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A longitudinal observational study of patient-centered nutritional, psychological and combined therapies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a condition characterised by severe and persistent fatigue, neurological disturbances, autonomic and endocrine dysfunctions and sleep difficulties that have a pronounced and significant impact on individuals' lives. Current NICE guidelines within the United Kingdom suggest that this condition should be treated with cognitive behavioural therapy and/or graded exercise therapy where appropriate. There is currently a lack of evidence-base concerning other, more integrative interventions that may be beneficial to those with ME/CFS.

Objectives: This study aimed to evaluate whether three patient-centered treatment modalities of psychology, nutrition and combined treatment, reduced symptomatology of ME/CFS over a 3-month time period and whether there were significant differences in these changes between groups.

Design and setting: This is a longitudinal observational study conducted at one private secondary health care facility in London, UK.

Participants: One-hundred and thirty-eight individuals (110 females, 79.7%; 42 participants in psychology, 44 in nutrition and 52 in combined) participated at baseline and 72 participants completed the battery of measures at follow-up (52.17% response rate; 14, 27, 31 participants in each group, respectively).

Outcome measures: Self-report measures of ME/CFS symptoms, functional ability, multidimensional fatigue, perceived control and maladaptive stress.

Results: Baseline comparisons showed those in the combined group had higher levels of fatigue. At follow-up, all groups saw improvements in fatigue, functional physical symptomatology and maladaptive stress; those within the psychology group also experienced a shift in perceived control over time. The psychology group demonstrated a significantly greater change in fatigue and perceived control than the combined group; however, the opposite relationship was observed for headaches.

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Conclusions: Patient-centered techniques for the treatment of ME/CFS appear promising in reducing symptomatology, fatigue and inappropriate responses to stressors and increasing function and perceived control. The need for further studies of integrative treatment with robust designs appears warranted.

Summary

Article focus

- This observational study investigated three (psychological, nutritional and combined) tailored patient-centered interventions for ME/CFS over time.
- Differences between the reported changes over time between groups were also assessed.

Key messages

- Patient-centered approaches for the management of ME/CFS reduce symptomatology over time.
- Functional ability, physical and social, increase with tailored interventions.
- Psychological intervention can help individuals to regain a sense of control over their condition.

Strengths and limitations of this study

- The findings here are an initial step to fill the gap in the extant literature regarding the utility of tailored, multidisciplinary and patient-centered treatments for ME/CFS.
- There is bias in this study as the participants were self-selected in the sense that they chose to attend the clinic and which treatment option they preferred (with advice).

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Introduction

Chronic Fatigue Syndrome or myalgic encephalomyelitis (ME/CFS) is a condition characterized by prolonged and debilitating fatigue, although the exact cause of this disorder is still under debate. Due to the lack of a definitive biological marker, diagnosis is made on the basis of the exclusion of other explanatory conditions. The most widely used case definition by the Centers for Disease Control [1] states that there must be at least six months severe fatigue of new and definite onset, not the result of ongoing exertion, not alleviated by rest and resulting in reduced levels of physical activity. The CDC definition also sets out a series of minor complaints that must accompany the fatigue (cognitive impairment, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, headaches of a new type, pattern or severity at onset, unrefreshing sleep and post-exertion malaise), with individuals needing to have the occurrence of four or more symptoms to be diagnosed with ME/CFS. Estimates of the prevalence of ME/CFS have been made as low as 3 and as high as 2,800 per 100,000 [2].

The most widely researched strategies for alleviating the symptoms of ME/CFS are Cognitive Behavior Therapy (CBT) and Graded Exercise Therapy (GET). Two reviews of studies on CBT [3 4] found that it significantly improved physical functioning in adult out-patients as compared with medical management counseling, guided support, education and support or relaxation. However, the longitudinal evidence for CBT is inconsistent and there is a lack of evidence with regard to CBT in combination with other treatments [4]. Regarding GET, a systematic review illustrated that this form of therapy was potentially beneficial for people with ME/CFS, especially when combined with a patient education programme [5]. However, drop-out rates were high in the GET groups suggesting that individuals with ME/CFS are adverse to this type of therapy.

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Although CBT and GET studies have shown some promising outcomes, there is no known cure for ME/CFS. Therefore National Institute for Health and Clinical Excellence (NICE) [6] recommends a number of symptom management strategies and interventions aimed at helping individuals to cope with their condition and reduce physical deconditioning brought about by the illness. Pharmacological interventions are, at times, suggested for patients with poor sleep or pain, for instance, low-dose antidepressants, as these have been shown to be effective [7-13]. However, patient expectations must be realistic as the drugs may help elevate mood and psychological outlook but not reduce fatigue and other symptomatology associated with ME/CFS[14]. Numerous drugs such as thyroxin, hydrocortisone and antiviral agents are not advised by NICE due to contradictory findings [15;16].

In terms of function and quality of life management, NICE offers general advice concerning sleep management, appropriate rest periods, and pacing. Sleep hygiene instruction, together with pharmacological treatment tailored to the individual patient can be beneficial in combating fatigue [17]. Dietary management may also reduce symptomatology for those with concurrent irritable bowel syndrome (IBS). Management approaches recommended for IBS, such as diet restriction, are thus also recommended for those with ME/CFS [18]. Dietary supplementation has been investigated in relation to ME/CFS. Fatty acids [19], folic acid [20], vitamin C [21], co-enzyme Q10 [22], magnesium [23], multivitamins [24] and minerals [25] have all been shown to reduce symptomatology in ME/CFS patients. However other studies have shown conflicting findings with regard to nutritional supplementation, therefore it is perhaps wise to treat with supplements on a case-by-case basis [26;27].

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Due to the lack of clear and definitive treatment strategies, individuals often seek out Complementary and Alternative Medicines (CAM). Although NICE does not propose the use of CAM they do acknowledge that many people with ME/CFS use such therapies and find them beneficial for symptom management. This view is due to the lack of published evidence for the effectiveness of these treatments. Examples of CAM treatments used by individuals with ME/CFS include religious healing, massage therapy, relaxation, meditation, homeopathy, acupuncture, naturopathy and herbal therapies [28;29]; patient satisfaction of such approaches CAM has been high, over 80% in some instances [28]. A recent systematic review of such interventions identified 70 controlled clinical trials (randomized and non-randomized) and found that 86% of these studies illustrated at least one positive effect, with 74% showing a decrease of illness-related symptomatology [30]. Meditative or mindfulness approaches warranted further investigation based on these results as did supplement programs of magnesium, l-carnitine, and S-adenosylmethionine. A subsequent review based solely on randomized controlled trials (RCTs) of CAM techniques identified 26 such studies and observed that qigong, massage and tuina (approaches based within Chinese Traditional Medicine and based upon relaxation and connection with the body) illustrated positive effects as did supplementation studies utilizing nicotinamide adenine dinucleotide (NADH) and magnesium [31]. However, within both reviews it was noted that the methodological quality of reporting was poor and the sample sizes in these studies were small; hence ability to draw strong conclusions on the efficacy of CAM methods is limited. Porter et al. (2010) did note that patient-centered, individualized treatment protocols which include a range of tailored strategies are a promising area for further investigation for this complex, multi-system illness.

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Objectives

There is still much debate and uncertainly regarding the most effective treatment for ME/CFS. Recent reviews of CAM techniques highlight the need for further exploration of patient-centered and individually tailored interventions for the alleviation of the condition's often debilitating and intrusive symptomatology. This study therefore aims to evaluate the effectiveness of three types of patient-centered approaches to the management of ME/CFS over time (baseline and follow-up) offered at a private health-care center in the UK.

Methods

Study design and setting

This is a longitudinal observational study which aimed to evaluate three treatment options offered to individuals with ME/CFS. The research was conducted at one private secondary health care facility. All prospective patients of the clinic are first asked to complete a comprehensive symptom profile and medical history, including questions relating to triggering factors, psychology sub-types and structural/biological sub-types (this is distinct from the research data collected). Subsequent to this, every individual receives a 15-minute screening with one of the practitioners who recommends the best course of action for his/her needs; this will be the psychology-related interventions, nutritional advice and support or a combination of the two.

All individuals requesting treatment at the private care setting were offered the opportunity to participate in the study. Those that expressed an interest were emailed a spreadsheet that contained the questionnaires and asked to complete it at their convenience. Informed consent was obtained prior to the completion of the questionnaires and the study was approved by the University of East London Ethics Committee. Participants were told that they could withdraw

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from the study at any time and that withdrawal would not affect their care at the clinic. Participants were able to ask questions at any point in the study and no deception was used as the participants were informed of the nature of the research program before they agreed to participate.

Psychology

The clinic offers a 3-month intervention which consists of a combination of Neuro-linguistic Programming (NLP), Emotional Freedom Techniques (EFT), life coaching and hypnotherapy/self-hypnosis constructed in a manner specific to the needs to those with ME/CFS. The primary aim of this approach is to reduce the anxiety that is associated with having a debilitating and unpredictable condition, improve emotional well-being and help individuals slowly manage and increase their activity within their own limits (i.e. pacing). The program is offered as a series of group sessions and the peer support is seen as an important component of the intervention, which is solidified via the use of moderated online support forums, narratives of previous client's experiences and online materials that can be accessed as often as necessary. In addition, or an alternative to this course, individuals receive a series of one-to-one sessions and for the most severely affected ME/CFS patients, telephone sessions are arranged and support materials can be accessed in their own homes.

Nutrition

Tailored nutritional therapy is achieved via one-to-one consultations with individuals. To begin, a very detailed history is taken based upon the information given in the aforementioned symptom profile. Qualified nutritional therapists (who have been given specialist training regarding ME/CFS from the clinic) then suggest tests consistent with symptomatology, for instance the Adrenal Stress Index Test, comprehensive stool

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analysis/gastro-intestinal function, vitamin & mineral status, etc. Results from these tests are then used to compose an evidence-driven diet and supplement program. As most cases of ME/CFS are complex involving multiple body systems, this process is often iterative and follow-up consultations are necessary to check progress and make alterations to the protocol.

Combined

Within the combined program, a multidisciplinary approach is taken with practitioners discussing the patients in case meetings to ensure that the psychological and nutritional aspects complement each other in order to achieve the best outcome.

Measures

Medical Outcomes Survey Short-Form 36 (SF-36)

This 36-item measure is the short form of the original Medical Outcomes Survey [32] to measure functional impairment and contains eight sub-sections: 1) physical activity limitations due to health problems; 2) social activity limitations due to physical or emotional problems; 3) usual role activity limitations due to physical health problems; 4) bodily pain; 5) general mental health; 6) role activity limitations in usual due to emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions [32]. The items are scored so that higher scores indicate greater functional ability. In terms of the psychometric properties of this measure, reliability estimates for all sub-scales are good, exceeding a Cronbach's alpha coefficient value of 0.70 [33]. In terms of validity, the SF-36 correlates amply, $r \geq 0.40$, with the frequency and severity of numerous symptoms and general health conditions [34;35].

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Multidimensional Health Locus of Control Scale (MHLCS)

Multidimensional Health Locus of Control [36-38] measures perceived control via three distinct sub-scales: 'internal', 'chance' and 'powerful others' which has two dimensions, that of 'doctors' and 'other people'. The instrument contains 18 items in total (six items each for the internal and chance scales and three items for both the powerful others scales) and is scored on a 6-point Likert scale from 'strongly agree' to 'strongly disagree'. Internal reliability of the instrument is good with Cronbach's alpha coefficients ranging from 0.67 for 'powerful others' to 0.77 for 'internal'. The measure correlates positively and significantly with associated scales from Levenson's [39] locus of control measure from which the MHLOC was based upon, which demonstrates good convergent validity [36].

Multidimensional Fatigue Inventory (MFI)

This 20-item measure contains five fatigue dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [40]. Items such as 'I tire easily' are rated on a 5-point scale (1 = yes, that is true; 5 = no, that is not true) with lower scores reflecting higher levels of fatigue. The MFI has good internal consistency with average Cronbach's alpha coefficient equaling 0.84 across the sub-scales. Convergent validity based on a sample of radiotherapy patients found correlations between the sub-scales and a visual analogue fatigue scale to be 0.77 for general fatigue, 0.70 for physical fatigue, 0.61 for reduced activity, 0.56 for reduced motivation ($p<0.001$) to 0.23 for mental fatigue ($p<0.01$) [40].

CDC CFS Symptom Inventory

CDC CFS Symptom Inventory [41] was used to measure specific ME/CFS symptoms and confirm diagnosis. This instrument is based upon the CDC case definition [1] and includes a

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fatigue item and the eight distinct symptoms are also including in the CDC guidelines and an additional ten associated symptoms. The format of this self-report measure is a six-point scale of perceived frequency (0 = absent, 5 = all the time) and severity (0 = none, 5 = very severe). The psychometric properties of this instrument are good: Cronbach's alpha coefficient = 0.88; *r* = .74 convergent validity with the Chalder Fatigue Scale [42]; *r* -.68 and -.87 convergent validity with the SF-36 'vitality' and 'bodily pain' sub-scales, respectively.

Maladaptive Stress Index

This 32-item measure contains three sub-scales (cognitive/mood, sleep and ME/CFS symptoms) and was designed specifically for this population [43]. Items such as 'I constantly reply or pre-empt situations and conversations' and scored on a 5-point scale where 1 = never true and 5 = always true; higher scores illustrate a greater degree of disturbance.

Statistical methods

The data was initially screened for missing data. Three cases contained substantial amounts of missing data; therefore these were excluded from the analysis. Once this was done, all the variables had less than 5% missing data, hence mean substitution was carried out in line with guidance [44]. The baseline data was subsequently of the quality for parametric tests, except for the variables CDC CFS swollen lymph nodes and glands, memory problems, abdominal pain and depression. However, the follow-up data suffered from high levels of skew and kurtosis which was not substantially alleviated by data transformation. This violated a key criterion for parametric testing, that of normality of distribution, so non-parametric tests were selected. In addition, as the sample sizes in each individual treatment group was small, the more conservative non-parametric tests were the preferred choice as even though tests such as analysis of variance are generally robust against non-normality, this does not hold true with

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small sample sizes. For baseline data, one-way analysis of variance tests and Kruskal-Wallis tests were used to investigate difference between groups, Wilcoxon sign-rank tests were employed to look for differences over time (baseline and 3-month follow-up) and Kruskal-Wallis tests were performed to investigate group differences in measures of change as evaluated by mean change scores, with Bonferroni-corrected Mann-Whitney tests calculated to identify post-hoc differences between groups if the Kruskal-Wallis tests were significant.

Results

Participants

One-hundred and thirty-eight individuals completed the questionnaire battery at time-one (excluding the four deleted cases); 42 participants in the psychology group, 44 in the nutrition group and 52 in the combined group. There was no significant association between gender and group (χ^2 (2) = 0.179, $p > .05$), all groups consisting of approximately one-fifth males (Table 1). There was not a significant difference in age ($F(2,135) = 0.000$, $p > .05$); in fact group means for age were near identical at 42.881, 42.864 and 42.843 for psychology, nutrition and combined group, respectively. There was also a non-significant result for illness duration ($F(2, 135) = 0.252$, $p > .05$). Therefore, in terms of demographics, the groups were comparable. With regard to the outcome measures, there were significant differences between the groups in terms of the MFI sub-scale 'general fatigue' ($F(2, 135) = 3.219$, $p < .05$), MFI 'physical fatigue' ($F(2, 135) = 3.343$, $p < .05$) and the CDC CFS symptom 'swollen lymph nodes and glands' ($H(2) = 7.161$, $p < .05$). To investigate the source of these differences, post-hoc tests were conducted (unrelated t-tests for the fatigue variables and Mann-Whitney tests for swollen lymph glands as the former did not meet criteria for parametric tests, all with Bonferroni correction for multiple comparisons). A significant difference was observed between the psychology and combined groups with regards to general fatigue ($t(92) = -2.449$,

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$p < .05$) and physical fatigue ($t(92) = -2.658$, $p < .05$) and also between the nutrition and psychology group in terms of the degree of lymph node and gland swelling ($U = 635.00$, $p < .05$). Within the fatigue measures, the combined group reported significantly higher levels of both general and physical fatigued than the psychology group whereas those undertaking nutritional support stated a higher occurrence swollen lymph nodes and glands.

Retention analysis

Seventy-two of the original 138 participants completed the battery of measures at the 3-month follow-up (52.17%). To investigate whether the individuals who did not complete the time-two measures were significantly different from those at baseline on demographic and outcome measures, a series of t-tests and Mann-Whitney tests were performed. Those that dropped-out of the research (although still receiving treatment at the clinic) differed significantly in terms of age ($t(136) = -2.227$, $p < .05$) and illness duration ($t(136) = -2.549$, $p < .05$). Those who remained in the study were of significantly older age (mean age of those that remained in the study = 45.056, SD = 11.535; mean age of drop-outs = 40.400, SD =12.932) and longer illness duration than those who dropped-out (mean age of those that remained in the study = 10.836, SD = 7.383; mean illness duration of drop-outs =7.571, SD = 7.472). Individuals who did not remain in the study did not differ significantly in terms of gender (χ^2 (2) = 1.222, $p > .05$) or any of the outcome measures.

Longitudinal data

In the sample as a whole, there were significant differences from baseline to follow-up within the internal and doctors sub-scale of the MHLCS and all the CDC CFS Symptom Inventory items bar swollen lymph nodes and glands, fever and abdominal pain. There were also significant differences in all areas of the SF-36, all the fatigue sub-scales of the MFI with the

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five sub-scales illustrating significant reductions in fatigue and, finally, reductions were also observed in the Maladaptive Stress Response.

Within the psychology group significant differences were also found in the SF-36 sub-scales 'physical functioning', 'role limitations due to physical problem', 'social functioning', 'general mental health', 'vitality, energy or fatigue' and 'general health perceptions'. Regarding perceived control, significant differences were found in internal locus of control and the perception that chance played an influential part in the individuals' lives. Again, all the MFI fatigue scales saw significant decreases over a 3-month period. Regarding ME/CFS specific symptoms, ratings of muscle aches or muscle pains, chills, memory problems, difficulty concentrating and sensitivity to light differed significantly from baseline to follow-up in the expected direction. There was also a significant reduction in the Maladaptive Stress Response over time.

The nutrition group saw significant improvements in role limitations due to physical problems, social functioning, vitality, energy or fatigue and general health perceptions. No significant differences were found from baseline to follow-up in perceived control in the nutrition group. Once again, all the MFI fatigue scales decreased over a 3-month period and numerous symptom-related indices also showed improvements; sore throat, swollen lymph glands, fatigue after exertion, muscle aches or muscle pains, pain in joints, chills, headaches, abdominal pain and sensitivity to light. The way in which the individuals in this group responded to stress also decreased over the 3-month time period.

