Gastrointestinal Symptoms, Dietary Habits, and the Effect on Health-Related Quality of Life among Australian Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients: A Cross-Sectional Study

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Abstract

Objective: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating condition of unknown aetiology. Gastrointestinal symptoms and dietary sensitivities appear to be implicated in ME/CFS presentation; however, this has not yet been described in Australian patients. Therefore, this study aimed to describe the gastrointestinal symptoms, dietary habits, and food intolerances and the effect of health-related quality of life (HRQoL) among Australian ME/CFS patients.

Methods: Data was collected for this cross-sectional study with an online self-administered questionnaire between February 2019 and January 2020. Patients across Australia were recruited through voluntary response to online advertisements. Eligible participants were subsequently invited to complete the online questionnaire via Lime Survey.

Results: Thirty-eight eligible participants were included in the study and were classified using the Fukuda, Canadian Consensus Criteria, and International Consensus Criteria case definitions. The majority of these patients were female (78.9%), of normal weight (55.3%), unemployed (60.5%), and had obtained an undergraduate level of education (52.6%). A noteworthy finding of this study was that 97.4% of Australian ME/CFS patients experienced gastrointestinal manifestations, with 94.6% of these patients experiencing bloating. Food avoidance was also highly prevalent (89.5%),

with the most avoided food group being refined sugar (73.5%). Food intolerances were experienced by 71.1% of the study population, with gluten or wheat intolerance the most frequently reported (70.4%). The majority of patients had accessed a healthcare professional due to gastrointestinal or dietary concerns (86.8%). Significant associations were observed between HRQoL with gastrointestinal symptoms, food intolerance, and food avoidance; however, no definitive conclusions could be deduced.

Conclusion: Gastrointestinal symptoms were frequently reported by Australian ME/CFS patients in this study and appear to have a noteworthy impact on both daily activities and diet. Dietary modification and food intolerance were also commonly reported. Therefore, it is integral to consider patients' gastrointestinal health and diet in the management of ME/CFS.

Introduction

Myalgic Encephalomyelitis (ME), commonly referred to as Chronic Fatigue Syndrome (CFS), is a debilitating illness estimated to affect between 0.4% and 1.0% of the global population [1] and approximately 0.04% of Australians [2]. Persistent fatigue is the hallmark symptom of ME/CFS [3-8]. Although the debilitating fatigue associated with ME/CFS cannot be explained by exercise, exertion and prolonged periods of standing or sitting with upright posture appear to worsen symptoms [6,7]. This is known as post-exertional neuroimmune exhaustion and may follow physical or mental exertion [6].

The clinical presentation of ME/CFS also involves a variety of systemic symptoms including cognitive disturbances, disturbed and unrefreshing sleep, bodily pain, thermostatic intolerance, and autonomic dysfunction [1,9-11]. The current absence of a laboratory test or clinical biomarker complicates diagnosis [1,9,10,12-14]. As a result, diagnosing the condition is largely dependent on the elimination of other possible medical conditions [1,10]. The most widely-accepted case definitions are the Fukuda criteria [3], Canadian Consensus Criteria (CCC) [4] and International Consensus Criteria (ICC) [5]. The Fukuda definition is broader and less stringent, where a diagnosis of ME/CFS according to the ICC definition is associated with more severe cases of the illness [15].

Gastrointestinal manifestations (including nausea, abdominal pain, and abnormal bowel activity) are commonly reported by ME/CFS patients [16]. As a result, patients are often inclined to alter their diet in an attempt to alleviate their symptoms [16,17]. New dietary sensitivities and food intolerances are also frequently observed among ME/CFS following illness onset [10,16,18-20]. Although several explanations to the gastrointestinal manifestations associated with ME/CFS have been proposed, the pathomechanisms underlying gastrointestinal symptoms in ME/CFS remain unclear [21-25].

There is limited information regarding gastrointestinal symptoms in the Royal Australasian College of Physicians' Clinical Practice Guidelines for Chronic Fatigue Syndrome [26]. Potential gastrointestinal symptoms that may be observed in ME/CFS are restricted to 'altered bowel habits' and 'abdominal pain and bloating' [26]. Thus, the role of gastrointestinal symptoms in the presentation of ME/CFS is not sufficiently highlighted in the clinical guidelines, which also neglect to discuss the commonly-associated gastrointestinal comorbidities associated with ME/

CFS, such as Irritable Bowel Syndrome (IBS) and small intestinal bacterial overgrowth (SIBO) [16,27,28]. As a result, the lack of information regarding gastrointestinal manifestations in the clinical guidelines creates the potential for patients' gastrointestinal symptoms to be overlooked.

With no currently available curative treatments, the disabling, multi-system illness imposes a serious burden on the lives of patients, rendering them unable to perform their normal pre-morbid daily activities [10,29,30]. Australian and international studies have identified that HRQoL is significantly compromised in ME/CFS patients when compared with healthy individuals [31–34]. Dietary modification has been posited to manage ME/CFS symptoms; however, the efficacy of this management strategy remains questionable [16].

The gastrointestinal manifestations and dietary habits of ME/CFS patients have not yet been well-described in the Australian or international patient populations. Therefore, the primary aim of this investigation is to describe the gastrointestinal symptoms, food intolerances, and dietary habits of ME/CFS patients in Australia. Although the prevalence of gastrointestinal manifestations has been examined in Australian ME/CFS patients, specific gastrointestinal symptoms and dietary habits have not been well-described. Therefore, this investigation aims to analyse the prevalence of gastrointestinal symptoms in greater detail than previous Australian studies to ameliorate this gap in the literature. This research will serve to update the current Australian clinical guidelines for ME/CFS and ultimately ensure gastrointestinal symptoms are more readily recognised and treated to improve patient quality of life.

Additionally, this study will also describe the dietary habits and food intolerances among Australian ME/CFS patients for the first time. This study will also contribute to the wider field of ME/CFS knowledge by analysing the relationship between patients' health-related quality of life (HRQoL) with gastrointestinal symptoms, dietary modification, and food intolerance, which has not yet been investigated. It is hoped that this study will elucidate the role of gastrointestinal manifestations and food intolerances in the presentation of ME/CFS to aid in the management of these symptoms and improve patient quality of life. Additionally, it is also hoped that this study will identify potentially beneficial dietary habits worthy of further investigation to develop appropriate dietary recommendations for ME/CFS patients.

Methods

Study design and setting

This investigation employs a cross-sectional study design to enquire into the gastrointestinal symptoms, dietary habits, healthcare access, and HRQoL of ME/CFS patients in Australia over a one-year period from 2019 to 2020. This study serves to collect patient-level data to investigate the role of gastrointestinal manifestations and dietary habits in ME/CFS at the National Centre for Neuroimmunology and Emerging Diseases (NCNED). Participants were recruited based on voluntary response to online advertisements. Eligibility criteria for this study required patients to be: (i) previously diagnosed with ME/CFS by a healthcare professional; (ii) aged between 18 and 65 years; and (iii) a resident of Australia.

Online questionnaire

Respondents to the online advertisements were assessed for

eligibility by completing an online questionnaire via LimeSurvey (LimeSurvey, Carsten, Schmitz, Hamburg, Germany) [35]. This questionnaire was generated by members of the NCNED research team and queried respondents' sociodemographic information and HRQoL. The eligibility questionnaire also investigated respondents' presentation of ME/CFS by employing components of the Fukuda, CCC, and ICC case definitions.

Eligible participants were subsequently invited to complete an online questionnaire that was similarly administered through Lime Survey. The items of this questionnaire were also generated by members of the NCNED research team and included gastrointestinal symptoms, dietary habits, food intolerances, and healthcare access in relation to diet and gastrointestinal manifestations. Following participants' completion of the online questionnaire, participants were anonymised with an alphanumeric code.

