0.13]	0.07	-0.32	3.82	<.05
Direct effect (c'): Gastroparesis symptoms → QoL	-0.18	[-0.31, -0.04]	0.07	-0.21	-2.62	0.01
[a]Total Indirect effect: Gastroparesis symptoms → QoL*	-0.09	[-0.19, -0.00]	0.04	-0.11	-	-
[a]Indirect effect: Gastroparesis symptoms → Fatigue → QoL*	-0.09	[-0.19, -0.03]	0.04	-0.11	-	-
[a]Indirect effect: Gastroparesis symptoms → Brain fog → QoL*	0.00	[-0.07, 0.09]	0.04	0.00	-	-

QoL: quality of life; CI: confidence interval; [a]coefficient, SE, and 95% confidence interval based on bootstrapped effect estimates. *Indirect effect significant based on 95% confidence interval of bootstrapped effect estimates.

DISCUSSION

Individuals living with gastroparesis experience a high disease burden, which includes experiences such as psychological distress, fatigue and poor QoL [13, 14]. While limited research exists, individuals also anecdotally report experiencing brain fog. Consequently, this study aimed to explore the phenomenology and relationships between gastroparesis symptoms, fatigue, brain fog, psychological distress and QoL.

This study found that almost all participants (97.3%) reported either experiencing brain fog 'right now' or that they do 'but not at this moment'. Approximately half of the participants (46.8%) reported experiencing brain fog at least once a week. Brain fog is not only frequent, but the episodes on average are long, approximately 10.42 hours. These findings suggests that brain fog is both highly prevalent and frequently experienced by people living with gastroparesis. A particularly important finding is that 68.4% of participants experience brain fog when not fatigued, suggesting that these participants perceive brain fog as a different construct to fatigue. This finding is consistent with brain fog studies in the literature, where 47-55% of participants living with gastrointestinal disorders reported experiencing brain fog [17, 21, 22]. These studies found that brain fog frequency was similar to the current study but on average, the brain fog episodes were reported to be shorter, approximately 1-2 hours on average.

The results supported the first hypothesis that gastroparesis symptoms would be positively associated with brain fog, fatigue,

psychological distress, and negatively related to QoL. This result supports previous literature findings and demonstrates the detrimental impact of gastroparesis symptoms on fatigue, psychological distress, and QoL [13, 14].

The results partially supported the second hypothesis that fatigue and brain fog would mediate the relationship between gastroparesis symptoms and QoL after controlling for psychological distress, such that symptom severity will be associated with higher fatigue and brain fog which will in turn be associated with lower QoL. It was found that fatigue partially mediated the relationship between gastroparesis symptoms and QoL after controlling for psychological distress, such that symptom severity was associated with higher fatigue and lower QoL. Brain fog, however was not a significant mediator in this relationship, suggesting that brain fog is not a pathway through which symptom severity decreases QoL. This finding is inconsistent with previous literature in IBD participants that found that brain fog partially mediated the influence of psychological distress on QoL [22]. The current findings may indicate that brain fog is not a pathway through which QoL is influenced by in individuals living with gastroparesis. Instead, there may be other processes responsible, such as psychological distress.

Limitations and future implications

Despite being the first study to empirically evaluate the phenomenology of brain fog in individuals living with gastroparesis and the links between gastroparesis symptoms, fatigue, brain fog, psychological distress, and QoL, it is not without limitations. It is important to recognise that this study was based on a convenience online sample at a single one time point. Therefore, there is a high risk of selection bias (reflected in the 97.3% who identified as experiencing brain fog) and inability to provide evidence of causation. The sample was taken from mostly females, educated and living with idiopathic gastroparesisș therefore, the results of this study are not generalisable. As women tend to report more intense and frequent bodily symptoms than men [29], this gender difference prevents may overestimate the impact of gastroparesis symptoms on fatigue, brain fog, psychological distress, and QoL. Further, due to the online study design, confirmation of diagnosis and not be undertaken. Participants in this study reported complex health states, with 92.1% having other physical and mental conditions. The inability to control for these additional physical and mental conditions may have influenced participants' reported experiences of multidimensional constructs, such as fatigue and brain fog.

In relation to future studies, further work is needed to better understand the true prevalence of brain fog and how it is experienced by those living with gastroparesis. Given the growing evidence regarding the commonality of brain fog and fatigue across gastrointestinal conditions, exploring the potential biopsychosocial factors that underpin them would be important. For example, research has indicated that long COVID and post chemotherapy are both associated with the development of brain fog and fatigue [30, 31] and that these associations are characterised by decreased hippocampal neurogenesis and a loss of myelinated subcortical axons along with elevations in CSF cytokines, neuroinflammation, and microglia activation [32]. Further research exploring these potential mechanistic process underpinning brain fog and fatigue would be important, including how they may differ across inflammatory (e.g., IBD) versus sensory-motor conditions (e.g., gastroparesis), and within known causes of gastroparesis (e.g., post infectious versus diabetes). Longitudinal studies informed by the wider brain-gut research are also required. It is likely that the true processes that underpin, maintain and protect against the expression of brain fog and fatigue will only be understood though longitudinal approaches. Finally, given the known impact of brain fog and fatigues, identifying and evaluating medical and psychological approaches [33, 34] to address these common symptoms would be important.

CONCLUSIONS

To the authors' knowledge this is the first study to empirically evaluate the phenomenology of brain fog in individuals living with gastroparesis and the links between gastroparesis symptoms, fatigue, brain fog, psychological distress, and QoL. The study provides evidence that the majority of participants (46.8%) experience brain fog at least once a week, lasting 10.42 hours on average. Greater gastroparesis symptoms exacerbated fatigue, brain fog, psychological distress, and reduced QoL. After controlling for psychological distress, fatigue, but not brain fog, was found to mediate the relationship between gastroparesis symptoms and QoL. Overall, it is clear that fatigue, brain fog, psychological distress adversely impact QoL in individuals living with gastroparesis, therefore screening for these issues is essential.

Conflicts of interest: None to declare.

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

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