In terms of general health as evaluated by the SF-36 measure, the group who received both psychological and nutritional intervention reported reductions in role limitations due to

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physical difficulties, social functioning, role limitations due to emotional difficulties and general health perceptions. No significant differences were found from baseline to follow-up in perceived control as measured by the MHLCS in the combined treatment group. Only one measure of fatigue, that of physical fatigue, saw significant improvements over time. Diarrhea, fatigue after exertion, chills, headaches and sinus and nasal symptoms all illustrated significant reductions over the 3-month interval, as did the Maladaptive Stress Response. (See Table 2 for descriptive and inferential statistics associated with these findings and Table 3 for percentage of change over time.)

Comparisons across groups

As shown in Table 3, three of the outcome measures differed significantly in terms of change from baseline to follow up, namely the MHLCS 'chance' sub-scale ($H(2) = 7.674$, $p < .05$), the MFI 'general fatigue' sub-scale ($H(2) = 6.790$, $p < .05$) and the CDC CFS symptom 'headaches' ($H(2) = 6.625$, $p < .05$). In terms of perceived control and general fatigue, the psychology group differed significantly as compared to the combined group ($U = 110.500$, $p < .05$) and ($U = 118.000$, $p < .05$), respectively, with the psychology group seeing a greater change over time as compared to the combined group on both measures. Regarding headaches, the combined group ($U = 118.000$, $p < .05$) improved significantly more than the psychology group. No other comparisons reached statistical significance with a Bonferroni correction for multiple comparisons.

Discussion

Key results

There was significant change over time of numerous measures in all groups investigated. The psychology group contained the most significant findings, including those concerned with

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daily functioning, fatigue, locus of control, the cognitive CDC CFS specific symptoms and the Maladaptive Stress Response. As expected, changes in perceived control were not observed in the nutrition group as this is not an area that is targeted in this program. However, the more immune-type symptoms such as sore throat, swollen lymph nodes or glands and pain in joints did see significant reductions over time as would be envisaged in treatment protocols based upon nutritional expertise. The group that exhibited the least significant findings was the combined group and, as noted below, this may be due to the greater general severity in this group and the need for a more lengthy intervention. Nevertheless, considering the small sample sizes in the groups at follow-up, these results are very promising and warrant further attention. In terms of these preliminary findings, the psychology group performed better with regard to lowering the belief that chance influences the course of the condition. This is an important observation as the unpredictable nature of ME/CFS can be one of the most difficult components for individuals to cope with [45] and helping patients gain an improved sense of control over the illness is of great potential benefit. The psychology group also demonstrated a significantly greater change score in general fatigue as compared with the combined group which may infer that in the short term, guiding individuals through the complex nature of the disorder, helping them to understand it and accept that the condition itself gives rise to stresses and psychological distress may be a good starting point for intervention (i.e. a stepped program could be developed).

Interpretation

As noted previously [30] patient-centered, individualized treatment protocols which include a range of tailored strategies is a favorable direction for dealing with a complex and multi-system disorder such as ME/CFS. The present study has demonstrated that such interventions are useful in lowering symptomatology, improving functioning and helping individuals gain a

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greater sense of control over their health status. Considering that the options available on the National Health Service, mainly CBT and GET, are often perceived as coping strategies at best, and physically damaging at worst [46], tailored treatments such as described here may be more palatable, and hence effective.

Limitations and Generalisability

This study did not have a control group so the results should be treated with caution. Also, the participants were not randomly assigned to groups as this was a naturalistic, observational study. Each individual was guided to appropriate treatment within an initial screening with clinic staff, therefore the group was dependent on the nature of the individual's symptoms and their personal choice as the programs on offer were privately funded. However, as can be seen in the baseline comparisons, the groups did not differ in terms of gender, age, illness duration or the majority of outcome measures. Notably, the groups did differ in general and physical fatigue with participants in the combined groups reporting greater fatigue than those in the psychology group which suggests that this group's general symptomatology was more severe. The combined group illustrated less improvement over time compared to the psychology and nutrition groups and it is feasible to infer that individuals with a greater number and degree of complaints are referred to the combined group within the clinic. Also, it should be noted that the interventions in the combined program are phased in as it was found that asking individuals to engage in numerous therapeutic activities resulted in high drop-out rates. Therefore, changes in outcome measures may not be noted at an interval of three months for that group. Further studies underway presently will investigate follow-ups at 6- and 12-months to identify whether the findings here are maintained over time and also whether those with greater severity benefit with a longer intervention. As the participants were self-selected onto these programs, the findings lack generalizability; future work should

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sample from the overall ME/CFS population and be randomly-assigned to groups in order to make valid assumptions regarding the illness-group as a whole.

Funding

No external funding was obtained for this research; the work was accomplished in-house at the clinic in question.

Data Sharing

Dataset available from the corresponding author at m.a.arroll@sa.uel.ac.uk. Consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low.

Contributorship

Alex Howard made a substantial contributions to conception and design and acquisition of data, whilst Megan Arroll made a substantial contribution to the analysis and interpretation of data. Both authors made a substantial
contribution to the drafting of the article and revisions for the critically of important intellectual content. Final approval of the version to be published was also granted by both authors.

Competing Interests

None

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List of abbreviations

ME: myalgic encephalomyelitis

CFS: Chronic Fatigue Syndrome

NICE: National Institute for Health and Clinical Excellence

CBT: Cognitive Behavioral Therapy

GET: Graded Exercise Therapy

CAM: Complementary and Alternative Medicine

NLP: Neuro-linguistic Programming

EFT: Emotional Freedom Technique

SF-36: Medical Outcomes Survey Short-Form 36

MHLCS: Multidimensional Health Locus of Control Scale

MFI: Multidimensional Fatigue Inventory

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Table 1. Baseline comparisons of sample demographics and outcome variables

		Mean	SD	95% CI for Mean		Test statistic	p-value
				Lower	Upper		
Gender	Psychology	9 (21.4%)[d]				.179[c]	.915
	Nutrition	8 (18.2%)[d]					
	Combined	11 (21.2%)[d]					
	Total	28 (20.3%)[d]					
Age	Psychology	42.881	13.986	38.523	47.239	.000[a]	1.000
	Nutrition	42.864	12.504	39.062	46.665		
	Combined	42.843	11.125	39.714	45.972		
	Total	42.861	12.406	40.765	44.957		
Illness duration	Psychology	8.874	8.252	6.302	11.445	.252[a]	.778
	Nutrition	10.023	7.375	7.781	12.265		
	Combined	9.625	7.291	7.595	11.655		
	Total	9.523	7.580	8.247	10.800		
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	.319[a]	.727
	Nutrition	47.855	26.226	39.882	55.829		
	Combined	45.299	25.479	38.206	52.393		
	Total	47.344	24.792	43.171	51.517		
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	.281[a]	.755
	Nutrition	7.574	17.500	2.254	12.895		
	Combined	9.774	21.051	3.914	15.635		
	Total	8.272	18.387	5.177	11.367		
SF-36	Psychology	61.548	25.614	53.566	69.530	1.002[a]	.370

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Bodily pain	Nutrition	55.625	30.242	46.431	64.819		
	Combined	53.606	27.019	46.084	61.128		
	Total	56.667	27.683	52.007	61.327		
SF-36	Psychology	37.202	21.824	30.402	44.003	.536[a]	.586
Social functioning	Nutrition	32.671	25.888	24.800	40.541		
	Combined	32.452	24.786	25.552	39.352		
	Total	33.967	24.212	29.892	38.043		
SF-36	Psychology	60.286	19.584	54.183	66.389	.124[a]	.884
General mental health	Nutrition	59.727	19.355	53.843	65.612		
	Combined	58.308	20.948	52.476	64.140		
	Total	59.362	19.911	56.011	62.714		
SF-36	Psychology	55.554	46.368	41.104	70.004	.390[a]	.678
Role limitations emotional	Nutrition	48.482	47.390	34.074	62.890		
	Combined	47.780	43.924	35.551	60.008		
	Total	50.370	45.590	42.695	58.044		
SF-36	Psychology	20.714	16.1386	15.685	25.743	.129[a]	.879
Vitality Energy or Fatigue	Nutrition	20.114	14.570	15.685	24.542		
	Combined	19.039	17.658	14.123	23.955		
	Total	19.891	16.159	17.171	22.611		
SF-36	Psychology	37.024	17.945	31.432	42.616	2.769[a]	.066
General health perceptions	Nutrition	28.636	15.528	23.915	33.357		
	Combined	30.962	17.575	26.069	35.854		
	Total	32.065	17.286	29.156	34.975		
MHLCS Internal	Psychology	.677	.159	.627	.726	1.216[a]	.300
	Nutrition	.622	.177	.568	.675		

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	Combined	.662	.174	.613	.710		
	Total	.653	.171	.625	.682		
MHLCS Chance	Psychology	.368	.156	.320	.417	.395[a]	.674
	Nutrition	.340	.133	.299	.380		
	Combined	.354	.155	.311	.397		
	Total	.354	.148	.329	.379		
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.119[a]	.888
	Nutrition	.417	.141	.374	.460		
	Combined	.407	.101	.379	.436		
	Total	.409	.124	.388	.430		
MHLCS Doctors	Psychology	.169	.082	.143	.194	.575[a]	.564
	Nutrition	.171	.089	.144	.197		
	Combined	.191	.147	.150	.232		
	Total	.178	.112	.159	.196		
MHLCS Other People	Psychology	.235	.075	.212	.259	1.051[a]	.352
	Nutrition	.264	.129	.225	.304		
	Combined	.245	.074	.224	.265		
	Total	.248	.095	.232	.264		
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	3.219[a]	.043*
	Nutrition	16.977	2.601	16.186	17.768		
	Combined	17.327	2.587	16.607	18.047		
	Total	16.797	2.716	16.340	17.254		
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	3.343[a]	.038*
	Nutrition	16.727	3.358	15.707	17.748		
	Combined	17.615	2.823	16.830	18.401		

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	Total	16.819	3.211	16.278	17.359		
MFI Reduced Activity	Psychology	13.857	4.112	12.576	15.138	1.030[a]	.360
	Nutrition	14.136	4.027	12.912	15.361		
	Combined	14.962	3.662	13.942	15.981		
	Total	14.362	3.921	13.702	15.022		
MFI Reduced Motivation	Psychology	10.357	4.287	9.021	11.693	1.324[a]	.270
	Nutrition	10.500	3.474	9.444	11.556		
	Combined	11.462	3.153	10.584	12.339		
	Total	10.819	3.639	10.206	11.431		
MFI Mental Fatigue	Psychology	13.524	4.363	12.164	14.883	.064[a]	.938
	Nutrition	13.682	4.328	12.366	14.998		
	Combined	13.846	4.345	12.637	15.056		
	Total	13.696	4.315	12.969	14.422		
CDC CFS Sore Throat	Psychology	2.571	3.109	1.603	3.540	1.414[a]	.247
	Nutrition	3.977	3.776	2.829	5.125		
	Combined	3.202	4.494	1.951	4.454		
	Total	3.257	3.898	2.601	3.914		
CDC CFS Swollen Lymph nodes Glands	Psychology	1.976	3.382	.922	3.030	7.161[b]	.028*
	Nutrition	5.561	6.491	3.587	7.534		
	Combined	3.462	4.881	2.103	4.820		
	Total	3.679	5.250	2.795	4.563		
CDC CFS Diarrhoea	Psychology	2.071	3.249	1.059	3.084	.850[a]	.430
	Nutrition	2.841	4.832	1.372	4.310		
	Combined	3.135	3.773	2.084	4.185		
	Total	2.717	3.998	2.044	3.390		

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CDC CFS Fatigue after exertion	Psychology	13.286	6.271	11.331	15.240	.219[a]	.803
	Nutrition	13.722	6.450	11.761	15.682		
	Combined	14.154	6.270	12.408	15.899		
	Total	13.752	6.292	12.693	14.811		
CDC CFS Muscle Aches or Muscle Pains	Psychology	8.286	6.747	6.183	10.388	.166[a]	.847
	Nutrition	9.091	6.383	7.151	11.031		
	Combined	8.519	6.932	6.589	10.449		
	Total	8.630	6.664	7.509	9.752		
CDC CFS Pain In Joints	Psychology	3.476	5.334	1.814	5.138	1.373[a]	.257
	Nutrition	4.696	5.560	3.006	6.386		
	Combined	5.474	6.386	3.696	7.251		
	Total	4.618	5.837	3.635	5.600		
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	.027[a]	.973
	Nutrition	1.394	2.562	.615	2.173		
	Combined	1.333	3.909	.245	2.421		
	Total	1.324	3.106	.801	1.846		
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	.206[a]	.814
	Nutrition	3.750	3.924	2.557	4.943		
	Combined	3.192	4.343	1.983	4.402		
	Total	3.420	4.283	2.699	4.141		
CDC CFS Unrefreshing Sleep	Psychology	12.905	6.792	10.788	15.021	.150[a]	.861
	Nutrition	12.250	7.088	10.095	14.405		
	Combined	12.154	7.147	10.164	14.144		
	Total	12.413	6.978	11.238	13.588		
CDC CFS Sleeping	Psychology	9.286	7.658	6.899	11.672	.085[a]	.918

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Problems	Nutrition	8.614	7.317	6.389	10.838		
	Combined	8.904	7.684	6.766	11.042		
	Total	8.928	7.509	7.664	10.192		
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	1.611[a]	.203
	Nutrition	7.646	7.040	5.506	9.786		
	Combined	6.346	5.857	4.715	7.977		
	Total	6.431	6.200	5.3871	7.474		
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.403[b]	.182
	Nutrition	9.409	7.183	7.225	11.593		
	Combined	8.173	7.610	6.055	10.292		
	Total	8.007	6.835	6.857	9.158		
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	.391[a]	.677
	Nutrition	9.822	7.641	7.499	12.145		
	Combined	9.135	6.942	7.202	11.067		
	Total	9.161	6.903	7.999	10.323		
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	1.162[a]	.316
	Nutrition	4.769	5.135	3.208	6.330		
	Combined	3.327	4.902	1.962	4.692		
	Total	3.832	4.966	2.996	4.668		
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	5.971[b]	.051
	Nutrition	5.064	5.165	3.493	6.634		
	Combined	3.750	4.635	2.460	5.041		
	Total	3.803	4.535	3.040	4.566		
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	1.192[a]	.307
	Nutrition	5.469	6.476	3.500	7.438		

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	Combined	4.789	6.304	3.034	6.544		
	Total	4.620	5.932	3.622	5.619		
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	.095[a]	.909
	Nutrition	3.285	4.090	2.026	4.543		
	Combined	3.392	4.788	2.046	4.739		
	Total	3.237	4.365	2.497	3.977		
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	.794[a]	.454
	Nutrition	5.031	6.097	3.177	6.884		
	Combined	4.481	6.360	2.710	6.251		
	Total	4.336	5.975	3.330	5.342		
CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	.160[b]	.923
	Nutrition	4.477	5.450	2.821	6.134		
	Combined	5.077	5.950	3.420	6.734		
	Total	4.544	5.231	3.663	5.424		
CDC CFS Maladaptive Stress Index Scale Score	Psychology	94.381	16.836	89.134	99.628	.465[a]	.629
	Nutrition	96.386	21.946	89.714	103.059		
	Combined	98.269	19.165	92.934	103.605		
	Total	96.486	19.373	93.225	99.747		

[a] *F*-statistic for one-way analysis of variance, d.f = 2,134

[b] *H*-statistic for Kruskal-Wallis test, d.f. = 2

[c] χ^2-statistic for comparison of nominal level data, d.f. = 2

[d] number of males

* test is significant at the $p < .05$ level

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Table 2. Outcome variable comparisons across time

		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	59.267	30.346	41.745	76.788	-2.707	.007**
	Nutrition	47.855	26.226	39.882	55.829	46.706	30.744	34.544	58.868	-1.136	.256
	Combined	45.299	25.479	38.206	52.393	49.288	26.403	39.604	58.973	-1.850	.064
	Total	47.344	24.791	43.171	51.517	50.260	28.818	43.488	57.032	-3.120	.002**
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	46.429	39.048	23.883	68.974	-2.379	.017*
	Nutrition	7.574	17.500	2.254	12.895	19.444	20.016	11.526	27.363	-2.907	.004**
	Combined	9.774	21.051	3.914	15.635	22.742	25.161	13.513	31.971	-2.225	.026*
	Total	8.272	18.387	5.177	11.367	26.111	28.225	19.479	32.744	-4.354	.001***
SF-36 Bodily pain	Psychology	61.548	25.614	53.566	69.530	63.929	29.786	46.731	81.127	-1.196	.232
	Nutrition	55.625	30.242	46.434	64.819	58.889	32.943	45.857	71.921	-1.800	.072
	Combined	53.606	27.019	46.084	61.128	58.629	27.301	48.615	68.643	-1.048	.294
	Total	56.667	27.683	52.007	61.327	59.757	29.649	52.790	66.724	-2.240	.025*
SF-36 Social functioning	Psychology	37.202	21.824	30.402	44.003	59.821	33.318	40.584	79.058	-2.689	.007**
	Nutrition	32.671	25.888	24.800	40.541	43.519	33.679	30.196	56.841	-2.476	.013*
	Combined	32.452	24.786	25.551	39.352	41.936	28.604	31.443	52.428	-2.426	.015*
	Total	33.967	24.212	29.892	38.043	46.007	31.805	38.533	53.481	-4.504	.001***
SF-36 General mental health	Psychology	60.286	19.584	54.183	66.389	74.571	13.276	66.906	82.237	-2.497	.013*
	Nutrition	59.727	19.355	53.843	65.612	64.741	20.548	56.612	72.869	-1.696	.090
	Combined	58.308	20.948	52.476	64.140	64.129	16.637	58.027	70.232	-.524	.600