Before exporting the results of the questionnaire to SPSS v26 [36] for statistical analysis, participants were screened to omit the results of those who met the study's exclusion criteria. Those with a Body Mass Index (BMI) under 18.5, those with current smoking status, and those having received a diagnosis of Coeliac disease, ulcerative colitis, or Crohn's disease were excluded from the study. Additionally, patients with a pre-existing chronic illness other than ME/CFS (including but not limited to autoimmune diseases, hypothyroidism, and diabetes) were also excluded. Such participants were excluded from this study to reduce the potential for confounding as a result of other clinical conditions. Those under the age of 18 or over the age of 65 were also excluded from the study.

Study variables

Sociodemographic characteristics

Sociodemographic data collected from the survey participants included their (i) gender (male, female, or other), (ii) age, (iii) age of onset, (iv) BMI, (v) location (by Australian state or territory), (vi) current employment (unemployed, part-time, or full-time), and (vii) education. BMI (kg/m^2) was calculated using participants' self-reported height and weight at the time of completing the questionnaire. Participants were then categorised as per the BMI classifications outlined by the World Health Organization [37]: Underweight (<18.5), normal weight (18.5 to 24.9), overweight (25.0 to 29.9), and obese (≥30.0). Education was measured in terms of the highest level of education obtained (primary school, high school, professional training other than university, undergraduate, or postgraduate or doctoral).

Gastrointestinal symptoms

The subsequent component of the questionnaire pertained to participants' gastrointestinal symptoms. The occurrence of gastrointestinal manifestations was reported as either yes or no. Chronic gastrointestinal illnesses that are common co-morbidities associated with ME/CFS, including IBS and SIBO, were also queried. The presence of these conditions was assessed in terms of the diagnosing healthcare professional, comprising a General Practitioner (GP), specialist, allied health professional, or if a self-diagnosis was made. It should be noted that, in this study, 'allied health professionals' refers to dietitians, nutritionists, chemists, and naturopaths. Specific gastrointestinal symptoms were then investigated among the participants reporting gastrointestinal manifestations. The frequency of each symptom was assessed with a four-point scale: Never, multiple times per month, multiple times per week, and multiple times

per day. The impact of gastrointestinal manifestations on the daily life of those participants experiencing gastrointestinal symptoms was also examined using a five-point scale: not at all, a little bit, fairly, quite a bit, and significantly.

Dietary habits

Following gastrointestinal symptomatology, the questionnaire enquired into participants' dietary habits. Participants were required to report if they had changed their diet (yes or no) due to (i) gastrointestinal manifestations or (ii) reasons other than gastrointestinal symptoms. Among those participants who reported changing their diet, the impact of this change was assessed with the same five-point scale used to evaluate the impact of gastrointestinal symptoms as outlined above. Additionally, all participants were asked if a specific diet plan was being followed (yes or no) and, among those participants following a specific diet plan, the type of diet being followed. Similarly, the questionnaire also investigated if certain food groups were being avoided (yes or no) and, among those participants avoiding certain food groups, which food groups were being avoided. Participants were then categorised depending on the length of time for which they had been following a particular diet or avoiding a particular food group as per the following: less than six months, between six months and one year, or greater than one year.

Food intolerances

The prevalence of food intolerances among the study population was also examined, in which participants were required to report if they experienced food intolerances (yes or no). Participants who reported food intolerance were subsequently asked if they were intolerant to a series of food groups (yes or no).

Healthcare access

The final component of the questionnaire assessed participants' healthcare service access regarding diet or gastrointestinal manifestations. Healthcare access was examined on a three-point scale: none, within the last six months, or prior to the last six months. Participants having accessed a healthcare professional within the last six months were subsequently required to provide their frequency of accessing a GP, specialist, allied health professional, or another health professional on a three-point scale: no, one to three times, or four or more times.

Health-related quality of life

Items from the 36-Item Short Form Health Survey (SF-36) [38] were utilised in the online eligibility questionnaire to examine patients' HRQoL. These items employed Likert scales from zero to 100 (in which the scores returned are directly proportional to the study participants' HRQoL) to assess HRQoL across seven domains: (i) physical functioning (PF); (ii) the role of limitations due to physical health problems (RP); (iii) bodily pain (BP); (iv) social functioning (SF); (v) general mental health (MH); (vi) the role of limitations due to emotional problems (RE); and (vii) general health perceptions (GH).

Statistical analysis

This study includes descriptive statistics of the data generated from the aforementioned online questionnaire. Frequency statistics were calculated using SPSS v26 [36]. All data are presented as the number of participants (percentage of total participants) unless stated otherwise. ME/CFS classification data is

provided as the most severe ME/CFS criteria met.

Multiple linear regression analysis was also performed to investigate the relationship of HRQoL with gastrointestinal symptoms, diet, food intolerance, and food avoidance. Regression models were generated for the seven HRQoL domains and were adjusted for age, gender, BMI, education, and employment. The dependent variables used in the forward stepwise procedure included all gastrointestinal symptoms, diet plans, food intolerances, and avoided food groups. Dependent variables were included within the regression model if $P < 0.10$, as per the lowest Akaike Information Criterion. The standardised β, t-value, and P-value for the dependent variables, as well the R^2-value, adjusted R^2-value, and P-value for the regression models, are tabulated below; however, complete statistics (including the unstandardised B (95% confidence intervals) and standard error of B (SE(B))) can be found in the Supplementary Tables provided.

Results

During the one-year study period from February 2019 to January 2020, 150 participants responded to the online advertisements released by the NCNED and were assessed for eligibility. Of these respondents, 40 patients met the inclusion criteria for the study and were invited to complete the online questionnaire. Two patients who had successfully completed the online questionnaire were excluded due to having a diagnosis of Coeliac disease (an exclusion criterion for this study).

Sociodemographic characteristics

The sociodemographic data of the 38 patients that met the study inclusion criteria are outlined in Table 1. All participants had received a formal diagnosis of ME/CFS by a healthcare professional prior to participating in the online questionnaires. Over half of the study population met the ICC case definition (52.6%), 31.6% of patients fulfilled the CCC definition and 15.8% met the Fukuda criteria. Most of the study participants were female (78.9%), of normal weight (55.3%), unemployed (60.5%), and had obtained an undergraduate level of education (52.6%). The average age of study participants was 42.8 years, with an average age of onset of 30.7 years. Victoria was the most commonly-reported place of residence (28.9%).

Table 1: Frequency of sociodemographic characteristics.

	N = 38 (%)
Classification	
Fukuda	6 (15.8%)
CCC	12 (31.6%)
ICC	20 (52.6%)
Gender	
Female	30 (78.9%)
Male	7 (18.4%)
Other	1 (2.6%)
Age (years, mean ± SD)	42.8 ± 10.8
Age of onset (years, mean ± SD)	30.7 ± 11.4
BMI (kg/m²)	
Underweight (<18.5)	0 (0.0%)
Normal weight (18.5 – 24.9)	21 (55.3%)
Overweight (25.0 – 29.9)	15 (39.5%)
Obese (≥30.0)	2 (5.3%)
Location	
New South Wales	8 (21.1%)
Victoria	11 (28.9%)
Queensland	10 (26.3%)
South Australia	1 (2.6%)
Western Australia	4 (10.5%)
Northern Territory	0 (0.0%)
Australian Capital Territory	2 (5.3%)
Tasmania	2 (5.3%)
Employment	
Unemployed	23 (60.5%)
Part-time	11 (28.9%)
Full-time	4 (10.5%)
Education	
Primary school	0 (0.0%)
High school	4 (10.5%)
Professional training	5 (13.2%)
Undergraduate	20 (52.6%)
Postgraduate	9 (23.7%)

Abbreviations: CCC Canadian Consensus Criteria; ICC: International Consensus Criteria; BMI: Body Mass Index.