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	Total	59.362	19.911	56.011	62.714	66.389	17.897	62.183	70.594	-2.665	.008**
SF-36 Role limitations emotional	Psychology	55.554	46.368	41.105	70.004	76.191	33.150	57.051	95.331	-.842	.400
	Nutrition	48.482	47.390	34.074	62.890	55.594	38.130	40.510	70.678	-1.788	.074
	Combined	47.780	43.924	35.551	60.008	67.742	32.756	55.727	79.757	-2.313	.021*
	Total	50.370	45.590	42.695	58.044	64.829	35.335	56.526	73.133	-3.159	.002**
SF-36 Vitality Energy or Fatigue	Psychology	20.714	16.139	15.685	25.743	41.071	20.586	29.186	52.957	-3.066	.002**
	Nutrition	20.114	14.5670	15.685	24.542	31.111	23.588	21.780	40.442	-2.734	.006**
	Combined	19.039	17.658	14.123	23.955	27.097	19.527	19.934	34.259	-1.558	.119
	Total	19.891	16.159	17.171	22.611	31.319	21.657	26.230	36.409	-4.205	.001***
SF-36 General health perceptions	Psychology	37.024	17.945	31.432	42.616	45.714	21.109	33.526	57.903	-2.561	.010*
	Nutrition	28.636	15.528	23.915	33.357	36.482	18.903	29.004	43.959	-2.157	.031*
	Combined	30.962	17.575	26.069	35.854	42.097	21.632	34.162	50.032	-2.423	.015*
	Total	32.065	17.286	29.156	34.975	40.694	20.561	35.863	45.526	-3.996	.001***
MHLCS Internal	Psychology	.677	.159	.627	.726	.821	.251	.676	.966	-2.983	.003**
	Nutrition	.622	.177	.568	.675	1.193	2.969	.019	2.368	-.687	.492
	Combined	.662	.174	.613	.710	.779	.318	.662	.896	-1.755	.079
	Total	.653	.171	.624	.682	.942	1.822	.514	1.371	-2.962	.003**
MHLCS Chance	Psychology	.368	.156	.320	.417	.351	.152	.263	.439	-2.594	.009**
	Nutrition	.340	.133	.299	.380	.911	3.020	-.284	2.105	-.143	.886
	Combined	.354	.155	.311	.397	.314	.133	.265	.363	-.672	.501
	Total	.354	.148	.329	.379	.545	1.853	.109	.980	-1.552	.121
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.441	.315	.259	.624	.000	1.000
	Nutrition	.418	.141	.374	.460	.804	2.244	-.084	1.691	-1.843	.065
	Combined	.407	.101	.379	.436	.434	.279	.331	.536	-.577	.564
	Total	.409	.124	.388	.430	.574	1.3880	.248	.900	-1.601	.109

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MHLCS Doctors	Psychology	.169	.082	.143	.194	.131	.093	.077	.185	-1.122	.262
	Nutrition	.171	.089	.144	.197	.657	2.668	-.398	1.713	-1.686	.092
	Combined	.191	.147	.150	.232	.153	.070	.128	.179	-1.384	.166
	Total	.178	.112	.159	.196	.338	1.635	-.0462	.722	-2.381	.017*
MHLCS Other People	Psychology	.235	.075	.212	.259	.268	.189	.159	.377	-.118	.906
	Nutrition	.264	.129	.225	.304	.739	2.652	-.311	1.788	-1.697	.090
	Combined	.245	.074	.224	.265	.252	.118	.209	.295	-.213	.831
	Total	.248	.095	.232	.264	.438	1.626	.055	.820	-1.186	.236
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	13.786	4.441	11.222	16.350	-2.657	.008**
	Nutrition	16.977	2.601	16.186	17.768	14.704	4.898	12.766	16.641	-2.548	.011*
	Combined	17.327	2.588	16.607	18.047	16.645	2.811	15.614	17.676	-.854	.393
	Total	16.797	2.716	16.340	17.254	15.361	4.136	14.389	16.333	-3.692	.001***
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	13.071	4.632	10.397	15.746	-2.810	.005**
	Nutrition	16.727	3.358	15.707	17.748	14.222	4.987	12.249	16.195	-2.791	.005**
	Combined	17.615	2.823	16.830	18.401	16.484	3.395	15.239	17.729	-2.364	.018*
	Total	16.819	3.211	16.278	17.359	14.972	4.453	13.926	16.019	-4.591	.001***
MFI Reduced Activity	Psychology	13.857	4.112	12.576	15.138	10.643	5.153	7.668	13.618	-2.142	.032*
	Nutrition	14.136	4.027	12.912	15.361	12.259	5.012	10.277	14.242	-2.164	.030*
	Combined	14.962	3.662	13.942	15.981	14.936	3.777	13.550	16.321	-.070	.944
	Total	14.362	3.921	13.702	15.022	13.097	4.798	11.970	14.225	-2.421	.015*
MFI Reduced Motivation	Psychology	10.357	4.287	9.021	11.693	7.286	4.214	4.853	9.719	-2.131	.033*
	Nutrition	10.500	3.474	9.444	11.556	8.963	3.736	7.485	10.441	-1.985	.047*
	Combined	11.462	3.153	10.584	12.339	10.774	3.095	9.639	11.910	-1.082	.279
	Total	10.819	3.639	10.206	11.431	9.417	3.767	8.532	10.302	-2.986	.003**
MFI	Psychology	13.524	4.363	12.164	14.883	10.500	4.468	7.920	13.080	-2.950	.003*

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Mental Fatigue	Nutrition	13.682	4.328	12.366	14.998	11.926	5.334	9.816	14.036	-2.082	.037*
	Combined	13.846	4.345	12.637	15.056	12.613	3.827	11.209	14.017	-1.586	.113
	Total	13.696	4.315	12.969	14.422	11.944	4.568	10.871	13.018	-3.661	.001***
CDC CFS Sore Throat	Psychology	2.571	3.109	1.603	3.540	1.429	2.278	.114	2.744	-1.365	.172
	Nutrition	3.977	3.776	2.829	5.125	1.741	2.087	.915	2.566	-2.211	.027*
	Combined	3.202	4.494	1.951	4.454	1.904	2.821	.870	2.939	-.804	.422
	Total	3.257	3.898	2.601	3.914	1.750	2.437	1.178	2.323	-2.387	.017*
CDC CFS Swollen Lymph nodes Glands	Psychology	1.976	3.382	.922	3.030	1.786	3.378	-.165	3.736	-.341	.733
	Nutrition	5.561	6.491	3.587	7.534	5.000	6.760	2.326	7.674	-2.212	.027*
	Combined	3.462	4.881	2.103	4.820	2.690	4.477	1.0458	4.332	-.725	.468
	Total	3.679	5.250	2.795	4.563	3.380	5.385	2.115	4.646	-1.684	.092
CDC CFS Diarrhoea	Psychology	2.071	3.249	1.059	3.084	1.643	2.818	.016	3.270	-.730	.465
	Nutrition	2.841	4.832	1.372	4.310	1.444	3.274	.149	2.740	-1.649	.099
	Combined	3.135	3.773	2.084	4.185	1.631	2.483	.720	2.542	-1.996	046*
	Total	2.717	3.998	2.044	3.390	1.563	2.827	.899	2.228	-2.481	.013*
CDC CFS Fatigue after exertion	Psychology	13.286	6.271	11.331	15.240	11.071	6.673	7.218	14.925	-1.550	.121
	Nutrition	13.722	6.450	11.761	15.682	11.815	7.217	8.960	14.670	-2.209	.027*
	Combined	14.154	6.270	12.408	15.899	11.436	6.275	9.134	13.738	-2.392	.017*.
	Total	13.752	6.292	12.693	14.811	11.507	6.629	9.949	13.065	-3.574	.001***
CDC CFS Muscle Aches or Muscle Pains	Psychology	8.286	6.747	6.183	10.388	7.429	6.892	3.450	11.408	-2.145	.032*
	Nutrition	9.091	6.383	7.151	11.031	7.222	6.278	4.739	9.706	-2.901	.004**
	Combined	8.519	6.932	6.589	10.449	6.188	5.528	4.160	8.215	-1.908	.056
	Total	8.630	6.664	7.509	9.752	6.817	6.029	5.400	8.234	-.3995	.001***
CDC CFS Pain In Joints	Psychology	3.476	5.334	1.814	5.138	2.786	4.458	.212	5.360	-1.778	.075
	Nutrition	4.696	5.560	3.006	6.386	3.926	5.099	1.909	5.943	-2.022	.043*

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	Combined	5.474	6.386	3.696	7.251	3.010	4.140	1.492	4.528	-1.840	.066
	Total	4.618	5.837	3.635	5.600	3.310	4.543	2.242	4.377	-3.141	.002**
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	1.643	4.181	-.771	4.057	-.135	.892
	Nutrition	1.394	2.562	.615	2.173	.630	2.041	-.178	1.437	-1.487	.137
	Combined	1.333	3.909	.245	2.421	.378	.709	.118	.638	-1.517	.129
	Total	1.324	3.106	.801	1.846	.718	2.272	.185	1.252	-1.876	.061
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	2.571	4.398	.032	5.111	-1.970	.049*
	Nutrition	3.750	3.924	2.557	4.943	2.222	4.098	.601	3.843	-3.401	.001***
	Combined	3.192	4.343	1.983	4.402	1.908	2.797	.882	2.934	-2.049	.040*
	Total	3.420	4.283	2.699	4.141	2.155	3.614	1.306	3.004	-4.206	.001***
CDC CFS Unrefreshing Sleep	Psychology	12.905	6.792	10.788	15.021	10.643	6.698	6.776	14.510	-.802	.422
	Nutrition	12.250	7.088	10.095	14.405	9.444	7.738	6.384	12.505	-1.421	.155
	Combined	12.154	7.147	10.164	14.143	10.161	7.959	7.242	13.080	-1.513	.130
	Total	12.413	6.978	11.238	13.588	9.986	7.557	8.210	11.762	-2.295	.022*
CDC CFS Sleeping Problems	Psychology	9.286	7.658	6.899	11.672	5.286	4.921	2.444	8.127	-1.738	.082
	Nutrition	8.614	7.317	6.389	10.838	9.482	9.200	5.842	13.121	-.190	.849
	Combined	8.904	7.681	6.766	11.042	6.529	6.749	4.053	9.004	-1.794	.073
	Total	8.928	7.509	7.664	10.192	7.394	7.585	5.612	9.177	-1.983	.047*
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	4.357	3.411	2.388	6.326	-1.200	.230
	Nutrition	7.646	7.040	5.506	9.786	5.185	6.294	2.695	7.675	-2.084	.037*
	Combined	6.346	5.857	4.715	7.977	4.050	3.527	2.756	5.343	-2.807	.005**
	Total	6.431	6.200	5.387	7.474	4.535	4.708	3.429	5.642	-3.000	.003**
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.500	3.995	1.193	5.807	-1.965	.049*
	Nutrition	9.409	7.183	7.225	11.593	8.667	7.681	5.628	11.705	-.338	.735
	Combined	8.173	7.610	6.055	10.292	6.148	4.905	4.349	7.947	-1.446	.148

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	Total	8.007	6.835	6.857	9.158	6.578	6.189	5.123	8.032	-2.053	.040*
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	5.143	5.559	1.933	8.353	-2.809	.005**
	Nutrition	9.822	7.641	7.499	12.145	7.778	6.941	5.032	10.524	-1.196	.232
	Combined	9.135	6.942	7.202	11.067	6.507	4.843	4.731	8.283	-1.899	.058
	Total	9.161	6.903	7.999	10.323	6.718	5.844	5.345	8.092	-3.440	.001***
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	2.286	2.946	.585	3.987	-.213	.832
	Nutrition	4.769	5.135	3.208	6.330	3.407	5.746	1.134	5.681	-1.686	.092
	Combined	3.327	4.902	1.962	4.692	3.458	3.585	2.144	4.773	-.855	.392
	Total	3.832	4.966	2.996	4.668	3.211	4.396	2.178	4.244	-.584	.559
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	2.786	4.003	.474	5.097	-.343	.732
	Nutrition	5.064	5.165	3.493	6.634	3.593	3.905	2.048	5.137	-1.968	.049*
	Combined	3.750	4.635	2.460	5.041	2.548	2.791	1.524	3.572	-.598	.550
	Total	3.803	4.535	3.040	4.566	2.986	3.470	2.171	3.801	-1.727	.084
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	2.357	2.437	.950	3.764	-.724	.469
	Nutrition	5.469	6.476	3.500	7.438	4.889	6.104	2.474	7.304	-1.400	.162
	Combined	4.789	6.304	3.034	6.544	3.804	6.710	1.343	6.266	-2.482	.013*
	Total	4.620	5.931	3.622	5.619	3.930	5.882	2.547	5.312	-2.971	.003**
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	1.571	2.209	.296	2.847	-1.556	.120
	Nutrition	3.285	4.090	2.026	4.543	2.407	4.060	.801	4.013	-1.849	.064
	Combined	3.392	4.788	2.046	4.739	2.526	3.631	1.194	3.858	-.976	.329
	Total	3.237	4.365	2.497	3.977	2.296	3.554	1.461	3.131	-2.538	.011*
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	1.214	2.517	-.239	2.668	-1.973	.049*
	Nutrition	5.031	6.097	3.177	6.884	4.111	6.198	1.659	6.563	-2.136	.033*
	Combined	4.481	6.360	2.710	6.251	3.297	5.557	1.259	5.335	-.787	.431
	Total	4.336	5.975	3.330	5.342	3.197	5.419	1.924	4.471	-2.542	.011*

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CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	1.571	3.228	-.292	3.435	-1.614	.106
	Nutrition	4.477	5.450	2.821	6.134	3.333	4.883	1.402	5.265	-1.584	.113
	Combined	5.077	5.950	3.420	6.734	2.766	3.324	1.547	3.985	-1.304	.192
	Total	4.544	5.230	3.663	5.424	2.747	3.964	1.815	3.678	-2.297	.022*
CDC CFS Maladaptive Stress Index Scale Score	Psychology	94.381	16.836	89.134	99.628	78.571	18.434	67.928	89.215	-3.111	.002**
	Nutrition	96.386	21.946	89.714	103.059	85.259	27.665	74.315	96.203	-3.443	.001***
	Combined	98.269	19.165	92.934	103.605	87.484	22.965	79.060	95.908	-2.215	.027*
	Total	96.486	19.373	93.225	99.747	84.917	24.004	79.276	90.557	-5.123	.001***

[a] *z*-statistic for Wilcoxon Signed-Rank Test

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Table 3. Change score comparisons between intervention groups

		% change over time for sig. results [a]	Mean	Std. Deviation	Std. Error	95% CI for Mean		H [b]	p-value
						Lower	Upper		
SF-36 Physical Functioning	Psychology	16.75	-13.629	14.990	4.006	-22.285	-4.974	3.215	.200
	Nutrition		-.407	19.967	3.843	-8.306	7.492		
	Combined		-6.813	18.242	3.276	-13.505	-.122		
	Total	5.80	-5.736	18.744	2.209	-10.141	-1.332		
SF-36	Psychology	84.61	-33.929	39.960	10.680	-57.001	-10.856	1.558	.459

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Role limitations physical	Nutrition	61.05	-14.509	21.005	4.042	-22.818	-6.199		
	Combined	57.02	-13.871	31.457	5.650	-25.409	-2.333		
	Total	63.32	-18.010	30.564	3.602	-25.192	-10.828		
SF-36	Psychology		-6.071	15.588	4.166	-15.072	2.929	.163	.922
Bodily pain	Nutrition		-6.574	18.800	3.618	-14.011	.863		
	Combined		-3.387	25.532	4.586	-12.752	5.978		
	Total	5.17	-5.104	21.252	2.505	-10.098	-.110		
SF-36	Psychology	37.81	-24.107	24.741	6.612	-38.392	-9.822	3.301	.192
Social functioning	Nutrition	24.93	-10.648	20.423	3.931	-18.727	-2.569		
	Combined	22.60	-11.290	24.013	4.313	-20.098	-2.482		
	Total	26.17	-13.542	23.149	2.728	-18.981	-8.102		
SF-36	Psychology	19.15	-12.000	14.294	3.820	-20.253	-3.747	4.404	.111
General mental health	Nutrition		-3.259	15.963	3.072	-9.574	3.056		
	Combined		-.645	16.911	3.037	-6.848	5.558		
	Total	10.58	-3.833	16.409	1.934	-7.689	.022		
SF-36	Psychology		-9.527	49.664	13.273	-38.202	19.148	.573	.751
Role limitations	Nutrition		-18.561	55.759	10.731	-40.618	3.497		
emotional	Combined	29.47	-18.284	52.240	9.383	-37.446	.878		
	Total	10.58	-16.685	52.496	6.187	-29.021	-4.349		
SF-36	Psychology	49.57	-17.500	15.902	4.250	-26.682	-8.318	4.988	.083
Vitality Energy or	Nutrition	35.35	-11.482	19.206	3.696	-19.079	-3.884		
Fatigue	Combined		-6.129	17.688	3.177	-12.617	.359		
	Total	22.30	-10.347	18.219	2.147	-14.628	-6.066		
SF-36	Psychology	19.01	-11.429	14.335	3.831	-19.705	-3.152	.627	.731
General health	Nutrition	29.73	-6.852	15.201	2.925	-12.865	-.839		

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perceptions	Combined	26.45	-10.161	22.154	3.97	-18.288	-2.035		
	Total	36.49	-9.167	18.251	2.151	-13.455	-4.878		
MHLCS Internal	Psychology	17.56	-.146	.203	.054	-.263	-.029	3.402	.183
	Nutrition		-.573	3.028	.583	-1.771	.625		
	Combined		-.106	.315	.057	-.222	.010		
	Total	30.67	-.289	1.859	.219	-.726	.148		
MHLCS Chance	Psychology	4.67	.077	.098	.026	.021	.134	7.674	.022*
	Nutrition		-.570	3.019	.581	-1.765	.624		
	Combined		.001	.081	.015	-.029	.031		
	Total		-.198	1.852	.218	-.633	.237		
MHLCS Powerful Others	Psychology		-.054	.284	.076	-.218	.109	1.571	.456
	Nutrition		-.375	2.282	.439	-1.277	.528		
	Combined		-.030	.277	.050	-.132	.072		
	Total		-.164	1.408	.166	-.495	.167		
MHLCS Doctors	Psychology		.020	.058	.0155	-.014	.053	0.076	.963
	Nutrition		-.492	2.678	.515	-1.551	.568		
	Combined		.057	.199	.036	-.016	.130		
	Total	47.49	-.156	1.647	.194	-.543	.231		
MHLCS Other People	Psychology		-.032	.166	.044	-.128	.064	2.479	.290
	Nutrition		-.446	2.692	.518	-1.510	.619		
	Combined		-.012	.096	.017	-.047	.023		
	Total		-.178	1.645	.193	-.565	.208		