Gastrointestinal symptoms

The frequency of gastrointestinal symptoms and their impact on patients' daily life is summarised in Table 2. The majority of the study population reported having experienced gastrointestinal symptoms (97.4%), with over half of the sample having received a diagnosis of IBS (57.9%). Of the participants experiencing gastrointestinal manifestations, bloating was the most frequently reported symptom (94.6%). The majority of the gastrointestinal symptoms investigated were most frequently experienced multiple times per month. This was observed for diarrhoea (37.8%), constipation (35.1%), stomach cramps (40.5%), flatulence (40.5%), and nausea (40.5%). For bloating, however, there was a bimodal distribution of patients, with 27.0% experiencing bloating multiple times per month and an equal proportion suffering from bloating multiple times per day. Blood in stool and early satiety were infrequently experienced among the study participants, with 81.1% and 27.9% of patients experiencing gastrointestinal symptoms never suffering from these symptoms respectively. Twelve participants reported other gastrointestinal symptoms (32.4%).

Furthermore, 35.1% of the patients reporting gastrointestinal manifestations declared that their gastrointestinal symptoms had a fair impact on their daily activities. It should also be noted that 21.6% of participants reported that their gastrointestinal symptoms impacted their daily life significantly.

Table 2: Frequency of gastrointestinal symptoms and overall impact on daily activities.

	N = 38 (%)
Gastrointestinal symptoms	
Yes	37 (97.4%)
No	1 (2.6%)
Diagnosis of IBS	
General practitioner	8 (21.1%)
Specialist	9 (23.7%)
Allied health professional	1 (2.6%)
Myself	4 (10.5%)
No	16 (42.1%)
Diagnosis of SIBO	
General practitioner	1 (2.6%)
Specialist	1 (2.6%)
Allied health professional	1 (2.6%)
Myself	1 (2.6%)
No	34 (89.5%)
Among those reporting gastrointestinal symptoms	N = 37 (%)
Diarrhoea	
Never	6 (16.2%)
Multiple times per month	14 (37.8%)
Multiple times per week	15 (40.5%)
Constipation	
Never	4 (10.8%)
Multiple times per month	13 (35.1%)
Multiple times per week	17 (45.9%)
Multiple times per day	3 (8.1%)
Stomach cramps	
Never	4 (10.8%)
Multiple times per month	15 (40.5%)
Multiple times per week	15 (40.5%)
Multiple times per day	3 (8.1%)
Flatulence	
Never	4 (10.8%)
Multiple times per month	15 (40.5%)
Multiple times per week	13 (31.5%)
Multiple times per day	5 (13.5%)
Bloating	
Never	2 (5.4%)
Multiple times per month	10 (27.0%)
Multiple times per week	15 (40.5%)
Multiple times per day	10 (27.0%)
Blood in stool	
Never	30 (81.1%)
Multiple times per month	5 (13.5%)
Multiple times per week	2 (5.4%)
Multiple times per day	2 (5.4%)
Multiple times per day	0 (0.0%)
Nausea	
Never	8 (21.6%)
Multiple times per month	15 (40.5%)
Multiple times per week	10 (27.0%)
Multiple times per day	4 (10.8%)
Early satiety	
Never	11 (29.7%)
Multiple times per month	10 (27.0%)
Multiple times per week	12 (32.4%)
Multiple times per day	4 (10.8%)
Other gastrointestinal	
Never	25 (67.6%)
Multiple times per month	4 (10.8%)
Multiple times per week	8 (21.6%)
Multiple times per day	0 (0.0%)
Impact of gastrointestinal symptoms on daily activities	
Not at all	2 (5.4%)
A little bit	7 (18.9%)
Fairly	13 (35.1%)
Quite a bit	7 (18.9%)
Significantly	8 (21.6%)

Abbreviations: IBS: Irritable Bowel Syndrome; SIBO: Small Intestinal Bacterial Overgrowth.

Dietary habits

Table 3 summarises patient responses in relation to diet, food avoidance, and the impact on dietary changes on patients' daily life. The majority of participants reported having changed their diet due to their gastrointestinal symptoms (78.9%), with 44.7% of patients stating that their gastrointestinal symptoms had influenced their diet significantly. A large portion of participants reported that symptoms other than gastrointestinal manifestations played a role in the changing of their diet (60.5%). Half of the study population followed a specific diet plan, with 73.7% of these participants following a wheat or gluten-free diet. Dairy or lactose-free and low-sugar diets were also frequently reported by the study participants following a diet plan (63.2%). Among these commonly-followed diets, study participants most frequently reported having followed the diet in question for at least one year. Interestingly, over half of dieting patients had adhered to a wheat or gluten-free diet for at least 12-months (52.6%).

Additionally, food avoidance was observed in a considerable percentage of the study population (89.5%). Refined sugar was the most frequently-reported food group avoided by participants avoiding at least one food, food group, or ingredient (73.5%). Equal proportions of patients avoiding at least one food, food group, or ingredient avoided dairy or lactose and wheat or gluten (64.7%). Processed foods or preservatives, greasy or fried foods, and alcohol were also frequently avoided within the study population (67.6%, 58.8%, and 55.9% respectively). Similarly to that of diet, the majority of patients avoiding at least one particular food group had been doing so for at least one year. Most of the study population reported that changing their diet or avoiding a particular food, food group, or ingre-

dient improved their gastrointestinal manifestations (68.4%), with 23.7% reporting a significant improvement in their gastrointestinal symptoms following dietary modification.

Table 3: Frequency of diet and dietary habits.

	N = 38 (%)
Changed diet due to gastrointestinal symptoms (impact of gastrointestinal symptoms on diet)	
Yes	30 (78.9%)
Not at all	0 (0.0%)
A little bit	4 (10.5%)
Fairly	4 (10.5%)
Quite a bit	5 (13.2%)
Significantly	17 (44.7%)
No	8 (21.1%)
Changed diet due to other symptoms (impact of other symptoms on diet)	
Yes	23 (60.5%)
Not at all	1 (2.6%)
A little bit	4 (10.5%)
Fairly	3 (7.9%)
Quite a bit	4 (10.5%)
Significantly	11 (28.9%)
No	15 (39.5%)
Following a specific diet plan	
Yes	19 (50.0%)
No	19 (50.0%)
Avoidance of food, food group, or ingredient	
Yes	34 (89.5%)
No	4 (10.5%)
Impact of diet change or food avoidance on gastrointestinal symptoms	
Worsened	0 (0.0%)
No change	9 (23.7%)
Slightly	17 (44.7%)
Significantly	9 (23.7%)
Neither changed diet nor avoided a food, food group, or ingredient	3 (7.9%)
Among those following a diet plan	**N = 19 (%)**
Paleo diet	
Less than six months	0 (0.0%)
Between six months and one year	1 (5.3%)
Greater than one year	0 (0.0%)
No	18 (94.7%)
Low FODMAP or IBS diet	
Less than six months	1 (5.3%)
Between six months and one year	1 (5.3%)
Greater than one year	7 (36.8%)
No	10 (52.6%)
Low sugar diet	
Less than six months	3 (15.8%)
Between six months and one year	3 (15.8%)
Greater than one year	6 (31.6%)
No	7 (36.8%)
Low sugar and low yeast or anti-Candida diet	
Less than six months	1 (5.3%)
Between six months and one year	0 (0.0%)
Greater than one year	1 (5.3%)
No	17 (89.5%)
Vegetarian diet	
Less than six months	0 (0.0%)
Between six months and one year	1 (5.3%)
Greater than one year	4 (21.1%)
No	14 (73.7%)
Vegan diet	
Less than six months	1 (5.3%)
Between six months and one year	1 (5.3%)
Greater than one year	1 (5.3%)
No	16 (84.2%)
Gluten or wheat-free diet	
Less than six months	3 (15.8%)
Between six months and one year	1 (5.3%)
Greater than one year	10 (52.6%)
No	5 (26.3%)
Dairy or lactose-free diet	
Less than six months	3 (15.8%)
Between six months and one year	0 (0.0%)
Greater than one year	9 (47.4%)
No	7 (36.8%)
Other diet	
Less than six months	0 (0.0%)
Between six months and one year	0 (0.0%)
Greater than one year	6 (31.6%)
No	13 (68.4%)
Among those avoiding a food, food group, or ingredient	**N = 34 (%)**
Avoidance of refined sugar*	
Less than six months	3 (8.8%)
Between six months and one year	2 (5.9%)
Greater than one year	19 (55.9%)
No	9 (26.5%)
Avoidance of greasy or fried foods*	
Less than six months	1 (2.9%)
Between six months and one year	1 (2.9%)
Greater than one year	17 (50.0%)
No	14 (41.2%)
Avoidance of processed foods or preservatives*	
Less than six months	1 (2.9%)
Between six months and one year	2 (5.9%)
Greater than one year	19 (55.9%)
No	11 (32.4%)

Avoidance of fruit*	
Less than six months	1 (2.9%)
Between six months and one year	0 (0.0%)
Greater than one year	9 (26.5%)
No	23 (67.6%)
Avoidance of gluten or wheat*	
Less than six months	3 (8.8%)
Between six months and one year	2 (5.9%)
Greater than one year	15 (44.1%)
No	12 (35.3%)
Avoidance of dairy or lactose*	
Less than six months	2 (5.9%)
Between six months and one year	2 (5.9%)
Greater than one year	17 (50.0%)
No	12 (35.3%)
Avoidance of meat products*	
Less than six months	1 (2.9%)
Between six months and one year	0 (0.0%)
Greater than one year	6 (17.6%)
No	26 (76.5%)
Avoidance of animal products*	
Less than six months	1 (2.9%)
Between six months and one year	1 (2.9%)
Greater than one year	6 (17.6%)
No	25 (73.5%)
Avoidance of caffeine	
Less than six months	3 (8.8%)
Between six months and one year	0 (0.0%)
Greater than one year	9 (26.5%)
No	22 (64.7%)
Avoidance of salt or overly salty foods	
Less than six months	1 (2.9%)
Between six months and one year	0 (0.0%)
Greater than one year	2 (5.9%)
No	31 (91.2%)
Avoidance of alcohol	
Less than six months	0 (0.0%)
Between six months and one year	1 (2.9%)
Greater than one year	18 (52.9%)
No	15 (44.1%)
Avoidance of other foods, food groups, or ingredients*	
Less than six months	3 (8.8%)
Between six months and one year	1 (2.9%)
Greater than one year	7 (20.6%)
No	22 (64.7%)

Abbreviations: FODMAP: Fermentable Oligo- Di- Mono- Saccharides And Polyols; IBS: Irritable Bowel Syndrome.

*Proportions do not add to 100%, as questions were left unanswered in survey.

Food intolerances

The frequencies of food intolerances among the study participants are displayed in Table 4. Most of the study participants reported at least one food intolerance (71.1%). The majority of participants who reported food intolerance were intolerant of wheat or gluten (70.4%). Dairy or lactose intolerance was also frequently reported (63.0%).

Table 4: Food intolerances.

	N = 38 (%)
Food intolerances	
Yes	27 (71.1%)
No	11 (28.9%)
Among those reporting food intolerance	**N = 27 (%)**
Gluten or wheat	
Yes	19 (70.4%)
No	8 (29.6%)
Dairy or lactose	
Yes	17 (63.0%)
No	10 (37.0%)
Animal or meat products	
Yes	7 (25.9%)
No	20 (74.1%)
Preservatives or highly processed foods	
Yes	4 (14.8%)
No	23 (85.2%)
Fructose, fructans, or high-FODMAP foods	
Yes	6 (22.2%)
No	21 (77.8%)
Greasy, fried, or high-fat foods	
Yes	4 (14.8%)
No	23 (85.2%)
Sugar or high-sugar foods	
Yes	7 (25.9%)
No	20 (74.1%)
Food additives	
Yes	5 (18.5%)
No	22 (81.5%)
Other	
Yes	21 (77.8%)
No	6 (22.2%)

Abbreviations: FODMAP: Fermentable Oligo- Di- Mono- Saccharides And Polyols.

Healthcare access

The study participants' healthcare access habits in terms of gastrointestinal symptoms and diet are outlined in Table 5. Most of the study population (86.8%) had accessed a healthcare professional in relation to their gastrointestinal symptoms or diet. Among the patients accessing a healthcare professional within the last six months (42.1%), GPs were the most frequently accessed, with 64.7% visiting a GP between one and three times and 23.5% at least four times within the last month. Interestingly, 47.1% of participants accessing a healthcare professional

within the last six months reported visiting a specialist. Allied health professionals also appear to be frequently accessed by ME/CFS patients, with 47.1% of those accessing a healthcare service in the six months visiting an allied health professional between one and three times and 17.6% at least four times in the last month.

Table 5: Healthcare access habits

	N = 38 (%)
Healthcare professional consultation regarding diet or gastrointestinal symptoms	
Within the past six months	17 (44.7%)
Prior to the past six months	16 (42.1%)
No	5 (13.2%)
Among those accessing a healthcare professional within the past six months	**N = 17 (%)**
GP	
One to three times	11 (64.7%)
Four or more times	4 (23.5%)
No	2 (11.8%)
Specialist	
One to three times	8 (47.1%)
Four or more times	0 (0.0%)
No	9 (52.9%)
Allied health professional	
One to three times	8 (47.1%)
Four or more times	3 (17.6%)
No	6 (35.3%)
Other heath professional	
One to three times	1 (5.9%)
Four or more times	2 (11.8%)
No	14 (82.4%)

Abbreviations: GP: General Practitioner.

Health-related quality of life

The results of the multiple linear regression analysis for the seven HRQoL domains are presented in Table 6 and Table 7. Table 6 provides the statistics returned for the physical HRQoL domain models (including PF, RP, BP, and GH), where Table 7 summarises the mental HRQoL domain models (including SF, MH, and RE). Complete statistics for each of the regression models generated are provided in Supplementary Tables.

Five of the seven models generated for the HRQoL domains were statistically significant. No significant associations were observed for RE (adjusted R^2= -0.173, P= 0.874). The avoidance of fruit and 'other' food intolerances were associated with higher BP scores (P= 0.033 and P= 0.014 respectively); however, the model for BP was also not significant (adjusted R^2= 0.301, P= 0.072).

The model generated for PF was significant (adjusted R^2= 0.919, P <0.001). Higher PF scores were associated with constipation, flatulence, blood in stool, and an intolerance to preservatives or processed foods ($P < 0.001$, $P < 0.001$, $P = 0.003$, and $P < 0.001$ respectively). PF also displayed significant negative associations with nausea and the avoidance of gluten or wheat (P= 0.018 and P= 0.027 respectively). Age, gender, BMI, and education were significant confounders of PF ($P < 0.001$), whereby age was associated with increased PF scores, PF scores were higher among males, and PF was negatively associated with BMI and education. RP was positively associated with the avoidance of processed foods or preservatives (P= 0.035), as well as the avoidance of salt or overly-salty foods ($P < 0.001$). A positive association was also observed between RP and bloating (P= 0.018). Gender was a significant confounder of the RP model (with males returning higher RP scores (P= 0.003)) and 71.3% of the model's variance could be explained by the independent variables (adjusted R^2= 0.713, $P < 0.001$). The GH model was also significant (adjusted R^2= 0.606, P= 0.006). GH was positively associated with intolerance to greasy, fried, or high-fat foods and the avoidance of animal products (P= 0.014 and $P < 0.001$ respectively), and was negatively associated with the avoidance of alcohol (P= 0.009). Education was a significant confounder of RP, in which higher levels of education were associated with decreased GH scores (P= 0.011).