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MFI General Fatigue	Psychology	13.58	2.571	2.766	.739	.975	4.168	6.790	.034*
	Nutrition	13.39	2.074	3.842	.740	.554	3.594		
	Combined		.419	2.233	.401	-.400	1.238		
	Total	8.55	1.458	3.126	.368	.724	2.193		
MFI Physical Fatigue	Psychology	17.74	2.857	2.797	.748	1.242	4.472	3.038	.219
	Nutrition	15.00	2.444	4.371	.841	.716	4.173		
	Combined	6.42	1.290	2.735	.491	.287	2.294		
	Total	10.98	2.028	3.468	.409	1.213	2.843		
MFI Reduced Activity	Psychology	23.20	1.857	2.932	.784	.165	3.550	1.734	.420
	Nutrition	13.28	1.148	2.685	.517	.086	2.210		
	Combined		.645	3.189	.572	-.525	1.815		
	Total	8.81	1.069	2.952	.348	.376	1.763		
MFI Reduced Motivation	Psychology	11.42	2.500	3.502	.936	.478	4.522	5.171	.075
	Nutrition	14.64	1.593	3.511	.676	.204	2.982		
	Combined		.129	3.471	.624	-1.144	1.402		
	Total	12.96	1.139	3.570	.421	.300	1.978		
MFI Mental Fatigue	Psychology	29.66	3.571	3.056	.817	1.807	5.336	4.551	.103
	Nutrition	12.83	1.519	3.631	.699	.082	2.955		
	Combined		1.161	4.267	.766	-.404	2.726		
	Total	12.79	1.764	3.880	.457	.852	2.676		
CDC CFS Sore Throat	Psychology		1.429	3.736	.998	-.728	3.586	1.298	.523
	Nutrition	56.23	1.185	2.661	.512	.133	2.238		
	Combined		.500	4.591	.825	-1.184	2.184		
	Total	46.26	.937	3.769	.444	.052	1.823		
CDC CFS Swollen Lymph	Psychology		-.143	2.932	.784	-1.835	1.550	0.462	.794

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nodes Glands	Nutrition	10.09	1.247	2.700	.520	.179	2.316		
	Combined		.794	6.549	1.176	-1.608	3.197		
	Total		.782	4.756	.560	-.336	1.900		
CDC CFS Diarrhoea	Psychology		-.286	1.490	.398	-1.146	.575	3.619	.164
	Nutrition		.926	2.868	.552	-.209	2.060		
	Combined	47.97	1.272	3.789	.681	-.118	2.662		
	Total	42.47	.839	3.134	.369	.103	1.576		
CDC CFS Fatigue after exertion	Psychology		2.286	4.811	1.286	-.492	5.063	0.379	.827
	Nutrition	13.90	2.593	5.507	1.060	.414	4.771		
	Combined	19.20	2.532	5.578	1.002	.486	4.578		
	Total	16.32	2.507	5.339	.629	1.252	3.761		
CDC CFS Muscle Aches or Muscle Pains	Psychology	10.34	2.500	4.034	1.078	.171	4.829	0.469	.791
	Nutrition	20.56	2.333	3.637	.700	.894	3.772		
	Combined		2.070	5.335	.958	.113	4.027		
	Total	21.01	2.253	4.459	.526	1.205	3.300		
CDC CFS Pain In Joints	Psychology		1.857	4.036	1.079	-.473	4.187	0.054	.973
	Nutrition	16.40	1.393	3.721	.716	-.079	2.865		
	Combined		1.978	5.622	1.010	-.084	4.040		
	Total	28.32	1.735	4.634	.546	.646	2.824		
CDC CFS Fever	Psychology		-.214	1.968	.526	-1.351	.922	0.399	.819
	Nutrition		.604	2.311	.445	-.310	1.519		
	Combined		1.245	4.816	.865	-.521	3.012		
	Total		.721	3.573	.421	-.118	1.561		
CDC CFS Chills	Psychology	23.40	1.571	2.738	.732	-.009	3.152	1.517	.468
	Nutrition	40.74	2.148	3.097	.596	.923	3.373		

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	Combined	40.23	1.447	3.986	.716	-.015	2.909		
	Total	37.00	1.734	3.421	.403	.930	2.538		
CDC CFS Unrefreshing Sleep	Psychology		1.857	6.803	1.818	-2.071	5.785	0.160	.948
	Nutrition		2.148	6.904	1.329	-.583	4.879		
	Combined		1.581	5.726	1.029	-.520	3.681		
	Total	19.55	1.847	6.3123	.744	.364	3.331		
CDC CFS Sleeping Problems	Psychology		2.786	5.352	1.430	-.304	5.876	3.218	.200
	Nutrition		-.222	5.139	.989	-2.255	1.811		
	Combined		1.762	4.871	.875	-.025	3.548		
	Total	17.17	1.217	5.133	.605	.011	2.423		
CDC CFS Headaches	Psychology		-.7143	2.091	.559	-1.922	.493	6.625	.036*
	Nutrition	32.19	1.572	3.507	.675	.184	2.959		
	Combined	36.18	2.467	4.944	.888	.653	4.280		
	Total	29.32	1.512	4.124	.486	.543	2.482		
CDC CFS Memory Problems	Psychology	44.73	2.857	4.655	1.244	.169	5.545	2.316	.314
	Nutrition		-.111	4.925	.947	-2.059	1.837		
	Combined		1.949	6.011	1.080	-.256	4.154		
	Total	17.86	1.353	5.435	.641	.076	2.630		
CDC CFS Difficulty Concentrating	Psychology	39.50	4.643	4.534	1.212	2.025	7.261	5.945	.051
	Nutrition		.815	4.359	.839	-.910	2.539		
	Combined		2.170	5.877	1.056	.015	4.326		
	Total	26.66	2.143	5.217	.615	.917	3.369		
CDC CFS Nausea	Psychology		.143	2.770	.740	-1.456	1.742	4.773	.092
	Nutrition		.660	2.667	.513	-.395	1.716		
	Combined		.251	4.468	.803	-1.388	1.890		

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	Total		.384	3.535	.417	-.447	1.214		
CDC CFS Abdominal Pain	Psychology		.286	1.729	.462	-.713	1.284	1.082	.582
	Nutrition	29.05	.882	2.165	.417	.025	1.738		
	Combined		.839	4.390	.789	-.771	2.449		
	Total		.747	3.234	.381	-.013	1.507		
CDC CFS Sinus Nasal Symptoms	Psychology		.929	3.125	.835	-.876	2.733	1.255	.534
	Nutrition		1.060	4.193	.807	-.599	2.719		
	Combined	20.56	1.906	5.923	1.063	-.267	4.078		
	Total	14.95	1.399	4.822	.568	.266	2.532		
CDC CFS Shortness Of Breath	Psychology		1.500	3.459	.924	-.497	3.497	0.707	.702
	Nutrition	18.28	.779	2.057	.403	-.052	1.609		
	Combined		.690	3.972	.725	-.793	2.173		
	Total	29.08	.885	3.243	.388	.112	1.658		
CDC CFS Sensitivity To Light	Psychology	64.58	1.429	2.472	.661	.001	2.856	0.939	.625
	Nutrition		1.568	3.764	.725	.079	3.057		
	Combined		.961	5.178	.930	-.938	2.860		
	Total	26.26	1.280	4.209	.496	.291	2.269		
CDC CFS Depression	Psychology		1.429	3.502	.936	-.593	3.451	0.490	.783
	Nutrition		.704	3.268	.629	-.589	1.996		
	Combined		1.363	5.345	.960	-.598	3.323		
	Total	39.55	1.129	4.282	.505	.122	2.135		
CDC CFS Maladaptive Stress Index Scale Score	Psychology	16.75	16.286	13.234	3.537	8.645	23.927	4.379	.112
	Nutrition	11.54	12.815	17.802	3.426	5.772	19.857		
	Combined	10.98	9.613	26.424	4.746	-.080	19.305		
	Total	11.99	12.111	21.201	2.499	7.129	17.093		

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[a] see table 2 for descriptive and inferential statistics

[b] *H*-statistic for Kruskal-Wallis test, d.f. = 2

* significant at the .05 level

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	9-10

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A preliminary prospective study of the comparative effectiveness of nutritional, psychological and combined therapies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) in a private care setting.

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Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	Complementary medicine, Nutrition and metabolism
Keywords:	COMPLEMENTARY MEDICINE, SOCIAL MEDICINE, REHABILITATION MEDICINE

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a condition ~~characterised~~characterized by severe and persistent fatigue, neurological disturbances, autonomic and endocrine dysfunctions and sleep difficulties that have a pronounced and significant impact on individuals' lives. Current NICE guidelines within the United Kingdom suggest that this condition should be treated with cognitive ~~behavioural~~behavioral therapy and/or graded exercise therapy where appropriate. There is currently a lack of evidence base concerning other, more integrative interventions that may be beneficial to those with ME/CFS.

Objectives: This study aimed to evaluate whether three patient-centered treatment modalities of psychology, nutrition and combined treatment, influenced symptom report measures in those with ~~reduced symptomatology of~~ ME/CFS over a 3-month time period and whether there were significant differences in these changes between groups.

Design and setting: This is a preliminary prospective~~longitudinal observational~~ study with one follow-up point conducted at a ~~one~~ private secondary health care facility in London, UK.

Participants: One-hundred and thirty-eight individuals (110 females, 79.7%; 42 participants in psychology, 44 in nutrition and 52 in combined) participated at baseline and 72 participants completed the battery of measures at follow-up (52.17% response rate; 14, 27, 31 participants in each group, respectively).

Outcome measures: Self-report measures of ME/CFS symptoms, functional ability, multidimensional fatigue, perceived control and maladaptive stress.

Results: Baseline comparisons showed those in the combined group had higher levels of fatigue. At follow-up, all groups saw improvements in fatigue, functional physical symptomatology and maladaptive stress; those within the psychology group also experienced a shift in perceived control over time. ~~The psychology group demonstrated a significantly greater change in fatigue and perceived control than the combined group; however, the opposite relationship was observed for headaches.~~

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Conclusions: This study provides early evidence that p~~P~~atient-centered techniques for the treatment of ME/CFS may influence ~~appear promising in reducing~~ symptomatology, fatigue, function, perceived control and inappropriate responses to stressors~~, and increasing function and perceived control.~~ However, these results must be viewed with caution as the allocation to groups was not randomized, there was no control group and the study suffered from high drop-out rates. ~~The need for further studies of integrative treatment with robust designs appears warranted.~~

Summary

Article focus

- This preliminary prospective ~~observational~~ study investigated three (psychological, nutritional and combined) tailored patient-centered interventions for ME/CFS over time.
- Differences between the reported changes over time between groups were also assessed.

Key messages

- Patient-centered approaches for the management of ME/CFS ~~reduce symptomatology~~influence symptomatology over time in some individuals with this disorder.
- Self-reported f~~F~~unctional ability~~,~~ (-physical and social)~~,~~ are influenced~~increase with~~ following tailored interventions lasting 3 months~~.~~
- ~~Psychological intervention can help individuals to regain a sense of control over their condition.~~ -
- This study provides preliminary evidence that tailored psychological, nutritional and Combined interventions may be effective treatments for some people with ME/CFS; however, due to the study's methodological limitations, it is important that this potential treatment effect is investigated further in high quality randomized controlled studies.

Strengths and limitations of this study

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- The findings here are an initial step to fill the gap in the extant literature regarding the utility of tailored, multidisciplinary and patient-centered treatments for ME/CFS.
- There is bias in this study as the participants were self-selected in the sense that they chose to attend the clinic and which treatment option they preferred (with advice), i.e. the study was not randomized.
- There were low retention rates in this study which may constitute a bias in that those who remained in the study may have experienced benefits and those who experienced little or no benefits may have dropped out.

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Introduction

Chronic Fatigue Syndrome or myalgic encephalomyelitis (ME/CFS) is a condition characterized by prolonged and debilitating fatigue, although the exact cause of this disorder is still under debate. Due to the lack of a definitive biological marker, diagnosis is made on the basis of the exclusion of other explanatory conditions. The most widely used case definition by the Centers for Disease Control [1] states that there must be at least six months severe fatigue of new and definite onset, not the result of ongoing exertion, not alleviated by rest and resulting in reduced levels of physical activity. The CDC definition also sets out a series of minor complaints that must accompany the fatigue (cognitive impairment, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, headaches of a new type, pattern or severity at onset, unrefreshing sleep and post-exertion malaise), with individuals needing to have the occurrence of four or more symptoms to be diagnosed with

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ME/CFS. Estimates of the prevalence of ME/CFS have been made as low as 3 and as high as 2,800 per 100,000 [2].

The most widely researched strategies for alleviating the symptoms of ME/CFS are Cognitive Behavior Therapy (CBT) and Graded Exercise Therapy (GET). Two reviews of studies on CBT [3,4] found that it significantly improved physical functioning in adult out-patients as compared with medical management, counseling, guided support, education and support or relaxation. ~~However, the longitudinal evidence for CBT is inconsistent and there is a lack of evidence with regard to CBT in combination with other treatments~~[4]. Regarding GET, a systematic review illustrated that this form of therapy was potentially beneficial for people with ME/CFS, especially when combined with a patient education programme[5]. However, drop-out rates were high in the GET groups suggesting that individuals with ME/CFS are a~~d~~verse to this type of therapy. Recently, a large scale, longitudinal study investigating CBT, GET, Adaptive Pacing Therapy (APT) and specialist medical care (SMC) found that CBT and GET (when added to SMC) were moderately effective outpatient treatments for this patient group as opposed to APT or SMC alone [6].

Although CBT and GET studies have shown some promising outcomes, there is no known cure for ME/CFS. Therefore the National Institute for Health and Clinical Excellence (NICE) [7~~6~~] recommends a number of symptom management strategies and interventions aimed at helping individuals to cope with their condition and reduce physical deconditioning brought about by the illness. Pharmacological interventions are, at times, suggested for patients with poor sleep or pain, for instance, low-dose antidepressants, as these have been shown to be effective [8-14~~7-13~~]. However, patient expectations must be realistic as the drugs may help elevate mood and psychological outlook but not reduce fatigue and other symptomatology

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associated with ME/CFS[15,14]. Numerous drugs such as thyroxin, hydrocortisone and antiviral agents are not advised by NICE due to contradictory findings[16,17,15,16].

In terms of function and quality of life management, NICE offers general advice concerning sleep management, appropriate rest periods, and pacing. Sleep hygiene instruction, together with pharmacological treatment tailored to the individual patient can be beneficial in combating fatigue [18,17]. Dietary management may also reduce symptomatology for those with concurrent irritable bowel syndrome (IBS). Management approaches recommended for IBS, such as diet restriction, are thus also recommended for those with ME/CFS[19,18]. Dietary supplementation has been investigated in relation to ME/CFS. Fatty acids [20,19], folic acid [21,20], vitamin C [22,21], co-enzyme Q10 [23,22], magnesium [24,23], multivitamins [25,24] and minerals [26,25] have all been shown to reduce symptomatology in ME/CFS patients. However other studies have shown conflicting findings with regard to nutritional supplementation, therefore it is perhaps wise to treat with supplements on a case-by-case basis[27,28,26,27].

Due to the lack of clear and definitive treatment strategies, individuals often seek out Complementary and Alternative Medicines (CAM). Although NICE does not recommend the use of CAM they do acknowledge that many people with ME/CFS use such therapies and find them beneficial for symptom management. This view is due to the lack of published evidence for the effectiveness of these treatments. Examples of CAM treatments used by individuals with ME/CFS include religious healing, massage therapy, relaxation, meditation, homeopathy, acupuncture, naturopathy and herbal therapies [29,30,28,29]; patient satisfaction with such approaches as CAM has been high, over 80% in some instances [29,28]. A recent systematic review of such interventions identified 70 controlled clinical trials (randomized and non-randomized) and found that 86% of these studies illustrated at least one positive effect, with

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74% showing a decrease of illness-related symptomatology [31~~30~~]. Meditative or mindfulness approaches warranted further investigation based on these results as did supplement programs of magnesium, l-carnitine, and S-adenosylmethionine. A subsequent review based solely on randomized controlled trials (RCTs) of CAM techniques identified 26 such studies and observed that qigong, massage and tuina (approaches based within Chinese Traditional Medicine and based upon relaxation and connection with the body) illustrated positive effects as did supplementation studies utilizing nicotinamide adenine dinucleotide (NADH) and magnesium [32~~31~~]. However, within both reviews it was noted that the methodological quality of reporting was poor and the sample sizes in these studies were small; hence ability to draw strong conclusions on the efficacy of CAM methods is limited. Porter et al. (2010) [31] did note that patient-centered, individualized treatment protocols which include a range of tailored strategies are a promising area for further investigation for this complex, multi-system illness.

Objectives

There is still much debate and uncertainty regarding the most effective treatment for ME/CFS. Recent reviews of CAM techniques highlight the need for further exploration of patient-centered and individually tailored interventions for the alleviation of the condition's often debilitating and intrusive symptomatology. This study therefore aims to provide preliminary evidence for the utility ~~evaluate the effectiveness of three~~of three types of patient-centered approaches to the management of ME/CFS over time (baseline and follow-up) offered at a private health-care center in the UK.

Methods

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Study design and setting

This preliminary prospective ~~a longitudinal observational~~ study ~~which~~ aimed to explore the effectiveness of ~~evaluate~~ three treatment options offered to individuals with ME/CFS. The research was conducted at one private secondary health care facility. All potential ~~prospective~~ patients of the clinic are first asked to complete a comprehensive symptom profile and medical history, including questions relating to triggering factors, psychology sub-types and structural/biological sub-types (this is distinct from the research data collected). Subsequent to this, every individual receives a 15-minute screening with one of the practitioners (please note, this was not either of the authors of the current study) who recommends the best course of action for his/her needs; this will be the psychology-related interventions, nutritional advice and support or a combination of the two.

All individuals requesting treatment at the private care setting were offered the opportunity to participate in the study. Those that expressed an interest (N = 145) were emailed a spreadsheet that contained the questionnaires and asked to complete it at their convenience. Informed consent was obtained prior to the completion of the questionnaires and the study was approved by the University of East London Ethics Committee. Participants were told that they could withdraw from the study at any time and that withdrawal would not affect their care at the clinic. Participants were able to ask questions at any point in the study and no deception was used as the participants were informed of the nature of the research program before they agreed to participate. Subsequently, participants were requested to complete the questionnaire pack on a second occasion, three months from the baseline measures.

Psychology

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The clinic offers a 3-month intervention which consists of a combination of Neuro-linguistic Programming (NLP), Emotional Freedom Technique (EFT), life coaching and hypnotherapy/self-hypnosis constructed in a manner specific to the needs of those with ME/CFS. The primary aim of this approach is to reduce the anxiety that is associated with having a debilitating and unpredictable condition, improve emotional well-being and help individuals slowly manage and increase their activity within their own limits (i.e. pacing). The program is offered as a series of group sessions and the peer support is seen as an important component of the intervention, which is solidified via the use of moderated online support forums, narratives of previous clients' experiences and online materials that can be accessed as often as necessary. In addition to, or as an alternative to this course, individuals receive a series of one-to-one sessions and for the most severely affected ME/CFS patients, telephone sessions are arranged and support materials can be accessed in their own homes.