Statistically significant regression models were returned for the SF and MH mental HRQoL domains (adjusted R^2= 0.806, $P < 0.001$ and adjusted R^2= 0.359, P= 0.047 respectively). Constipation, bloating, and the avoidance of salt or overly-salty foods were associated with higher SF scores ($P = 0.008$, $P < 0.001$, and P= 0.016 respectively). SF was indirectly proportional to the avoidance of fruit ($P < 0.001$). The SF model was confounded by age, gender, and employment ($P < 0.001$, $P < 0.001$ and $P = 0.004$ respectively). Improved MH scores were associated with intolerance to 'other' foods ($P = 0.012$), with no significant confounding variables.

Table 6: Multivariate analysis of physical HRQoL domains.

	PF			RP			BP			GH		
	β	t	P	β	t	P	β	t	P	β	t	P
Sociodemographic data												
Age (years)	0.702	7.286***	<0.001	0.300	1.937	0.075	-0.363	-1.240	0.234	0.066	0.328	0.748
Gender	0.667	6.827***	<0.001	0.724	3.597**	0.003	-0.006	-0.028	0.978	-0.181	-1.103	0.290
BMI (kg/m²)	-1.196	-11.214***	<0.001	-0.098	-0.693	0.501	-0.149	-0.684	0.504	-0.288	-1.668	0.119
Employment	0.122	1.280	0.233	-0.213	-1.549	0.145	-0.683	-3.383**	0.004	0.140	0.715	0.487
Education	-0.733	-7.966***	<0.001	0.329	1.749	0.104	0.143	0.689	0.502	-0.530	-2.951*	0.011
Gastrointestinal symptoms												
Diarrhoea												
Constipation	1.434	11.573***	<0.001									
Stomach cramps												
Flatulence	0.504	6.068***	<0.001									
Bloating				0.443	2.720*	0.018						
Blood in stool	0.363	4.062**	0.003									
Nausea	-0.337	-2.896*	0.018									
Early satiety												
Other												
Food intolerance												
Wheat or gluten	0.202	1.843	0.098									
Dairy or lactose												
Animal or meat products												
Preservatives or highly-processed foods	1.139	8.020***	<0.001									
Fructose, fructans, or high-FODMAP foods												
Greasy, fried, or high-fat foods							0.620				2.835*	0.014
Sugar or high-sugar foods												

	Model 1 (R²=0.767)			Model 2 (R²=0.530)			Model 3 (R²=0.830)			Model 4 (R²=0.967)		
	B	t	P	B	t	P	B	t	P	B	t	P
Food additives	-0.347	-1.893	0.081									
Other				0.784	2.771*	0.014						
Food avoidance												
Refined sugar												
Greasy or fried foods												
Processed foods or preservatives				0.530	2.350*	0.033	0.350	2.353*	0.035			
Fruit										-0.188	-1.975	0.080
Gluten or wheat										-0.272	-2.634*	0.027
Dairy or lactose												
Other												
Meat products												
Animal products	0.858	5.171***	<0.001									
Caffeine												
Salt or overly-salty foods							0.792	4.792***	<0.001			
Alcohol	-0.523	-3.045**	0.009				-0.281	-1.969	0.071			
Other												
R²	0.767			0.530			0.830			0.967		
Adjusted R²	0.606			0.310			0.713			0.919		
P-value	**0.006**			0.072			**<0.001***			**<0.001***		

Abbreviations: *PF* Physical Functioning; *RP*: Role of limitations due to physical health problems; *BP*: Bodily Pain; *GH*: General health perceptions; *BMI* Body Mass Index; *FODMAP*: Fermentable Oligo- Di- Mono-Saccharides And Polyols; *IBS*: Irritable Bowel Syndrome.

*P < 0.05, **P < 0.01, ***P < 0.001

Table 7: Multivariate analysis of mental HRQoL domains.

	SF			MH			RE		
	β	*t*	*P*	*β*	*t*	*P*	*β*	*t*	*P*
Sociodemographic data									
Age (years)	0.831	**5.445*****	<0.001	-0.037	-0.134	0.895	-0.035	-0.119	0.907
Gender	0.788	**5.157*****	<0.001	-0.254	-1.278	0.221	-0.066	-0.253	0.803
BMI (kg/m²)	-0.307	-1.898	0.082	-0.134	-0.642	0.531	0.318	1.181	0.254
Employment	-0.427	**-3.519****	0.004	-0.218	-1.168	0.261	-0.034	-0.142	0.889
Education	-0.003	-0.017	0.987	-0.406	-2.065	0.057	0.074	0.289	0.776
Gastrointestinal symptoms									
Diarrhoea				-0.396	-2.120	0.051			
Constipation	0.425	**3.178****	0.008						
Stomach cramps									
Flatulence									
Bloating	0.626	**5.062*****	<0.001						
Blood in stool									
Nausea									
Early satiety									
Other									
Food intolerance									
Greasy, fried, or high-fat foods									
Wheat or gluten									
Dairy or lactose									
Animal or meat products									
Preservatives or highly-processed foods									
Fructose, fructans, or high-FODMAP foods	0.288	1.936	0.077						
Sugar or high-sugar foods									
Food additives									
Other				0.742	**2.841***	0.012			
Food avoidance									
Refined sugar									
Greasy or fried foods									
Processed foods or preservatives									
Fruit	-0.606	**-4.556*****	<0.001						
Gluten or wheat									
Dairy or lactose									
Other									
Meat products									
Animal products									
Caffeine									
Salt or overly-salty foods	0.441	**2.798***	0.016						

Alcohol								
Other								
R²		0.894			0.563			0.094
Adjusted *R²*		0.806			0.359			-0.173
P-value		**<0.001*****			**0.047***			0.874

Abbreviations: *SF* Social Functioning; *MH* General mental health; *RE* Role of limitations due to emotional problems
*P < 0.05, **P < 0.01, ***P < 0.001

Discussion

This study served to describe the role of gastrointestinal manifestations, dietary habits, and food intolerances in the presentation of ME/CFS in an Australian cohort. Gastrointestinal health and dietary sensitivities, such as the development of multiple new sensitivities (including food intolerances, as well as chemical and drug sensitivities), have previously bene reported by ME/CFS patients and are suggested to be implicated in the illness' clinical presentation [18-20,39]. This study also served to describe the relationship between patients' gastrointestinal symptoms, food intolerances, and food avoidance habits with their HRQoL, as this has not yet been investigated in an Australian ME/CFS patient population. The primary findings of this study include that gastrointestinal manifestations are a prominent component of ME/CFS symptomatology. Additionally, dietary modification and food intolerance are both frequent among ME/CFS patients. It also appears that gastrointestinal symptoms, food intolerances, and food avoidance influence patients' HRQoL.

The sociodemographic distribution of the study participants was consistent with the current literature, including both the findings of investigations at the NCNED and international research [10,31,39-41]. The majority of participants were female with an average age of 42.8 years, as similarly observed in previous studies [10,31,41]. Over half of the study population was of normal weight, which reflected the BMI distribution of other epidemiological studies [10,31,40]. As similarly observed in other studies [31,39], approximately 60% of the study population was unemployed. Interestingly, over half of the sample population had obtained an undergraduate level of education, a notably higher proportion when compared with other studies [10,31,39]. Despite this, the sociodemographic structure of this study population is consistent with the current literature.

A key novel finding of this study was the high prevalence of gastrointestinal symptoms among ME/CFS patients. Almost all participants in the study reported having experienced gastrointestinal manifestations (97.4%). Long-term signs or symptoms involving the gastrointestinal system were observed in 0.6% of 21,315 Australians of all ages participating in the National Health Survey from 2017 to 2018 [42]. Thus, as the prevalence of gastrointestinal symptoms among the current study participants is substantially greater that of the general Australian population, it appears that gastrointestinal manifestations are a noteworthy component of ME/CFS presentation.

The prevalence of gastrointestinal symptoms observed in the present study is also considerably higher than other studies that commented on gastrointestinal symptoms among ME/CFS patients [10,31,40]. Moderate to severe gastrointestinal manifestations were reported by 55.2% of patients included in

a recent study conducted by Eaton-Fitch et al. [31]. Similarly to the present investigation, the Eaton-Fitch et al. study utilised a cross-sectional study design where patients were recruited based on voluntary participation. However, the sample size was considerably higher (*N*= 480) when compared with the present study, which may explain the noticeably higher percentage of patients experiencing gastrointestinal symptoms in the current study population. Additionally, those experiencing mild gastrointestinal symptoms were grouped with patients who did not report gastrointestinal manifestations in the Eaton-Fitch et al. study. Thus, the true proportion of patients experiencing gastrointestinal symptoms may be higher than reported by Eaton-Fitch et al.

The results of the current study also suggest that bloating is a key component of the gastrointestinal symptomatology associated with ME/CFS. Bloating was the most frequently experienced gastrointestinal symptom, with 92.1% of all study participants (and 94.6% of study participants experiencing gastrointestinal manifestations) reporting this symptom. Johnston et al. observed bloating in only 34.8% of study participants meeting the Fukuda or ICC case definitions [10]. Similarly to the present investigation, the authors employed a cross-sectional study design that relied on voluntary participation; however, the Johnston et al. study had a considerably larger study population (*N*= 535). A 2014 study with a smaller sample size (*N*= 94) reported gastrointestinal manifestations in 62% of ME/CFS patients meeting the Fukuda criteria [43]. Interestingly, Johnston et al. observed a decreased prevalence of bloating among ME/CFS patients meeting only the Fukuda criteria (30.9%) when compared with those meeting the ICC case definition (38.6%) [10].

Also, a considerable proportion of patients experiencing gastrointestinal symptoms in the present study reported diarrhoea (81.6%). Słomko et al. observed this in only 40.6% of patients meeting the Fukuda criteria (*N* = 69) in Poland surveyed between 2014 and 2016 [40]. Furthermore, Słomko et al. observed that 37.7% of ME/CFS patients reported gastrointestinal pain [40], which was similarly observed in 35.4% of Fukuda and ICC patients in the Johnston et al. study [10]. Stomach cramps were reported by approximately 86.8% of participants experiencing gastrointestinal symptoms in the present study, as was constipation, which was only reported by 30.4% of patients in the Polish cohort [40].

The comparatively high prevalence of specific gastrointestinal symptoms among the current study participants is likely attributable to the small sample size. Also, the present study may have seen a higher prevalence of bloating, diarrhoea, stomach cramps, and constipation than previously observed, as the self-administered questionnaire in this study queried the frequency

of gastrointestinal symptoms on a four-point scale and, therefore, may have been more sensitive than the reporting methods employed by other studies. In addition to the varying sample sizes, it should be noted that cultural differences in diet may also explain inconsistencies in the prevalence of gastrointestinal symptoms between these geographically different ME/CFS patient populations [44].

Over half of the patients included in the current study reported being diagnosed with IBS (57.9%), where a diagnosis of SIBO was reported by only 10.5% of patients. The prevalence of gastrointestinal comorbidity was noticeably lower among the general population compared with the present study. Of the Australians participating in the 2017-18 National Health Survey, 1.3% suffered from IBS or another gastrointestinal disease other than ulcers, hernias, and gallstones [42]. Thus, it appears that gastrointestinal comorbidity is also an important component of ME/CFS presentation. However, there exists disparity in the prevalence of gastrointestinal comorbidity between ME/CFS patient populations in the current literature. Despite Słomko et al. reporting IBS in only 17.7% of study participants [40], the results of the present study are supported by an investigation conducted in Spain between 2008 and 2015 [39], which observed intestinal dysbiosis or IBS in 71.3% of participants.

Therefore, a large proportion of study participants in the present study experienced gastrointestinal symptoms and a considerable percentage of patients reported gastrointestinal comorbidity. Coupled with this, 94.6% of patients experiencing gastrointestinal symptoms noted that these symptoms impacted their daily activities, with 21.6% reporting that this impact was significant. Thus, it appears that gastrointestinal disturbances have a noteworthy role in the clinical presentation of ME/CFS.

The current study also identified novel research findings that dietary modification was common among Australian ME/CFS patients. Gastrointestinal symptoms were responsible for a change in diet among 78.9% of patients, with 44.7% of patients reporting that their gastrointestinal manifestations had a significant influence on their dietary habits. Additionally, 60.5% of study participants reported that symptoms other than gastrointestinal disturbances contributed to their change in diet. Although only half of the study population followed a specific diet plan, 89.5% of study participants reported avoiding at least one food, food group, or ingredient. There is limited literature available that examines dieting and food avoidance among ME/CFS patient populations to compare with the results of this study. However, 13% of Australians over the age of 15 years who participated in the Australian Health Survey (AHS) from 2011 to 2012 were following a specific diet plan [45]. Dietary modification has been posited as a potentially beneficial intervention for the management of ME/CFS symptoms [16,18], which may explain the large proportion of patients reporting having altered their diet when compared with the general population.

Similarly, food intolerance was also frequently reported among the study population (71.1%). Approximately 17% of Australians over the age of two years who participated in the AHS reported avoiding a food due to allergy or intolerance [45]. It should be noted that, for both the AHS population and the current study participants, that the prevalence of food intolerances relied on self-reported food intolerances and does not correspond to physiologically-confirmed food allergies. As a result, the prevalence of food intolerance may be overestimated among both the Australian population and the study participants.

It is known that the clinical presentation of ME/CFS involves new dietary sensitivities [18-20]. However, the prevalence of food intolerance in this investigation is relatively large when compared with other studies. The study conducted by Johnston et al. observed food intolerances in 33.9% of patients [10]. Additionally, Castro-Marrero et al. reported that only 10.6% of ME/CFS patients meeting both the Fukuda and CCC definitions experienced food intolerances [39]. As all study participants in the Castro-Marrero et al. study met the CCC case definition, this study population may be less heterogeneous in clinical presentation than the Johnston et al. study, which investigated ME/CFS patients meeting the Fukuda or ICC definitions. Also, the size of the Castro-Marrero et al. study population was over three times greater than that of the Johnston et al. study ($N= 1,757$). Thus, both the Castro-Marrero et al. and Johnston et al. studies had a considerably larger sample size than the present study, which may explain the noticeably higher prevalence of food intolerance in the current study population. Additionally, the current study population is likely more heterogeneous in clinical presentation when compared with study participants in the Castro-Marrero et al. and Johnston et al. studies, as the present study investigated ME/CFS patients meeting the Fukuda, CCC, or ICC definitions.

Gluten or wheat intolerance was the most frequently-reported food intolerance by the study participants (70.4%), closely followed by self-reported dairy or lactose intolerance (63.0%). Similar results were observed by Trabal et al. in a 2012 study, whereby 78.6% of study participants avoided dairy and 53.6% avoided gluten-containing grains due to symptom exacerbation [46]. Interestingly, neither gluten or wheat nor dairy or lactose were the most frequently avoided food group, as refined sugar was avoided by 72.7% of patients that avoided at least one food, food group, or ingredient. Sugar avoidance has been proposed in the suppression of yeast infections associated with ME/CFS; however, there remains a lack of conclusive evidence [17]. Thus, the avoidance of refined sugar observed in this study may pertain to fatigue symptoms, rather than gastrointestinal disturbances. Following refined sugar, gluten or wheat and dairy or lactose were the most commonly avoided food groups, with equal proportions of the study participants avoiding these food groups (64.7%). Cow's milk or dairy and gluten were the most frequently avoided foods due to intolerance or allergy by Australians who participated in the AHS; however, avoidance of these food groups among the general population was considerably less prevalent when compared with the present study population (4.5% and 2.5% respectively) [45].