Over the three-month period of this preliminary study, the participants experienced one of three treatment options. The first option included 13 hours of practitioner contact time in a mix of group training in person, group telephone conference calls and one-to-one telephone sessions, the second option was four hours of one-to-one telephone sessions and the final option was three hours of in person sessions. Participants all had access to various support materials which included CDs and online resources. The amount of time spent on these was patient-led, but was in the region of a further six hours. All the practitioners offering this option are qualified in hypnotherapy, NLP, life coaching and EFT and undergo an intensive period of training in the clinic's own integrative approach (please see Howard and Arroll [33] for more details of this approach) and ongoing supervision (individual and group supervision on a biweekly basis) from the department director, who is the only senior practitioner in the team.

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Nutrition

Tailored nutritional therapy is achieved via one-to-one consultations with individuals. To begin, a very detailed history is taken based upon the information given in the aforementioned symptom profile. Qualified nutritional therapists (who have been given specialist training regarding ME/CFS from the clinic) then suggest tests consistent with symptomatology, for instance the Adrenal Stress Index Test, comprehensive stool analysis/gastro-intestinal function, vitamin & mineral status, etc. Results from these tests are then used to compose an evidence-driven diet and supplement program. As most cases of ME/CFS are complex involving multiple body systems, this process is often iterative and follow-up consultations are necessary to check progress and make alterations to the protocol. The nutritional therapy program consists of an initial one-hour evaluation (which includes the tailored advice) and follow-up approximately every six weeks; therefore, during the course of the present study, the participants received a minimum of two one-hour sessions with email support for any queries and detailed nutritional guidance. All the nutritional therapists are qualified to diploma level and members of (voluntary) regulatory bodies such as the British Association for Applied Nutrition and Nutritional Therapy (BANT) and the Complementary and Natural Healthcare Council (CNHC). Similar to the psychology department, the nutrition department is led by one senior practitioner who supervises the team with individual and group supervisory arrangements.

Combined

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Within the combined program, a multidisciplinary approach is taken with practitioners discussing the patients in case meetings to ensure that the psychological and nutritional aspects complement each other in order to achieve the best outcome. It should be noted that the interventions in the combined program are phased-in as it was found that asking individuals to engage in numerous therapeutic activities at the same time resulted in high drop-out rates.

Primary Outcome Measures

Medical Outcomes Survey Short-Form 36 (SF-36)

This 36-item measure is the short form of the original Medical Outcomes Survey [34~~32~~] to measure functional impairment and contains eight sub-sections: 1) physical activity limitations due to health problems; 2) social activity limitations due to physical or emotional problems; 3) usual role activity limitations due to physical health problems; 4) bodily pain; 5) general mental health; 6) role activity limitations due to emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions [34~~32~~]. The items are scored so that higher scores indicate greater functional ability. In terms of the psychometric properties of this measure, reliability estimates for all sub-scales are good, exceeding a Cronbach's alpha coefficient value of 0.70 [35~~33~~]. In terms of validity, the SF-36 correlates amply, $r \geq 0.40$, with the frequency and severity of numerous symptoms and general health conditions [36;37 ~~34;35~~].

~~*Multidimensional Health Locus of Control Scale (MHLCS)*~~

~~Multidimensional Health Locus of Control [36-38] measures perceived control via three distinct sub-scales: 'internal', 'chance' and 'powerful others' which has two dimensions, that of~~

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~~'doctors' and 'other people'. The instrument contains 18 items in total (six items each for the internal and chance scales and three items for both the powerful others scales) and is scored on a 6 point Likert scale from 'strongly agree' to 'strongly disagree'. Internal reliability of the instrument is good with Cronbach's alpha coefficients ranging from 0.67 for 'powerful others' to 0.77 for 'internal'. The measure correlates positively and significantly with associated scales from Levenson's [39] locus of control measure from which the MHLOC was based upon, which demonstrates good convergent validity [36].~~

Multidimensional Fatigue Inventory (MFI)

This 20-item measure contains five fatigue dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [38,40]. Items such as 'I tire easily' are rated on a 5-point scale (1 = yes, that is true; 5 = no, that is not true) with lower scores reflecting higher levels of fatigue. The MFI has good internal consistency with average Cronbach's alpha coefficient equaling 0.84 across the sub-scales. Convergent validity based on a sample of radiotherapy patients found correlations between the sub-scales and a visual analog fatigue scale to be 0.77 for general fatigue, 0.70 for physical fatigue, 0.61 for reduced activity, 0.56 for reduced motivation (p<0.001) to 0.23 for mental fatigue (p<0.01) [38,40]

Secondary Outcome Measures (ME/CFS-specific)

CDC CFS Symptom Inventory

CDC CFS Symptom Inventory [39,41] was used to measure specific ME/CFS symptoms and confirm diagnosis. This instrument is based upon the CDC case definition [1] and includes a fatigue item and the eight distinct symptoms are also included in the CDC guidelines with an additional ten associated symptoms. The format of this self-report measure is a six-point scale of perceived frequency (0 = absent, 5 = all the time) and severity (0 = none, 5 = very severe). The psychometric properties of this instrument are good: Cronbach's alpha coefficient = 0.88;

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r = .74 convergent validity with the Chalder Fatigue Scale [40,42]; *r* -.68 and -.87 convergent validity with the SF-36 'vitality' and 'bodily pain' sub-scales, respectively.

Secondary Outcome Measures (psychological)

Multidimensional Health Locus of Control Scale (MHLCS)

Multidimensional Health Locus of Control [41-43] measures perceived control via three distinct sub-scales: 'internal', 'chance' and 'powerful others' which has two dimensions, that of 'doctors' and 'other people'. The instrument contains 18 items in total (six items each for the 'internal' and 'chance' scales and three items for both the 'powerful others' scales) and is scored on a 6-point Likert scale from 'strongly agree' to 'strongly disagree'. Internal reliability of the instrument is good with Cronbach's alpha coefficients ranging from 0.67 for 'powerful others' to 0.77 for 'internal'. The measure correlates positively and significantly with associated scales from Levenson's [44] locus of control measure from which the MHLOC was based, which demonstrates good convergent validity [41].

Maladaptive Stress Index

This 32-item measure contains three sub-scales (cognitive/mood, sleep and ME/CFS symptoms) and was designed specifically for this population [45,43]. Items such as 'I constantly replay or pre-empt situations and conversations' are scored on a 5-point scale where 1 = never true and 5 = always true; higher scores illustrate a greater degree of disturbance.

Statistical methods

The data was initially screened for missing data. Four cases contained substantial amounts of missing data; therefore these were excluded from the analysis (one individual from the nutrition group and three from the combined group). Once this was done, all the variables had

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less than 5% missing data, hence mean substitution was carried out in line with guidance [4644]. The baseline data was subsequently of the quality for parametric tests, except for the variables CDC CFS swollen lymph nodes and glands, memory problems, abdominal pain and depression. However, the follow-up data suffered from high levels of skew and kurtosis which was not substantially alleviated by data transformation. This violated a key criterion for parametric testing, that of normality of distribution, so non-parametric tests were selected. In addition, as the sample sizes in each individual treatment group were small, the more conservative non-parametric tests were the preferred choice as even though tests such as analysis of variance are generally robust against non-normality, this does not hold true with small sample sizes. ~~For baseline data,~~ One-way analysis of variance tests and Kruskal-Wallis tests (the former for those variables that met the criteria for parametric tests, and the latter that did not) were used to investigate baseline variation ~~difference between groups, Wilcoxon sign rank tests were employed to look for differences over time (baseline and 3-month follow-up)~~ and multivariate analysis of covariance (MANCOVA) tests were used to account for this variation and test to for differences between the three groups. ~~Kruskal-Wallis tests were performed to investigate group differences in measures of change as evaluated by mean change scores, with Bonferroni corrected Mann Whitney tests calculated to identify post hoc differences between groups if the Kruskal Wallis tests were significant.~~ Wilcoxon sign-rank tests were employed to look for differences over time (baseline and 3-month follow-up) and if differences were significant, percentage change was calculated. Please note, as this is an exploratory study with only one time-point and no control group, any significant findings do not infer clinical significance, rather statistical significance, and as such exact p-values are presented.

Results

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Participants

Of the 145 individuals who expressed an interest in the study, 142 time-one questionnaires were returned, equating to a 97.9% response rate at baseline (two participants from the psychology group and one from the combined group dropped out at this stage). Therefore, excluding the four cases deleted due to insufficient data, 138 ~~One hundred and thirty eight~~ cases were used for baseline analysis; ~~individuals completed the questionnaire battery at time one (excluding the four deleted cases);~~ 42 participants in the psychology group, 44 in the nutrition group and 52 in the combined group. There was no significant association between gender and group (χ^2 (2) = 0.179, p = .915 ~~> .05~~), all groups consisting of approximately one-fifth males (Table 1). There was not a significant difference in age (F(2,135) = 0.0010, p = 1.000 ~~> .05~~); in fact group means for age were near identical at 42.881, 42.864 and 42.843 for psychology, nutrition and combined groups, respectively. There was also a non-significant result for illness duration (F(2, 135) = 0.252, p = .778 ~~> .05~~). Therefore, in terms of demographics, the groups were comparable. With regard to the outcome measures, there were significant differences between the groups in terms of the MFI sub-scale 'general fatigue' (F(2, 135) = 3.219, p = .043 ~~< .05~~), MFI 'physical fatigue' (F(2, 135) = 3.343, p = .038 ~~< .05~~) and the CDC CFS symptom 'swollen lymph nodes and glands' (H(2) = 7.161, p = .028 ~~< .05~~). To investigate the source of these differences, post-hoc tests were conducted (unrelated t-tests for the fatigue variables and Mann-Whitney tests for swollen lymph glands as the former did not meet criteria for parametric tests, all with Bonferroni correction for multiple comparisons). A significant difference was observed between the psychology and combined groups with regards to general fatigue (t(92) = -2.449, p = .016 ~~< .05~~) and physical fatigue (t(92) = -2.658, p = .009 ~~< .05~~) and also between the nutrition and psychology group in terms of the degree of lymph node and gland swelling (U = 635.00, p = .009 ~~< .05~~). Within the fatigue measures, the combined group reported

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significantly higher levels of both general and physical fatigued than the psychology group whereas those undertaking nutritional support stated a higher occurrence of swollen lymph nodes and glands.

Retention analysis

Seventy-two of the original 138 participants (14 participants in the psychology group, 27 in the nutrition group and 31 in the combined group) completed the battery of measures at the 3-month follow-up, resulting in retention rates of ~~(~~52.17% in the study overall, 33.33% in the psychology group, 61.36% in the nutrition group and 59.62% in the combined group~~)~~. To investigate whether the individuals who did not complete the time-two measures were significantly different from those at baseline on demographic and outcome measures, a series of t-tests and Mann-Whitney tests were performed. Those that dropped out of the research (although still receiving treatment at the clinic) differed significantly in terms of age ($t(136) = -2.227$, $p = .028$~~< .05~~) and illness duration ($t(136) = -2.549$, $p = .012$~~< .05~~). Those who remained in the study were of significantly older age (mean age of those that remained in the study = 45.056, SD = 11.535; mean age of drop-outs = 40.400, SD =12.932) and longer illness duration than those who dropped out (mean age of those that remained in the study = 10.836, SD = 7.383; mean illness duration of drop-outs =7.571, SD = 7.472). Individuals who did not remain in the study did not differ significantly in terms of gender (χ^2 (2) = 1.222, $p = .269$~~> .05~~) or any of the outcome measures.

~~Longitudinal data~~ Comparison from time-one to time-two

Primary outcomes

The following percentage change scores represent statistically significant changes, rather than clinically significant shifts, as this was an exploratory study. (Please see Table 2 for the exact

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p-value for each repeated measures comparison.) In the sample as a whole, there were improvements in all areas of the SF-36, with a 5.80% improvement in physical functioning, a 63.32% improvement in role limitations due to physical difficulties, a 5.17% improvement in bodily pain, a 26.17% improvement in social functioning, a 10.58% improvement in role limitations due to emotional difficulties, a 22.30% improvement in vitality, energy or fatigue and a 36.49% improvement in general health perception. When looking at the fatigue sub-scales of the MFI, all five sub-scales showed significant reductions in fatigue; 8.55% in general fatigue, 10.98% in physical fatigue, 8.81% in reduced activity, 12.96% in reduced motivation and 12.79% in mental fatigue.

Within the group of individuals who opted for a purely psychological intervention, improvements were seen in physical functioning (16.75%), role limitations due to physical problems (84.61%), social functioning (37.81%), general mental health (19.15%), vitality, energy or fatigue (49.57%) and general health perceptions (19.01%). Also, all the MFI fatigue scales decreased over a 3-month period, 13.58% in general fatigue, 17.74% in physical fatigue, 23.20% in reduced activity, 11.42% in reduced motivation and 29.66% in mental fatigue.

The nutrition group saw improvements in role limitations due to physical problems (61.05%), social functioning (24.93%), vitality, energy or fatigue (35.35%). and general health perceptions (29.73%). Once again, all the MFI fatigue scales decreased over a 3-month period, 13.39% in general fatigue, 15.00% in physical fatigue, 13.28% in reduced activity, 14.64% in reduced motivation and 12.83% in mental fatigue.

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In terms of general health as evaluated by the SF-36 measure, the group who received both psychological and nutritional intervention reported reductions in role limitations due to physical difficulties (57.02%), social functioning (22.61%), role limitations due to emotional difficulties (29.47%) and general health perceptions (26.45%). In the combined group, only one measure of fatigue, that of physical fatigue, saw significant improvements over time (6.42%).

Secondary outcomes (ME/CFS-specific)

Within the CFS Symptom Inventory, there were improvements in occurrence of sore throats (46.26%), diarrhea (42.47%), fatigue after exertion (16.32%), muscle aches or muscle pains (21.01%), pain in joints (28.32%) chills (37.00%), unrefreshing sleep (19.55%), sleeping problems (17.17%), headaches (29.47%), memory problems (17.86%), difficulty concentrating (26.66%), sinus and nasal symptoms (14.95%), shortness of breath (29.08%), sensitivity to light (26.26%) and depression (39.55%) in the merged sample. Within those taking part in the psychology intervention, ratings of muscle aches or muscle pains (10.34%), chills (23.40%), memory problems (44.73%), difficulty concentrating (39.50%) and sensitivity to light (64.58%) decreased. In the nutrition group, numerous symptom-related indices also showed improvements; sore throat (56.23%), swollen lymph glands (10.09%), fatigue after exertion (13.90%), muscle aches or muscle pains (20.56%), pain in joints (16.40%), chills (40.74%), headaches (32.19%), abdominal pain (29.05%), and sensitivity to light (18.28%). Those in the combined group saw significant reductions over the 3-month interval in diarrhea (47.97%), fatigue after exertion (19.20%), chills (40.23%), headaches (36.18%) and sinus and nasal symptoms (20.56%). (Please see Table 3 for the descriptive and inferential statistics associated with these findings and the exact p-value for each repeated measures comparison.)

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Secondary outcomes (psychological)

There were no significant differences from time-one to time-two in the MHLCS sub-scale of 'chance', 'powerful others' and 'other people', however the MHLCS did illustrate significant increases in internal locus of control (30.67%) and that of doctors (47.49%) in the sample as a whole. Reductions were also observed in the Maladaptive Stress Response (11.99%) in the entire group. In the psychology group, a significant increase of 17.56% was observed in internal locus of control, a decrease of 4.67% in the perception that chance played an influential part in the individuals' lives and a significant reduction in the Maladaptive Stress Response of 16.75%. No significant differences were found from baseline to follow-up in perceived control in the nutrition group, however the way in which the individuals in this group responded to stress also decreased, by 11.54%. No significant differences were found from baseline to follow-up in perceived control as measured by the MHLCS in the combined treatment group although there was a statistically significant difference in the Maladaptive Stress Response (10.98%). (Please see Table 4 for the descriptive and inferential statistics associated with these findings and the exact p-value for each repeated measures comparison.)

~~In the sample as a whole, there were significant differences from baseline to follow-up within the internal and doctors sub-scale of the MHLCS and all the CDC-CFS Symptom Inventory items bar swollen lymph nodes and glands, fever and abdominal pain. There were also significant differences in all areas of the SF-36, all the fatigue sub-scales of the MFI with the five sub-scales illustrating significant reductions in fatigue and, finally, reductions were also observed in the Maladaptive Stress Response.~~

~~Within the psychology group significant differences were also found in the SF-36 sub-scales 'physical functioning', 'role limitations due to physical problem', 'social functioning',~~

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‘general mental health’, ‘vitality, energy or fatigue’ and ‘general health perceptions’. Regarding perceived control, significant differences were found in internal locus of control and the perception that chance played an influential part in the individuals’ lives. Again, all the MFI fatigue scales saw significant decreases over a 3 month period. Regarding ME/CFS specific symptoms, ratings of muscle aches or muscle pains, chills, memory problems, difficulty concentrating and sensitivity to light differed significantly from baseline to follow-up in the expected direction. There was also a significant reduction in the Maladaptive Stress Response over time.

The nutrition group saw significant improvements in role limitations due to physical problems, social functioning, vitality, energy or fatigue and general health perceptions. No significant differences were found from baseline to follow up in perceived control in the nutrition group. Once again, all the MFI fatigue scales decreased over a 3 month period and numerous symptom related indices also showed improvements; sore throat, swollen lymph glands, fatigue after exertion, muscle aches or muscle pains, pain in joints, chills, headaches, abdominal pain and sensitivity to light. The way in which the individuals in this group responded to stress also decreased over the 3 month time period.

In terms of general health as evaluated by the SF 36 measure, the group who received both psychological and nutritional intervention reported reductions in role limitations due to physical difficulties, social functioning, role limitations due to emotional difficulties and general health perceptions. No significant differences were found from baseline to follow up in perceived control as measured by the MHLCS in the combined treatment group. Only one measure of fatigue, that of physical fatigue, saw significant improvements over time. Diarrhea, fatigue after exertion, chills, headaches and sinus and nasal symptoms all illustrated

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~~significant reductions over the 3 month interval, as did the Maladaptive Stress Response. (See Table 2 for descriptive and inferential statistics associated with these findings and Table 3 for percentage of change over time.)~~

~~**Comparisons across groups**~~

Once correction for baseline variation was achieved, there were no significant differences between the three groups in terms of change scores.