Multiple linear regression analysis returned significant associations between patients' HRQoL and their gastrointestinal symptoms, food intolerances, and food avoidance habits. However, many of the associations returned by the multivariate analysis were unexpected, which is likely attributable to the study's small sample size. Unusually, higher HRQoL scores were associated with many gastrointestinal symptom and food intolerance variables. Although PF scores were negatively associated with nausea, positive associations were observed between constipation, flatulence, blood in stool, and intolerance to preservatives and processed foods with PF, bloating with RP, intolerance to greasy, fried, or high-fat foods with GH, constipation and bloating with SF, and intolerance to 'other' foods and MH.

The effect of food avoidance on ME/CFS patients' HRQoL also remains unclear. Higher HRQoL scores were associated

with the avoidance of processed foods or preservatives (RP), salt or overly-salty foods (RP and SF), and animal products (GH). Interestingly, food avoidance was also found to be detrimental to HRQoL, in which the avoidance of fruit was associated with reduced SF scores. The negative association between gluten or wheat avoidance with PF was unexpected given the high prevalence of gluten or wheat intolerance in the study population. Additionally, as reduced tolerance to alcohol is a known component of ME/CFS presentation [47], it appears unusual for alcohol avoidance to be associated with reduced HRQoL (GH). Therefore, the effect of patients' gastrointestinal symptoms, food intolerances, and food avoidance habits on their HRQoL remains unclear.

Healthcare access in terms of gastrointestinal and diet concerns was also investigated by this study, in which 86.8% of patients reported consulting a healthcare professional regarding their gastrointestinal symptoms or diet. Thus, it is clear that gastrointestinal health and diet are of concern to many ME/CFS patients and should be taken into consideration in the management of the condition. Additionally, the access of a specialist by just under half of patients who accessed a healthcare professional in the past six months further highlights the burden of gastrointestinal and diet concerns on ME/CFS patients.

Finally, it should be noted that this study is not without limitations. The small sample population is an important limitation when analysing the results, particularly when comparing these results with studies that observed a lesser burden of gastrointestinal symptoms on ME/CFS patients [10,31,39,40]. Additionally, although population data was available, the individual data could not be accessed. As a result, statistical analysis could not be performed to determine if the prevalence of gastrointestinal symptoms, gastrointestinal comorbidity, dieting, and food intolerance among ME/CFS was significantly different to that of the general Australian population. Misalignment between the online questionnaire employed in the present study and the two population surveys further restricted comparison between the study participants and the general population.

Despite this, the current investigation is a pilot study that reports novel findings concerning the gastrointestinal symptoms and dietary habits of Australian ME/CFS patients and foregrounds the potential implications of gastrointestinal manifestations in ME/CFS. This study also investigates the relationship of gastrointestinal symptoms and dietary habits on HRQoL for the first time in an Australian ME/CFS patient population. Finally, this study comments on patients' healthcare access in relation to gastrointestinal symptoms and diet, thereby highlighting the burden of gastrointestinal manifestations and dietary changes associated with ME/CFS on the healthcare system. The use of online self-administered questionnaires is also an advantage of this study. Administering the questionnaires online aimed to reduce some selection bias by increasing accessibility to potential study participants (particularly severe or house-bound patients) who may find difficulty in presenting for an interview in person or completing a telephone interview due to the disabling nature of ME/CFS. Finally, although this investigation could not be compared with similar studies (due to being a pilot study), this research has elucidated avenues for future research. Thus, this pilot study has foregrounded the extent to which gastrointestinal manifestations are involved in ME/CFS presentation and the potential role of diet in ME/CFS management.

It is recommended that future research with a larger study population be undertaken in this area to further support the observations reported in this current pilot investigation. The effect of gastrointestinal symptoms and dietary habits should also be investigated further with a larger study population to more accurately describe the burden and impact of gastrointestinal symptoms, food intolerances, and food avoidance habits on ME/CFS patients' HRQoL. Additionally, it is also recommended that a prospective study be performed to observe changes in patients' gastrointestinal symptoms over disease progression. A prospective study design would also provide greater evidence to support the potential role of gastrointestinal symptoms, food intolerance, and food avoidance in ME/CFS patients' HRQoL. Such studies would be useful for formulating validated diet recommendations for managing ME/CFS to improve patient prognosis.

Conclusion

This cross-sectional study highlights the extent to which gastrointestinal symptoms and diet are implicated in the clinical presentation of ME/CFS in an Australian cohort. The prevalence of gastrointestinal symptoms among patients in this study was considerably higher than previously observed, with 97.4% of study participants reporting gastrointestinal manifestations. Gastrointestinal symptoms impacted daily activities in 94.6% of patients experiencing gastrointestinal manifestations, with 21.6% of such patients reporting this impact as significant. This study also identified that a large proportion of patients sought advice from a GP or other healthcare professional in relation to their gastrointestinal manifestations or diet. Thus, gastrointestinal health and diet appear to be integral factors that should be considered in the management of ME/CFS to facilitate a greater quality of life among patients. Multivariate analysis returned significant associations between HRQoL with gastrointestinal symptoms, dietary modification, and food intolerance; however, the role of dietary habits on ME/CFS patients' HRQoL remains unclear. Thus, there is a need for further research in this area with a larger sample size to confirm the trends identified by this study.

Declarations

Ethics approval and consent to participate

This study was approved by Griffith University Human Research Ethics Committee (GU: 2019/1005 & GU: 2016/807) and Gold Coast University Hospital Human Research Ethics Committee (HREC/2019/QGC/56469). Written consent was required and obtained prior to the commencement of this project. The authors have no ethical conflicts to disclose.

Availability of data and materials

The datasets generated and/or analysed during this manuscript are not publicly available due to confidentiality agreements but de-identified data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BW performed all data analysis and wrote the manuscript in consultation with NEF, HC, DS, and SMG. NEF oversaw data analysis and contributed to the interpretation of the results. RP, HC, DS, and SMG developed the necessary tools for this research. All authors critically reviewed and approved the final version of the manuscript.

References

1. Capelli E, Zola R, Lorusso L, Venturini L, Sardi F, et al. Chronic fatigue syndrome/myalgic encephalomyelitis: An update. Int J Immunopathol Pharmacol. 2010; 23: 981-989.

2. Lloyd AR, Hickie I, Boughton CR, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. Med J Aust. 1990; 153: 522-528.

3. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. Ann Intern Med. 1994; 121: 953-959.

4. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, et al. Myalgic encephalomyelitis/chronic fatigue syndrome. J Chronic Fatigue Syndr. 2003; 11: 7-115.

5. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, et al. Myalgic encephalomyelitis: International consensus criteria. J Intern Med. 2011; 270: 327-338.

6. Cortes Rivera M, Mastronardi C, Silva-Aldana CT, Arcos-Burgos M, Lidbury BA. Myalgic encephalomyelitis/chronic fatigue syndrome: A comprehensive review. Diagnostics (Basel). 2019; 9.

7. Institute of Medicine. Review of the evidence on major ME/CFS symptoms and manifestations. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness [Internet]. Washington, DC: National Academies Press (US); 2015.

8. Green CR, Cowan P, Elk R, O'Neil KM, Rasmussen AL. National institutes of health pathways to prevention workshop: Advancing the research on myalgic encephalomyelitis/chronic fatigue syndrome. Ann Intern Med. 2015; 162: 860-865.