~~As shown in Table 3, three of the outcome measures differed significantly in terms of change from baseline to follow up, namely the MHLCS 'chance' sub scale ($H(2) = 7.674$, $p < .05$), the MFI 'general fatigue' sub scale ($H(2) = 6.790$, $p < .05$) and the CDC CFS symptom 'headaches' ($H(2) = 6.625$, $p < .05$). In terms of perceived control and general fatigue, the psychology group differed significantly as compared to the combined group ($U = 110.500$, $p < .05$) and ($U = 118.000$, $p < .05$), respectively, with the psychology group seeing a greater change over time as compared to the combined group on both measures. Regarding headaches, the combined group ($U = 118.000$, $p < .05$) improved significantly more than the psychology group. No other comparisons reached statistical significance with a Bonferroni correction for multiple comparisons.~~

Discussion

Key results

There was statistically significant (rather than known clinically significant) change over time of numerous measures in all groups investigated. However, this is not to say that these changes were due to the interventions as the design of this study was exploratory, rather than experimental (please see below for a further critique of the design).The psychology group contained the most significant findings, including those concerned with daily functioning,

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fatigue, locus of control, the cognitive CDC CFS specific symptoms and the Maladaptive Stress Response. As expected, changes in perceived control were not observed in the nutrition group as this is not an area that is targeted in this program. However, the more immune-type symptoms such as sore throat, swollen lymph nodes or glands and pain in joints did see significant reductions over time as would be envisaged in treatment protocols based upon nutritional expertise. The group that exhibited the least significant findings was the combined group and, as noted below, this may be due to the greater general severity of symptoms in this group and the need for a more lengthy intervention. Nevertheless, considering the small sample sizes in the groups at follow-up, these results are very promising and warrant further attention. ~~In terms of these preliminary findings, the psychology group performed better with regard to lowering the belief that chance influences the course of the condition. This is an important observation as the unpredictable nature of ME/CFS can be one of the most difficult components for individuals to cope with [45] and helping patients gain an improved sense of control over the illness is of great potential benefit. The psychology group also demonstrated a significantly greater change score in general fatigue as compared with the combined group which may infer that in the short term, guiding individuals through the complex nature of the disorder, helping them to understand it and accept that the condition itself gives rise to stresses and psychological distress may be a good starting point for intervention (i.e. a stepped program could be developed).~~

Interpretation

As noted previously [31~~30~~] patient-centered, individualized treatment protocols which include a range of tailored strategies is a favorable direction for dealing with a complex and multi-system disorder such as ME/CFS. The present study has demonstrated that such interventions may be ~~are~~ useful in lowering symptomatology, improving functioning and helping

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individuals gain a greater sense of control over their health status. ~~Considering that the options available on the National Health Service, mainly CBT and GET, are often perceived as coping strategies at best, and physically damaging at worst [46], tailored treatments such as described here may be more palatable, and hence effective.~~

Limitations and Generalisability

This study was a preliminary study in a naturalistic setting and as such did not have a robust design. There was not a~~did not have a~~ control group and the participants were not randomly assigned to groups, therefore ~~so~~ the results should be treated with caution. In order to ascertain whether the changes in symptom and functional reports were due to the interventions, a randomized control trial should be conducted (RCT). ~~Also, the participants were not randomly assigned to groups as this was a naturalistic,observational study.~~ Also, there was a high drop-out rate from time-one to time-two and this rate differed across groups. The highest drop-out rate was in the psychology group; whilst we cannot be sure why this occurred, it is postulated that the retention was poor in the group as the individuals in the psychology program had more activities to engage in and may have felt overburdened with the research questionnaires in addition to their session and homework (this would not be the case in the combined group as the therapeutic activities are phased-in as mentioned above).

In this study, e~~E~~ach individual was guided to appropriate treatment within an initial screening with clinic staff~~,~~; therefore the group was dependent on the nature of the individual's symptoms and their personal choice as the programs on offer were privately funded. ~~However, as can be seen in the baseline comparisons, the groups did not differ in terms of gender, age, illness duration or the majority of outcome measures.~~ Notably, the groups did differ in general and physical fatigue with participants in the combined groups reporting

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greater fatigue than those in the psychology group which suggests that this group's general symptomatology was more severe. The combined group illustrated less change~~improvement~~ over time compared to the psychology and nutrition groups and it is feasible to infer that individuals with a greater number and degree of complaints are referred to the combined group within the clinic. ~~Also, it should be noted that the interventions in the combined program are phasedin as it was found that asking individuals to engage in numerous therapeutic activities resulted in high drop out rates~~. Also, those in the combined group will not experience the intensity of each intervention as this has been demonstrated to result in non-compliance; t~~T~~herefore, changes in outcome measures in this group may not be noted at an interval of three months ~~for that group~~. Further studies underway presently will investigate follow-ups at 6- and 12-months to identify whether the findings here are maintained over time and also whether those with greater symptom severity benefit with a longer intervention. As the participants were self-selected onto these programs, the findings lack generalizability; future work should sample from the overall ME/CFS population and be randomly-assigned to groups in order to make valid assumptions regarding the illness-group as a whole.

Funding

No external funding was obtained for this research; the work was accomplished in-house at the clinic in question.

Data Sharing

Dataset available from the corresponding author at m.a.arroll@sa.uel.ac.uk. Consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low.

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Contributorship

Alex Howard made substantial contributions to the conception and design and acquisition of data, whilst Megan Arroll made a substantial contribution to the analysis and interpretation of data. Both authors made a substantial contribution to the drafting of the article and revisions for the critical review of important intellectual content. Final approval of the version to be published was also granted by both authors.

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Competing Interests

Alex Howard is the founder and CEO of The Optimum Health Clinic and Megan Arroll is the Director of Research at the Optimum Health Clinic, where this study was conducted.

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List of abbreviations

ME: myalgic encephalomyelitis

CFS: Chronic Fatigue Syndrome

NICE: National Institute for Health and Clinical Excellence

CBT: Cognitive Behavioral Therapy

GET: Graded Exercise Therapy

APT: Adaptive Pacing Therapy

SMC: specialist medical care

CAM: Complementary and Alternative Medicine

NLP: Neuro-linguistic Programming

EFT: Emotional Freedom Technique

SF-36: Medical Outcomes Survey Short-Form 36

MHLCS: Multidimensional Health Locus of Control Scale

MFI: Multidimensional Fatigue Inventory

RCT: randomized controlled trial

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Table 1. Baseline comparisons of sample demographics and outcome variables

				95% CI for Mean		Test	
		Mean	SD	Lower	Upper	statistic	p-value
Gender	Psychology	9 (21.4%)[d]				.179[e]	.915
	Nutrition	8 (18.2%)[d]					
	Combined	11 (21.2%)[d]					
	Total	28 (20.3%)[d]					
Age	Psychology	42.881	13.986	38.523	47.239	.000[a]	1.000
	Nutrition	42.864	12.504	39.062	46.665		
	Combined	42.843	11.125	39.714	45.972		
	Total	42.861	12.406	40.765	44.957		
Illness duration	Psychology	8.874	8.252	6.302	11.445	.252[a]	.778
	Nutrition	10.023	7.375	7.781	12.265		
	Combined	9.625	7.291	7.595	11.655		
	Total	9.523	7.580	8.247	10.800		
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	.319[a]	.727
	Nutrition	47.855	26.226	39.882	55.829		
	Combined	45.299	25.479	38.206	52.393		
	Total	47.344	24.792	43.171	51.517		
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	.281[a]	.755
	Nutrition	7.574	17.500	2.254	12.895		
	Combined	9.774	21.051	3.914	15.635		
	Total	8.272	18.387	5.177	11.367		
SF-36	Psychology	61.548	25.614	53.566	69.530	1.002[a]	.370

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Bodily pain	Nutrition	55.625	30.242	46.431	64.819		
	Combined	53.606	27.019	46.084	61.128		
	Total	56.667	27.683	52.007	61.327		
SF-36	Psychology	37.202	21.824	30.402	44.003	.536[a]	.586
Social functioning	Nutrition	32.671	25.888	24.800	40.541		
	Combined	32.452	24.786	25.552	39.352		
	Total	33.967	24.212	29.892	38.043		
SF-36	Psychology	60.286	19.584	54.183	66.389	.124[a]	.884
General mental health	Nutrition	59.727	19.355	53.843	65.612		
	Combined	58.308	20.948	52.476	64.140		
	Total	59.362	19.911	56.011	62.714		
SF-36	Psychology	55.554	46.368	41.104	70.004	.390[a]	.678
Role limitations emotional	Nutrition	48.482	47.390	34.074	62.890		
	Combined	47.780	43.924	35.551	60.008		
	Total	50.370	45.590	42.695	58.044		
SF-36	Psychology	20.714	16.1386	15.685	25.743	.129[a]	.879
Vitality Energy or Fatigue	Nutrition	20.114	14.570	15.685	24.542		
	Combined	19.039	17.658	14.123	23.955		
	Total	19.891	16.159	17.171	22.611		
SF-36	Psychology	37.024	17.945	31.432	42.616	2.769[a]	.066
General health perceptions	Nutrition	28.636	15.528	23.915	33.357		
	Combined	30.962	17.575	26.069	35.854		
	Total	32.065	17.286	29.156	34.975		
MHLCS Internal	Psychology	.677	.159	.627	.726	1.216[a]	.300
	Nutrition	.622	.177	.568	.675		

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	Combined	.662	.174	.613	.710		
	Total	.653	.171	.625	.682		
MHLCS Chance	Psychology	.368	.156	.320	.417	.395[a]	.674
	Nutrition	.340	.133	.299	.380		
	Combined	.354	.155	.311	.397		
	Total	.354	.148	.329	.379		
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.119[a]	.888
	Nutrition	.417	.141	.374	.460		
	Combined	.407	.101	.379	.436		
	Total	.409	.124	.388	.430		
MHLCS Doctors	Psychology	.169	.082	.143	.194	.575[a]	.564
	Nutrition	.171	.089	.144	.197		
	Combined	.191	.147	.150	.232		
	Total	.178	.112	.159	.196		
MHLCS Other People	Psychology	.235	.075	.212	.259	1.051[a]	.352
	Nutrition	.264	.129	.225	.304		
	Combined	.245	.074	.224	.265		
	Total	.248	.095	.232	.264		
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	3.219[a]	.043*
	Nutrition	16.977	2.601	16.186	17.768		
	Combined	17.327	2.587	16.607	18.047		
	Total	16.797	2.716	16.340	17.254		
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	3.343[a]	.038*
	Nutrition	16.727	3.358	15.707	17.748		
	Combined	17.615	2.823	16.830	18.401		

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	Total	16.819	3.211	16.278	17.359		
MFI Reduced Activity	Psychology	13.857	4.112	12.576	15.138	1.030[a]	.360
	Nutrition	14.136	4.027	12.912	15.361		
	Combined	14.962	3.662	13.942	15.981		
	Total	14.362	3.921	13.702	15.022		
MFI Reduced Motivation	Psychology	10.357	4.287	9.021	11.693	1.324[a]	.270
	Nutrition	10.500	3.474	9.444	11.556		
	Combined	11.462	3.153	10.584	12.339		
	Total	10.819	3.639	10.206	11.431		
MFI Mental Fatigue	Psychology	13.524	4.363	12.164	14.883	.064[a]	.938
	Nutrition	13.682	4.328	12.366	14.998		
	Combined	13.846	4.345	12.637	15.056		
	Total	13.696	4.315	12.969	14.422		
CDC CFS Sore Throat	Psychology	2.571	3.109	1.603	3.540	1.414[a]	.247
	Nutrition	3.977	3.776	2.829	5.125		
	Combined	3.202	4.494	1.951	4.454		
	Total	3.257	3.898	2.601	3.914		
CDC CFS Swollen Lymph nodes Glands	Psychology	1.976	3.382	.922	3.030	7.161[b]	.028*
	Nutrition	5.561	6.491	3.587	7.534		
	Combined	3.462	4.881	2.103	4.820		
	Total	3.679	5.250	2.795	4.563		
CDC CFS DiarrhoeaDiarrhea	Psychology	2.071	3.249	1.059	3.084	.850[a]	.430
	Nutrition	2.841	4.832	1.372	4.310		
	Combined	3.135	3.773	2.084	4.185		
	Total	2.717	3.998	2.044	3.390		

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CDC CFS Fatigue after exertion	Psychology	13.286	6.271	11.331	15.240	.219[a]	.803
	Nutrition	13.722	6.450	11.761	15.682		
	Combined	14.154	6.270	12.408	15.899		
	Total	13.752	6.292	12.693	14.811		
CDC CFS Muscle Aches or Muscle Pains	Psychology	8.286	6.747	6.183	10.388	.166[a]	.847
	Nutrition	9.091	6.383	7.151	11.031		
	Combined	8.519	6.932	6.589	10.449		
	Total	8.630	6.664	7.509	9.752		
CDC CFS Pain In Joints	Psychology	3.476	5.334	1.814	5.138	1.373[a]	.257
	Nutrition	4.696	5.560	3.006	6.386		
	Combined	5.474	6.386	3.696	7.251		
	Total	4.618	5.837	3.635	5.600		
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	.027[a]	.973
	Nutrition	1.394	2.562	.615	2.173		
	Combined	1.333	3.909	.245	2.421		
	Total	1.324	3.106	.801	1.846		
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	.206[a]	.814
	Nutrition	3.750	3.924	2.557	4.943		
	Combined	3.192	4.343	1.983	4.402		
	Total	3.420	4.283	2.699	4.141		
CDC CFS Unrefreshing Sleep	Psychology	12.905	6.792	10.788	15.021	.150[a]	.861
	Nutrition	12.250	7.088	10.095	14.405		
	Combined	12.154	7.147	10.164	14.144		
	Total	12.413	6.978	11.238	13.588		
CDC CFS Sleeping	Psychology	9.286	7.658	6.899	11.672	.085[a]	.918

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Problems	Nutrition	8.614	7.317	6.389	10.838		
	Combined	8.904	7.684	6.766	11.042		
	Total	8.928	7.509	7.664	10.192		
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	1.611[a]	.203
	Nutrition	7.646	7.040	5.506	9.786		
	Combined	6.346	5.857	4.715	7.977		
	Total	6.431	6.200	5.3871	7.474		
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.403[b]	.182
	Nutrition	9.409	7.183	7.225	11.593		
	Combined	8.173	7.610	6.055	10.292		
	Total	8.007	6.835	6.857	9.158		
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	.391[a]	.677
	Nutrition	9.822	7.641	7.499	12.145		
	Combined	9.135	6.942	7.202	11.067		
	Total	9.161	6.903	7.999	10.323		
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	1.162[a]	.316
	Nutrition	4.769	5.135	3.208	6.330		
	Combined	3.327	4.902	1.962	4.692		
	Total	3.832	4.966	2.996	4.668		
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	5.971[b]	.051
	Nutrition	5.064	5.165	3.493	6.634		
	Combined	3.750	4.635	2.460	5.041		
	Total	3.803	4.535	3.040	4.566		
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	1.192[a]	.307
	Nutrition	5.469	6.476	3.500	7.438		

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	Combined	4.789	6.304	3.034	6.544		
	Total	4.620	5.932	3.622	5.619		
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	.095[a]	.909
	Nutrition	3.285	4.090	2.026	4.543		
	Combined	3.392	4.788	2.046	4.739		
	Total	3.237	4.365	2.497	3.977		
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	.794[a]	.454
	Nutrition	5.031	6.097	3.177	6.884		
	Combined	4.481	6.360	2.710	6.251		
	Total	4.336	5.975	3.330	5.342		
CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	.160[b]	.923
	Nutrition	4.477	5.450	2.821	6.134		
	Combined	5.077	5.950	3.420	6.734		
	Total	4.544	5.231	3.663	5.424		
CDC CFS Maladaptive Stress Index Scale Score	Psychology	94.381	16.836	89.134	99.628	.465[a]	.629
	Nutrition	96.386	21.946	89.714	103.059		
	Combined	98.269	19.165	92.934	103.605		
	Total	96.486	19.373	93.225	99.747		

[a] *F*-statistic for one-way analysis of variance, d.f = 2,134

[b] *H*-statistic for Kruskal-Wallis test, d.f. = 2

[c] χ^2-statistic for comparison of nominal level data, d.f. = 2

[d] number of males

* test is significant at the $p < .05$ level

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Table 2. Outcome variable comparisons across time

		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	59.267	30.346	41.745	76.788	-2.707	.007**
	Nutrition	47.855	26.226	39.882	55.829	46.706	30.744	34.544	58.868	-1.136	.256
	Combined	45.299	25.479	38.206	52.393	49.288	26.403	39.604	58.973	-1.850	.064
	Total	47.344	24.791	43.171	51.517	50.260	28.818	43.488	57.032	-3.120	.002**
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	46.429	39.048	23.883	68.974	-2.379	.017*
	Nutrition	7.574	17.500	2.254	12.895	19.444	20.016	11.526	27.363	-2.907	.004**
	Combined	9.774	21.051	3.914	15.635	22.742	25.161	13.513	31.971	-2.225	.026*
	Total	8.272	18.387	5.177	11.367	26.111	28.225	19.479	32.744	-4.354	.001***
SF-36 Bodily pain	Psychology	61.548	25.614	53.566	69.530	63.929	29.786	46.731	81.127	-1.196	.232
	Nutrition	55.625	30.242	46.434	64.819	58.889	32.943	45.857	71.921	-1.800	.072
	Combined	53.606	27.019	46.084	61.128	58.629	27.301	48.615	68.643	-1.048	.294
	Total	56.667	27.683	52.007	61.327	59.757	29.649	52.790	66.724	-2.240	.025*
SF-36 Social functioning	Psychology	37.202	21.824	30.402	44.003	59.821	33.318	40.584	79.058	-2.689	.007**
	Nutrition	32.671	25.888	24.800	40.541	43.519	33.679	30.196	56.841	-2.476	.013*
	Combined	32.452	24.786	25.551	39.352	41.936	28.604	31.443	52.428	-2.426	.015*
	Total	33.967	24.212	29.892	38.043	46.007	31.805	38.533	53.481	-4.504	.001***
SF-36 General mental health	Psychology	60.286	19.584	54.183	66.389	74.571	13.276	66.906	82.237	-2.497	.013*
	Nutrition	59.727	19.355	53.843	65.612	64.741	20.548	56.612	72.869	-1.696	.090
	Combined	58.308	20.948	52.476	64.140	64.129	16.637	58.027	70.232	-.524	.600

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	Total	59.362	19.911	56.011	62.714	66.389	17.897	62.183	70.594	-2.665	.008**
SF-36 Role limitations emotional	Psychology	55.554	46.368	41.105	70.004	76.191	33.150	57.051	95.331	-.842	.400
	Nutrition	48.482	47.390	34.074	62.890	55.594	38.130	40.510	70.678	-1.788	.074
	Combined	47.780	43.924	35.551	60.008	67.742	32.756	55.727	79.757	-2.313	.021*
	Total	50.370	45.590	42.695	58.044	64.829	35.335	56.526	73.133	-3.159	.002**
SF-36 Vitality Energy or Fatigue	Psychology	20.714	16.139	15.685	25.743	41.071	20.586	29.186	52.957	-3.066	.002**
	Nutrition	20.114	14.5670	15.685	24.542	31.111	23.588	21.780	40.442	-2.734	.006**
	Combined	19.039	17.658	14.123	23.955	27.097	19.527	19.934	34.259	-1.558	.119
	Total	19.891	16.159	17.171	22.611	31.319	21.657	26.230	36.409	-4.205	.001***
SF-36 General health perceptions	Psychology	37.024	17.945	31.432	42.616	45.714	21.109	33.526	57.903	-2.561	.010*
	Nutrition	28.636	15.528	23.915	33.357	36.482	18.903	29.004	43.959	-2.157	.031*
	Combined	30.962	17.575	26.069	35.854	42.097	21.632	34.162	50.032	-2.423	.015*
	Total	32.065	17.286	29.156	34.975	40.694	20.561	35.863	45.526	-3.996	.001***
MHLCS Internal	Psychology	.677	.159	.627	.726	.821	.251	.676	.966	-2.983	.003**
	Nutrition	.622	.177	.568	.675	1.193	2.969	.019	2.368	-.687	.492
	Combined	.662	.174	.613	.710	.779	.318	.662	.896	-1.755	.079
	Total	.653	.171	.624	.682	.942	1.822	.514	1.371	-2.962	.003**
MHLCS Chance	Psychology	.368	.156	.320	.417	.351	.152	.263	.439	-2.594	.009**
	Nutrition	.340	.133	.299	.380	.911	3.020	-.284	2.105	-.143	.886
	Combined	.354	.155	.311	.397	.314	.133	.265	.363	-.672	.501
	Total	.354	.148	.329	.379	.545	1.853	.109	.980	-1.552	.121
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.441	.315	.259	.624	.000	1.000
	Nutrition	.418	.141	.374	.460	.804	2.244	-.084	1.691	-1.843	.065
	Combined	.407	.101	.379	.436	.434	.279	.331	.536	-.577	.564
	Total	.409	.124	.388	.430	.574	1.3880	.248	.900	-1.601	.109

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MHLCS Doctors	Psychology	.169	.082	.143	.194	.131	.093	.077	.185	-1.122	.262
	Nutrition	.171	.089	.144	.197	.657	2.668	-.398	1.713	-1.686	.092
	Combined	.191	.147	.150	.232	.153	.070	.128	.179	-1.384	.166
	Total	.178	.112	.159	.196	.338	1.635	-.0462	.722	-2.381	.017*
MHLCS Other People	Psychology	.235	.075	.212	.259	.268	.189	.159	.377	-.118	.906
	Nutrition	.264	.129	.225	.304	.739	2.652	-.311	1.788	-1.697	.090
	Combined	.245	.074	.224	.265	.252	.118	.209	.295	-.213	.831
	Total	.248	.095	.232	.264	.438	1.626	.055	.820	-1.186	.236
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	13.786	4.441	11.222	16.350	-2.657	.008**
	Nutrition	16.977	2.601	16.186	17.768	14.704	4.898	12.766	16.641	-2.548	.011*
	Combined	17.327	2.588	16.607	18.047	16.645	2.811	15.614	17.676	-.854	.393
	Total	16.797	2.716	16.340	17.254	15.361	4.136	14.389	16.333	-3.692	.001***
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	13.071	4.632	10.397	15.746	-2.810	.005**
	Nutrition	16.727	3.358	15.707	17.748	14.222	4.987	12.249	16.195	-2.791	.005**
	Combined	17.615	2.823	16.830	18.401	16.484	3.395	15.239	17.729	-2.364	.018*
	Total	16.819	3.211	16.278	17.359	14.972	4.453	13.926	16.019	-4.591	.001***
MFI Reduced Activity	Psychology	13.857	4.112	12.576	15.138	10.643	5.153	7.668	13.618	-2.142	.032*
	Nutrition	14.136	4.027	12.912	15.361	12.259	5.012	10.277	14.242	-2.164	.030*
	Combined	14.962	3.662	13.942	15.981	14.936	3.777	13.550	16.321	-.070	.944
	Total	14.362	3.921	13.702	15.022	13.097	4.798	11.970	14.225	-2.421	.015*
MFI Reduced Motivation	Psychology	10.357	4.287	9.021	11.693	7.286	4.214	4.853	9.719	-2.131	.033*
	Nutrition	10.500	3.474	9.444	11.556	8.963	3.736	7.485	10.441	-1.985	.047*
	Combined	11.462	3.153	10.584	12.339	10.774	3.095	9.639	11.910	-1.082	.279
	Total	10.819	3.639	10.206	11.431	9.417	3.767	8.532	10.302	-2.986	.003**
MFI	Psychology	13.524	4.363	12.164	14.883	10.500	4.468	7.920	13.080	-2.950	.003*

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Mental Fatigue	Nutrition	13.682	4.328	12.366	14.998	11.926	5.334	9.816	14.036	-2.082	.037*
	Combined	13.846	4.345	12.637	15.056	12.613	3.827	11.209	14.017	-1.586	.113
	Total	13.696	4.315	12.969	14.422	11.944	4.568	10.871	13.018	-3.661	.001***
CDC CFS	Psychology	2.571	3.109	1.603	3.540	1.429	2.278	.114	2.744	-1.365	.172
Sore Throat	Nutrition	3.977	3.776	2.829	5.125	1.741	2.087	.915	2.566	-2.211	.027*
	Combined	3.202	4.494	1.951	4.454	1.904	2.821	.870	2.939	-.804	.422
	Total	3.257	3.898	2.601	3.914	1.750	2.437	1.178	2.323	-2.387	.017*
CDC CFS	Psychology	1.976	3.382	.922	3.030	1.786	3.378	-.165	3.736	-.341	.733
Swollen	Nutrition	5.561	6.491	3.587	7.534	5.000	6.760	2.326	7.674	-2.212	.027*
Lymph nodes	Combined	3.462	4.881	2.103	4.820	2.690	4.477	1.0458	4.332	-.725	.468
Glands	Total	3.679	5.250	2.795	4.563	3.380	5.385	2.115	4.646	-1.684	.092
CDC CFS	Psychology	2.071	3.249	1.059	3.084	1.643	2.818	.016	3.270	-.730	.465
DiarrhoeaDiarrhea	Nutrition	2.841	4.832	1.372	4.310	1.444	3.274	.149	2.740	-1.649	.099
	Combined	3.135	3.773	2.084	4.185	1.631	2.483	.720	2.542	-1.996	046*
	Total	2.717	3.998	2.044	3.390	1.563	2.827	.899	2.228	-2.481	.013*
CDC CFS	Psychology	13.286	6.271	11.331	15.240	11.071	6.673	7.218	14.925	-1.550	.121
Fatigue after	Nutrition	13.722	6.450	11.761	15.682	11.815	7.217	8.960	14.670	-2.209	.027*
exertion	Combined	14.154	6.270	12.408	15.899	11.436	6.275	9.134	13.738	-2.392	.017*.
	Total	13.752	6.292	12.693	14.811	11.507	6.629	9.949	13.065	-3.574	.001***
CDC CFS	Psychology	8.286	6.747	6.183	10.388	7.429	6.892	3.450	11.408	-2.145	.032*
Muscle Aches	Nutrition	9.091	6.383	7.151	11.031	7.222	6.278	4.739	9.706	-2.901	.004**
or Muscle	Combined	8.519	6.932	6.589	10.449	6.188	5.528	4.160	8.215	-1.908	.056
Pains	Total	8.630	6.664	7.509	9.752	6.817	6.029	5.400	8.234	-.3995	.001***
CDC CFS	Psychology	3.476	5.334	1.814	5.138	2.786	4.458	.212	5.360	-1.778	.075
Pain In Joints	Nutrition	4.696	5.560	3.006	6.386	3.926	5.099	1.909	5.943	-2.022	.043*

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	Combined	5.474	6.386	3.696	7.251	3.010	4.140	1.492	4.528	-1.840	.066
	Total	4.618	5.837	3.635	5.600	3.310	4.543	2.242	4.377	-3.141	.002**
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	1.643	4.181	-.771	4.057	-.135	.892
	Nutrition	1.394	2.562	.615	2.173	.630	2.041	-.178	1.437	-1.487	.137
	Combined	1.333	3.909	.245	2.421	.378	.709	.118	.638	-1.517	.129
	Total	1.324	3.106	.801	1.846	.718	2.272	.185	1.252	-1.876	.061
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	2.571	4.398	.032	5.111	-1.970	.049*
	Nutrition	3.750	3.924	2.557	4.943	2.222	4.098	.601	3.843	-3.401	.001***
	Combined	3.192	4.343	1.983	4.402	1.908	2.797	.882	2.934	-2.049	.040*
	Total	3.420	4.283	2.699	4.141	2.155	3.614	1.306	3.004	-4.206	.001***
CDC CFS Unrefreshing Sleep	Psychology	12.905	6.792	10.788	15.021	10.643	6.698	6.776	14.510	-.802	.422
	Nutrition	12.250	7.088	10.095	14.405	9.444	7.738	6.384	12.505	-1.421	.155
	Combined	12.154	7.147	10.164	14.143	10.161	7.959	7.242	13.080	-1.513	.130
	Total	12.413	6.978	11.238	13.588	9.986	7.557	8.210	11.762	-2.295	.022*
CDC CFS Sleeping Problems	Psychology	9.286	7.658	6.899	11.672	5.286	4.921	2.444	8.127	-1.738	.082
	Nutrition	8.614	7.317	6.389	10.838	9.482	9.200	5.842	13.121	-.190	.849
	Combined	8.904	7.681	6.766	11.042	6.529	6.749	4.053	9.004	-1.794	.073
	Total	8.928	7.509	7.664	10.192	7.394	7.585	5.612	9.177	-1.983	.047*
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	4.357	3.411	2.388	6.326	-1.200	.230
	Nutrition	7.646	7.040	5.506	9.786	5.185	6.294	2.695	7.675	-2.084	.037*
	Combined	6.346	5.857	4.715	7.977	4.050	3.527	2.756	5.343	-2.807	.005**
	Total	6.431	6.200	5.387	7.474	4.535	4.708	3.429	5.642	-3.000	.003**
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.500	3.995	1.193	5.807	-1.965	.049*
	Nutrition	9.409	7.183	7.225	11.593	8.667	7.681	5.628	11.705	-.338	.735
	Combined	8.173	7.610	6.055	10.292	6.148	4.905	4.349	7.947	-1.446	.148

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	Total	8.007	6.835	6.857	9.158	6.578	6.189	5.123	8.032	-2.053	.040*
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	5.143	5.559	1.933	8.353	-2.809	.005**
	Nutrition	9.822	7.641	7.499	12.145	7.778	6.941	5.032	10.524	-1.196	.232
	Combined	9.135	6.942	7.202	11.067	6.507	4.843	4.731	8.283	-1.899	.058
	Total	9.161	6.903	7.999	10.323	6.718	5.844	5.345	8.092	-3.440	.001***
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	2.286	2.946	.585	3.987	-.213	.832
	Nutrition	4.769	5.135	3.208	6.330	3.407	5.746	1.134	5.681	-1.686	.092
	Combined	3.327	4.902	1.962	4.692	3.458	3.585	2.144	4.773	-.855	.392
	Total	3.832	4.966	2.996	4.668	3.211	4.396	2.178	4.244	-.584	.559
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	2.786	4.003	.474	5.097	-.343	.732
	Nutrition	5.064	5.165	3.493	6.634	3.593	3.905	2.048	5.137	-1.968	.049*
	Combined	3.750	4.635	2.460	5.041	2.548	2.791	1.524	3.572	-.598	.550
	Total	3.803	4.535	3.040	4.566	2.986	3.470	2.171	3.801	-1.727	.084
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	2.357	2.437	.950	3.764	-.724	.469
	Nutrition	5.469	6.476	3.500	7.438	4.889	6.104	2.474	7.304	-1.400	.162
	Combined	4.789	6.304	3.034	6.544	3.804	6.710	1.343	6.266	-2.482	.013*
	Total	4.620	5.931	3.622	5.619	3.930	5.882	2.547	5.312	-2.971	.003**
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	1.571	2.209	.296	2.847	-1.556	.120
	Nutrition	3.285	4.090	2.026	4.543	2.407	4.060	.801	4.013	-1.849	.064
	Combined	3.392	4.788	2.046	4.739	2.526	3.631	1.194	3.858	-.976	.329
	Total	3.237	4.365	2.497	3.977	2.296	3.554	1.461	3.131	-2.538	.011*
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	1.214	2.517	-.239	2.668	-1.973	.049*
	Nutrition	5.031	6.097	3.177	6.884	4.111	6.198	1.659	6.563	-2.136	.033*
	Combined	4.481	6.360	2.710	6.251	3.297	5.557	1.259	5.335	-.787	.431
	Total	4.336	5.975	3.330	5.342	3.197	5.419	1.924	4.471	-2.542	.011*

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CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	1.571	3.228	-.292	3.435	-1.614	.106
	Nutrition	4.477	5.450	2.821	6.134	3.333	4.883	1.402	5.265	-1.584	.113
	Combined	5.077	5.950	3.420	6.734	2.766	3.324	1.547	3.985	-1.304	.192
	Total	4.544	5.230	3.663	5.424	2.747	3.964	1.815	3.678	-2.297	.022*
CDC CFS Maladaptive Stress Index Scale Score	Psychology	94.381	16.836	89.134	99.628	78.571	18.434	67.928	89.215	-3.111	.002**
	Nutrition	96.386	21.946	89.714	103.059	85.259	27.665	74.315	96.203	-3.443	.001***
	Combined	98.269	19.165	92.934	103.605	87.484	22.965	79.060	95.908	-2.215	.027*
	Total	96.486	19.373	93.225	99.747	84.917	24.004	79.276	90.557	-5.123	.001***

[a] z statistic for Wilcoxon Signed Rank Test

Table 3. Change score comparisons between intervention groups

		% change over time for sig. results [a]	Mean	Std. Deviation	Std. Error	95% CI for Mean		*H* [b]	p-value
						Lower	Upper		
SF-36 Physical Functioning	Psychology	16.75	-13.629	14.990	4.006	-22.285	-4.974	3.215	.200
	Nutrition		-.407	19.967	3.843	-8.306	7.492		
	Combined		-6.813	18.242	3.276	-13.505	-.122		
	Total	5.80	-5.736	18.744	2.209	-10.141	-1.332		
SF-36	Psychology	84.61	-33.929	39.960	10.680	-57.001	-10.856	1.558	.459

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Role limitations physical	Nutrition	61.05	-14.509	21.005	4.042	-22.818	-6.199		
	Combined	57.02	-13.871	31.457	5.650	-25.409	-2.333		
	Total	63.32	-18.010	30.564	3.602	-25.192	-10.828		
SF-36	Psychology		-6.071	15.588	4.166	-15.072	2.929	-.163	.922
Bodily pain	Nutrition		-6.574	18.800	3.618	-14.011	.863		
	Combined		-3.387	25.532	4.586	-12.752	5.978		
	Total	5.17	-5.104	21.252	2.505	-10.098	-.110		
SF-36	Psychology	37.81	-24.107	24.741	6.612	-38.392	-9.822	3.301	.192
Social functioning	Nutrition	24.93	-10.648	20.423	3.931	-18.727	-2.569		
	Combined	22.60	-11.290	24.013	4.313	-20.098	-2.482		
	Total	26.17	-13.542	23.149	2.728	-18.981	-8.102		
SF-36	Psychology	19.15	-12.000	14.294	3.820	-20.253	-3.747	4.404	.111
General mental health	Nutrition		-3.259	15.963	3.072	-9.574	3.056		
	Combined		-.645	16.911	3.037	-6.848	5.558		
	Total	10.58	-3.833	16.409	1.934	-7.689	.022		
SF-36	Psychology		-9.527	49.664	13.273	-38.202	19.148	.573	.751
Role limitations	Nutrition		-18.561	55.759	10.731	-40.618	3.497		
emotional	Combined	29.47	-18.284	52.240	9.383	-37.446	.878		
	Total	10.58	-16.685	52.496	6.187	-29.021	-4.349		
SF-36	Psychology	49.57	-17.500	15.902	4.250	-26.682	-8.318	4.988	.083
Vitality Energy or	Nutrition	35.35	-11.482	19.206	3.696	-19.079	-3.884		
Fatigue	Combined		-6.129	17.688	3.177	-12.617	.359		
	Total	22.30	-10.347	18.219	2.147	-14.628	-6.066		
SF-36	Psychology	19.01	-11.429	14.335	3.831	-19.705	-3.152	.627	.731
General health	Nutrition	29.73	-6.852	15.201	2.925	-12.865	-.839		

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perceptions	Combined	26.45	-10.161	22.154	3.97	-18.288	-2.035		
	Total	36.49	-9.167	18.251	2.151	-13.455	-4.878		
MHLCS Internal	Psychology	17.56	-.146	.203	.054	-.263	-.029	3.402	.183
	Nutrition		-.573	3.028	.583	-1.771	.625		
	Combined		-.106	.315	.057	-.222	.010		
	Total	30.67	-.289	1.859	.219	-.726	.148		
MHLCS Chance	Psychology	4.67	.077	.098	.026	.021	.134	7.674	.022*
	Nutrition		-.570	3.019	.581	-1.765	.624		
	Combined		.001	.081	.015	-.029	.031		
	Total		-.198	1.852	.218	-.633	.237		
MHLCS Powerful Others	Psychology		-.054	.284	.076	-.218	.109	1.571	.456
	Nutrition		-.375	2.282	.439	-1.277	.528		
	Combined		-.030	.277	.050	-.132	.072		
	Total		-.164	1.408	.166	-.495	.167		
MHLCS Doctors	Psychology		.020	.058	.0155	-.014	.053	0.076	.963
	Nutrition		-.492	2.678	.515	-1.551	.568		
	Combined		.057	.199	.036	-.016	.130		
	Total	47.49	-.156	1.647	.194	-.543	.231		
MHLCS Other People	Psychology		-.032	.166	.044	-.128	.064	2.479	.290
	Nutrition		-.446	2.692	.518	-1.510	.619		
	Combined		-.012	.096	.017	-.047	.023		
	Total		-.178	1.645	.193	-.565	.208		