9. Afari N, Buchwald D. Chronic fatigue syndrome: A review. Am J Psychiatry. 2003; 160: 221-36.

10. Johnston SC, Staines DR, Marshall-Gradisnik SM. Epidemiological characteristics of chronic fatigue syndrome/myalgic encephalomyelitis in Australian patients. Clin Epidemiol. 2016; 8: 97-107.

11. Shor S. Pathogenesis of chronic fatigue syndrome: A multisystem hypothesis. J Chronic Fatigue Syndr. 2011; 11: 51-68.

12. Knight S, Elders S, Rodda J, Harvey A, Lubitz L, et al. Epidemiology of paediatric chronic fatigue syndrome in Australia. Arch Dis Child. 2019; 104: 733-738.

13. Johnston S, Brenu EW, Staines DR, Marshall-Gradisnik S. The adoption of chronic fatigue syndrome/myalgic encephalomyelitis case definitions to assess prevalence: A systematic review. Ann Epidemiol. 2013; 23: 371-376.

14. Yang T, Yang Y, Wang D, Li C, Qu Y, et al. The clinical value of cytokines in chronic fatigue syndrome. J Transl Med. 2019; 17: 213.

15. Brown AA, Jason LA, Evans MA, Flores S. Contrasting case definitions: The ME international consensus criteria vs. the Fukuda et al. CFS criteria. N Am J Psychol. 2013; 15: 103-120.

16. Campagnolo N, Johnston S, Collatz A, Staines D, Marshall-Gradisnik S. Dietary and nutrition interventions for the therapeutic treatment of chronic fatigue syndrome/myalgic encephalomy-

17. elitis: A systematic review. J Hum Nutr Diet. 2017; 30: 247-259.

17. Morris DH, Stare FJ. Unproven diet therapies in the treatment of the chronic fatigue syndrome. Arch Fam Med. 1993; 2: 181-186.

18. Loblay RH, Swain AR. The role of food intolerance in chronic fatigue syndrome. The clinical and scientific basis of ME/CFS. New York: The Nightingale Research Foundation. 1992; p. 521-538.

19. Friedberg F, Bateman L, Bested AC, Friedman KJ, Gurwitt A, et al. ME/CFS: A primer for clinical practitioners. 2012 ed. Chicago, USA: International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis. 2012.

20. Underhill R, Friedman KJ. New pediatric case definition helps pediatricians diagnose chronic fatigue syndrome (ME/CFS). (n.d.). 2007.

21. Burnet RB, Chatterton BE. Gastric emptying is slow in chronic fatigue syndrome. BMC Gastroenterol. 2004; 4: 32.

22. Lakhan SE, Kirchgessner A. Gut inflammation in chronic fatigue syndrome. Nutr Metab. 2010; 7: 10p-p.

23. Newberry F, Hsieh S-Y, Wileman T, Carding SR. Does the microbiome and virome contribute to myalgic encephalomyelitis/ chronic fatigue syndrome? Clin Sci. 2018; 132: 523-542.

24. Borody TJ, Nowak A, Finlayson S. The GI microbiome and its role in chronic fatigue syndrome: A summary of bacteriotherapy. AC-NEM. 2012; 31: 3-8.

25. Du Preez S, Corbitt M, Cabanas H, Eaton N, Staines D, et al. A systematic review of enteric dysbiosis in chronic fatigue syndrome/ myalgic encephalomyelitis. Syst Rev. 2018; 7: 241.

26. Royal Australasian College of Physicians. Chronic fatigue syndrome: Clinical practice guidelines – 2002 [Internet]. Sydney, Australia: Royal Australasian College of Physicians; 2002; 56P.

27. Friedberg F, Bateman L, Bested AC, Davenport T, Friedman KJ, Gurwitt A, et al. ME/CFS: A primer for clinical practitioners. 2014 ed. Chicago, USA: International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2014.

28. Aaron LA, Herrell R, Ashton S, Belcourt M, Schmaling K, Goldberg J, et al. Comorbid clinical conditions in chronic fatigue: a co-twin control study. J Gen Intern Med. 2001; 16: 24-31.

29. Bozzini S, Albergati A, Capelli E, Lorusso L, Gazzaruso C, et al. Cardiovascular characteristics of chronic fatigue syndrome. Biomed Rep. 2018; 8: 26-30.

30. Yancey JR, Thomas SM. Chronic fatigue syndrome: Diagnosis and treatment. Am Fam Physician. 2012; 86: 741-746.

31. Eaton-Fitch N, Johnston SC, Zalewski P, Staines D, Marshall-Gradisnik S. Health-related quality of life in patients with myalgic encephalomyelitis/chronic fatigue syndrome: An Australian cross-sectional study. Qual Life Res. 2020.

32. Falk Hvidberg M, Brinth LS, Olesen AV, Petersen KD, Ehlers L. The health-related quality of life for patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). PLoS One. 2015; 10: e0132421.

33. Nacul LC, Lacerda EM, Campion P, Pheby D, Drachler MdL, Leite JC, et al. The functional status and well being of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers. BMC Public Health. 2011; 11: 402.

34. Strand EB, Mengshoel AM, Sandvik L, Helland IB, Abraham S, Nes LS. Pain is associated with reduced quality of life and functional status in patients with myalgic encephalomyelitis/chronic fatigue syndrome. Scand J Pain. 2018; 19: 61-72.

35. Schmitz C. LimeSurvey: An open source survey tool [computer program]. Hamberg, Germany. 2012.

36. IMB Corp. IBM SPSS Statistics, Version 26.0 [computer program]. Armonk, New York. 2019.

37. Weir CB, Jan A. BMI classification percentile and cut off points. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2020.

38. Stevenson CE. SF-36: Interim norms for Australian data. Canberra: Australian Institute of Health and Welfare; 1996.

39. Castro-Marrero J, Faro M, Aliste L, Saez-Francas N, Calvo N, et al. Comorbidity in chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide population-based cohort study. Psychosomatics. 2017; 58: 533-543.

40. Słomko J, Newton JL, Kujawski S, Tafil-Klawe M, Klawe J, et al. Prevalence and characteristics of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in Poland: A cross-sectional study. BMJ Open. 2019; 9: e023955-e.

41. Earl KE, Sakellariou GK, Sinclair M, Fenech M, Croden F, et al. Vitamin D status in chronic fatigue syndrome/myalgic encephalomyelitis: A cohort study from the North-West of England. BMJ Open. 2017; 7: e015296-e.

42. Australian Bureau of Statistics. National Health Survey: First Results, 2017-18 [Internet]. Canberra: Commonwealth of Australia. 2018.

43. Maes M, Leunis JC, Geffard M, Berk M. Evidence for the existence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) with and without abdominal discomfort (irritable bowel) syndrome. Neuro Endocrinol Lett. 2014; 35: 445-53.

44. Fang X, Francisconi CF, Fukudo S, Gerson MJ, Kang JY, et al. Multicultural aspects in functional gastrointestinal disorders (FGIDs). Gastroenterology. 2016; 150: 1344-54.

45. Australian Bureau of Statistics. Australian Health Survey: Nutrition First Results – Foods and Nutrients, 2011-12 [Internet]. Canberra: Commonwealth of Australia. 2014.

46. Trabal J, Leyes P, Fernández-Solá J, Forga M, Fernández-Huerta J. Patterns of food avoidance in chronic fatigue syndrome: Is there a case for dietary recommendations? Nutr Hosp. 2012; 27:659-662.

47. Chu L, Valencia IJ, Garvert DW, Montoya JG. Onset patterns and course of myalgic encephalomyelitis/chronic fatigue syndrome. Front Pediatr. 2019; 7: 12.