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MFI General Fatigue	Psychology	13.58	2.571	2.766	.739	.975	4.168	6.790	.034*
	Nutrition	13.39	2.074	3.842	.740	.554	3.594		
	Combined		.419	2.233	.401	-.400	1.238		
	Total	8.55	1.458	3.126	.368	.724	2.193		
MFI Physical Fatigue	Psychology	17.74	2.857	2.797	.748	1.242	4.472	3.038	.219
	Nutrition	15.00	2.444	4.371	.841	.716	4.173		
	Combined	6.42	1.290	2.735	.491	.287	2.294		
	Total	10.98	2.028	3.468	.409	1.213	2.843		
MFI Reduced Activity	Psychology	23.20	1.857	2.932	.784	.165	3.550	1.734	.420
	Nutrition	13.28	1.148	2.685	.517	.086	2.210		
	Combined		.645	3.189	.572	-.525	1.815		
	Total	8.81	1.069	2.952	.348	.376	1.763		
MFI Reduced Motivation	Psychology	11.42	2.500	3.502	.936	.478	4.522	5.171	.075
	Nutrition	14.64	1.593	3.511	.676	.204	2.982		
	Combined		.129	3.471	.624	-1.144	1.402		
	Total	12.96	1.139	3.570	.421	.300	1.978		
MFI Mental Fatigue	Psychology	29.66	3.571	3.056	.817	1.807	5.336	4.551	.103
	Nutrition	12.83	1.519	3.631	.699	.082	2.955		
	Combined		1.161	4.267	.766	-.404	2.726		
	Total	12.79	1.764	3.880	.457	.852	2.676		
CDC CFS Sore Throat	Psychology		1.429	3.736	.998	-.728	3.586	1.298	.523
	Nutrition	56.23	1.185	2.661	.512	.133	2.238		
	Combined		.500	4.591	.825	-1.184	2.184		
	Total	46.26	.937	3.769	.444	.052	1.823		
CDC CFS Swollen Lymph	Psychology		-.143	2.932	.784	-1.835	1.550	0.462	.794

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nodes Glands	Nutrition	10.09	1.247	2.700	.520	.179	2.316		
	Combined		.794	6.549	1.176	-1.608	3.197		
	Total		.782	4.756	.560	-.336	1.900		
CDC CFS DiarrhoeaDiarrhea	Psychology		-.286	1.490	.398	-1.146	.575	3.619	.164
	Nutrition		.926	2.868	.552	-.209	2.060		
	Combined	47.97	1.272	3.789	.681	-.118	2.662		
	Total	42.47	.839	3.134	.369	.103	1.576		
CDC CFS Fatigue after exertion	Psychology		2.286	4.811	1.286	-.492	5.063	0.379	.827
	Nutrition	13.90	2.593	5.507	1.060	.414	4.771		
	Combined	19.20	2.532	5.578	1.002	.486	4.578		
	Total	16.32	2.507	5.339	.629	1.252	3.761		
CDC CFS Muscle Aches or Muscle Pains	Psychology	10.34	2.500	4.034	1.078	.171	4.829	0.469	.791
	Nutrition	20.56	2.333	3.637	.700	.894	3.772		
	Combined		2.070	5.335	.958	.113	4.027		
	Total	21.01	2.253	4.459	.526	1.205	3.300		
CDC CFS Pain In Joints	Psychology		1.857	4.036	1.079	-.473	4.187	0.054	.973
	Nutrition	16.40	1.393	3.721	.716	-.079	2.865		
	Combined		1.978	5.622	1.010	-.084	4.040		
	Total	28.32	1.735	4.634	.546	.646	2.824		
CDC CFS Fever	Psychology		-.214	1.968	.526	-1.351	.922	0.399	.819
	Nutrition		.604	2.311	.445	-.310	1.519		
	Combined		1.245	4.816	.865	-.521	3.012		
	Total		.721	3.573	.421	-.118	1.561		
CDC CFS Chills	Psychology	23.40	1.571	2.738	.732	-.009	3.152	1.517	.468
	Nutrition	40.74	2.148	3.097	.596	.923	3.373		

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	Combined	40.23	1.447	3.986	.716	-.015	2.909		
	Total	37.00	1.734	3.421	.403	.930	2.538		
CDC CFS Unrefreshing Sleep	Psychology		1.857	6.803	1.818	-2.071	5.785	0.160	.948
	Nutrition		2.148	6.904	1.329	-.583	4.879		
	Combined		1.581	5.726	1.029	-.520	3.681		
	Total	19.55	1.847	6.3123	.744	.364	3.331		
CDC CFS Sleeping Problems	Psychology		2.786	5.352	1.430	-.304	5.876	3.218	.200
	Nutrition		-.222	5.139	.989	-2.255	1.811		
	Combined		1.762	4.871	.875	-.025	3.548		
	Total	17.17	1.217	5.133	.605	.011	2.423		
CDC CFS Headaches	Psychology		-.7143	2.091	.559	-1.922	.493	6.625	.036*
	Nutrition	32.19	1.572	3.507	.675	.184	2.959		
	Combined	36.18	2.467	4.944	.888	.653	4.280		
	Total	29.32	1.512	4.124	.486	.543	2.482		
CDC CFS Memory Problems	Psychology	44.73	2.857	4.655	1.244	.169	5.545	2.316	.314
	Nutrition		-.111	4.925	.947	-2.059	1.837		
	Combined		1.949	6.011	1.080	-.256	4.154		
	Total	17.86	1.353	5.435	.641	.076	2.630		
CDC CFS Difficulty Concentrating	Psychology	39.50	4.643	4.534	1.212	2.025	7.261	5.945	.051
	Nutrition		.815	4.359	.839	-.910	2.539		
	Combined		2.170	5.877	1.056	.015	4.326		
	Total	26.66	2.143	5.217	.615	.917	3.369		
CDC CFS Nausea	Psychology		.143	2.770	.740	-1.456	1.742	4.773	.092
	Nutrition		.660	2.667	.513	-.395	1.716		
	Combined		.251	4.468	.803	-1.388	1.890		

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	Total		.384	3.535	.417	-.447	1.214		
CDC CFS Abdominal Pain	Psychology		.286	1.729	.462	-.713	1.284	1.082	.582
	Nutrition	29.05	.882	2.165	.417	.025	1.738		
	Combined		.839	4.390	.789	-.771	2.449		
	Total		.747	3.234	.381	-.013	1.507		
CDC CFS Sinus Nasal Symptoms	Psychology		.929	3.125	.835	-.876	2.733	1.255	.534
	Nutrition		1.060	4.193	.807	-.599	2.719		
	Combined	20.56	1.906	5.923	1.063	-.267	4.078		
	Total	14.95	1.399	4.822	.568	.266	2.532		
CDC CFS Shortness Of Breath	Psychology		1.500	3.459	.924	-.497	3.497	0.707	.702
	Nutrition	18.28	.779	2.057	.403	-.052	1.609		
	Combined		.690	3.972	.725	-.793	2.173		
	Total	29.08	.885	3.243	.388	.112	1.658		
CDC CFS Sensitivity To Light	Psychology	64.58	1.429	2.472	.661	.001	2.856	0.939	.625
	Nutrition		1.568	3.764	.725	.079	3.057		
	Combined		.961	5.178	.930	-.938	2.860		
	Total	26.26	1.280	4.209	.496	.291	2.269		
CDC CFS Depression	Psychology		1.429	3.502	.936	-.593	3.451	0.490	.783
	Nutrition		.704	3.268	.629	-.589	1.996		
	Combined		1.363	5.345	.960	-.598	3.323		
	Total	39.55	1.129	4.282	.505	.122	2.135		
CDC CFS Maladaptive Stress Index Scale Score	Psychology	16.75	16.286	13.234	3.537	8.645	23.927	4.379	.112
	Nutrition	11.54	12.815	17.802	3.426	5.772	19.857		
	Combined	10.98	9.613	26.424	4.746	.080	19.305		
	Total	11.99	12.111	21.201	2.499	7.129	17.093		

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[a] see table 2 for descriptive and inferential statistics

[b] *H* statistic for Kruskal-Wallis test, d.f. = 2

* significant at the .05 level

Table 1. Demographics for gender, age and illness duration across the three treatment groups

		Mean	SD	95% CI for Mean		Test statistic	p-value
				Lower	Upper		
Gender	Psychology	9 (21.4%)[d]				.179[c]	.915
	Nutrition	8 (18.2%)[d]					
	Combined	11 (21.2%)[d]					
	Total	28 (20.3%)[d]					
Age	Psychology	42.881	13.986	38.523	47.239	.000[a]	1.000
	Nutrition	42.864	12.504	39.062	46.665		
	Combined	42.843	11.125	39.714	45.972		
	Total	42.861	12.406	40.765	44.957		
Illness duration	Psychology	8.874	8.252	6.302	11.445	.252[a]	.778
	Nutrition	10.023	7.375	7.781	12.265		
	Combined	9.625	7.291	7.595	11.655		
	Total	9.523	7.580	8.247	10.800		

Table 2. Comparisons across time within the primary outcome measures

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		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	59.267	30.346	41.745	76.788	-2.707	.007**
	Nutrition	47.855	26.226	39.882	55.829	46.706	30.744	34.544	58.868	-1.136	.256
	Combined	45.299	25.479	38.206	52.393	49.288	26.403	39.604	58.973	-1.850	.064
	Total	47.344	24.791	43.171	51.517	50.260	28.818	43.488	57.032	-3.120	.002**
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	46.429	39.048	23.883	68.974	-2.379	.017*
	Nutrition	7.574	17.500	2.254	12.895	19.444	20.016	11.526	27.363	-2.907	.004**
	Combined	9.774	21.051	3.914	15.635	22.742	25.161	13.513	31.971	-2.225	.026*
	Total	8.272	18.387	5.177	11.367	26.111	28.225	19.479	32.744	-4.354	.001***
SF-36 Bodily pain	Psychology	61.548	25.614	53.566	69.530	63.929	29.786	46.731	81.127	-1.196	.232
	Nutrition	55.625	30.242	46.434	64.819	58.889	32.943	45.857	71.921	-1.800	.072
	Combined	53.606	27.019	46.084	61.128	58.629	27.301	48.615	68.643	-1.048	.294
	Total	56.667	27.683	52.007	61.327	59.757	29.649	52.790	66.724	-2.240	.025*
SF-36 Social functioning	Psychology	37.202	21.824	30.402	44.003	59.821	33.318	40.584	79.058	-2.689	.007**
	Nutrition	32.671	25.888	24.800	40.541	43.519	33.679	30.196	56.841	-2.476	.013*
	Combined	32.452	24.786	25.551	39.352	41.936	28.604	31.443	52.428	-2.426	.015*
	Total	33.967	24.212	29.892	38.043	46.007	31.805	38.533	53.481	-4.504	.001***
SF-36 General mental health	Psychology	60.286	19.584	54.183	66.389	74.571	13.276	66.906	82.237	-2.497	.013*
	Nutrition	59.727	19.355	53.843	65.612	64.741	20.548	56.612	72.869	-1.696	.090
	Combined	58.308	20.948	52.476	64.140	64.129	16.637	58.027	70.232	-.524	.600
	Total	59.362	19.911	56.011	62.714	66.389	17.897	62.183	70.594	-2.665	.008**
SF-36	Psychology	55.554	46.368	41.105	70.004	76.191	33.150	57.051	95.331	-.842	.400

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Role limitations emotional	Nutrition	48.482	47.390	34.074	62.890	55.594	38.130	40.510	70.678	-1.788	.074
	Combined	47.780	43.924	35.551	60.008	67.742	32.756	55.727	79.757	-2.313	.021*
	Total	50.370	45.590	42.695	58.044	64.829	35.335	56.526	73.133	-3.159	.002**
SF-36 Vitality Energy or Fatigue	Psychology	20.714	16.139	15.685	25.743	41.071	20.586	29.186	52.957	-3.066	.002**
	Nutrition	20.114	14.5670	15.685	24.542	31.111	23.588	21.780	40.442	-2.734	.006**
	Combined	19.039	17.658	14.123	23.955	27.097	19.527	19.934	34.259	-1.558	.119
	Total	19.891	16.159	17.171	22.611	31.319	21.657	26.230	36.409	-4.205	.001***
SF-36 General health perceptions	Psychology	37.024	17.945	31.432	42.616	45.714	21.109	33.526	57.903	-2.561	.010*
	Nutrition	28.636	15.528	23.915	33.357	36.482	18.903	29.004	43.959	-2.157	.031*
	Combined	30.962	17.575	26.069	35.854	42.097	21.632	34.162	50.032	-2.423	.015*
	Total	32.065	17.286	29.156	34.975	40.694	20.561	35.863	45.526	-3.996	.001***
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	13.786	4.441	11.222	16.350	-2.657	.008**
	Nutrition	16.977	2.601	16.186	17.768	14.704	4.898	12.766	16.641	-2.548	.011*
	Combined	17.327	2.588	16.607	18.047	16.645	2.811	15.614	17.676	-.854	.393
	Total	16.797	2.716	16.340	17.254	15.361	4.136	14.389	16.333	-3.692	.001***
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	13.071	4.632	10.397	15.746	-2.810	.005**
	Nutrition	16.727	3.358	15.707	17.748	14.222	4.987	12.249	16.195	-2.791	.005**
	Combined	17.615	2.823	16.830	18.401	16.484	3.395	15.239	17.729	-2.364	.018*
	Total	16.819	3.211	16.278	17.359	14.972	4.453	13.926	16.019	-4.591	.001***
MFI Reduced Activity	Psychology	13.857	4.112	12.576	15.138	10.643	5.153	7.668	13.618	-2.142	.032*
	Nutrition	14.136	4.027	12.912	15.361	12.259	5.012	10.277	14.242	-2.164	.030*
	Combined	14.962	3.662	13.942	15.981	14.936	3.777	13.550	16.321	-.070	.944
	Total	14.362	3.921	13.702	15.022	13.097	4.798	11.970	14.225	-2.421	.015*
MFI Reduced	Psychology	10.357	4.287	9.021	11.693	7.286	4.214	4.853	9.719	-2.131	.033*
	Nutrition	10.500	3.474	9.444	11.556	8.963	3.736	7.485	10.441	-1.985	.047*

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Motivation	Combined	11.462	3.153	10.584	12.339	10.774	3.095	9.639	11.910	-1.082	.279
	Total	10.819	3.639	10.206	11.431	9.417	3.767	8.532	10.302	-2.986	.003**
MFI	Psychology	13.524	4.363	12.164	14.883	10.500	4.468	7.920	13.080	-2.950	.003*
Mental Fatigue	Nutrition	13.682	4.328	12.366	14.998	11.926	5.334	9.816	14.036	-2.082	.037*
	Combined	13.846	4.345	12.637	15.056	12.613	3.827	11.209	14.017	-1.586	.113
	Total	13.696	4.315	12.969	14.422	11.944	4.568	10.871	13.018	-3.661	.001***

[a]*z*-statistic for Wilcoxon Signed-Rank Test

Table 3. Comparisons across time within the secondary outcome measures (ME/CFS-specific)

		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value
CDC CFS	Psychology	2.571	3.109	1.603	3.540	1.429	2.278	.114	2.744	-1.365	.172
Sore Throat	Nutrition	3.977	3.776	2.829	5.125	1.741	2.087	.915	2.566	-2.211	.027*
	Combined	3.202	4.494	1.951	4.454	1.904	2.821	.870	2.939	-.804	.422
	Total	3.257	3.898	2.601	3.914	1.750	2.437	1.178	2.323	-2.387	.017*
CDC CFS	Psychology	1.976	3.382	.922	3.030	1.786	3.378	-.165	3.736	-.341	.733
Swollen	Nutrition	5.561	6.491	3.587	7.534	5.000	6.760	2.326	7.674	-2.212	.027*
Lymph nodes	Combined	3.462	4.881	2.103	4.820	2.690	4.477	1.0458	4.332	-.725	.468
Glands	Total	3.679	5.250	2.795	4.563	3.380	5.385	2.115	4.646	-1.684	.092
CDC CFS	Psychology	2.071	3.249	1.059	3.084	1.643	2.818	.016	3.270	-.730	.465

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Diarrhea	Nutrition	2.841	4.832	1.372	4.310	1.444	3.274	.149	2.740	-1.649	.099
	Combined	3.135	3.773	2.084	4.185	1.631	2.483	.720	2.542	-1.996	046*
	Total	2.717	3.998	2.044	3.390	1.563	2.827	.899	2.228	-2.481	.013*
CDC CFS Fatigue after exertion	Psychology	13.286	6.271	11.331	15.240	11.071	6.673	7.218	14.925	-1.550	.121
	Nutrition	13.722	6.450	11.761	15.682	11.815	7.217	8.960	14.670	-2.209	.027*
	Combined	14.154	6.270	12.408	15.899	11.436	6.275	9.134	13.738	-2.392	.017*.
	Total	13.752	6.292	12.693	14.811	11.507	6.629	9.949	13.065	-3.574	.001***
CDC CFS Muscle Aches or Muscle Pains	Psychology	8.286	6.747	6.183	10.388	7.429	6.892	3.450	11.408	-2.145	.032*
	Nutrition	9.091	6.383	7.151	11.031	7.222	6.278	4.739	9.706	-2.901	.004**
	Combined	8.519	6.932	6.589	10.449	6.188	5.528	4.160	8.215	-1.908	.056
	Total	8.630	6.664	7.509	9.752	6.817	6.029	5.400	8.234	-.3995	.001***
CDC CFS Pain In Joints	Psychology	3.476	5.334	1.814	5.138	2.786	4.458	.212	5.360	-1.778	.075
	Nutrition	4.696	5.560	3.006	6.386	3.926	5.099	1.909	5.943	-2.022	.043*
	Combined	5.474	6.386	3.696	7.251	3.010	4.140	1.492	4.528	-1.840	.066
	Total	4.618	5.837	3.635	5.600	3.310	4.543	2.242	4.377	-3.141	.002**
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	1.643	4.181	-.771	4.057	-.135	.892
	Nutrition	1.394	2.562	.615	2.173	.630	2.041	-.178	1.437	-1.487	.137
	Combined	1.333	3.909	.245	2.421	.378	.709	.118	.638	-1.517	.129
	Total	1.324	3.106	.801	1.846	.718	2.272	.185	1.252	-1.876	.061
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	2.571	4.398	.032	5.111	-1.970	.049*
	Nutrition	3.750	3.924	2.557	4.943	2.222	4.098	.601	3.843	-3.401	.001***
	Combined	3.192	4.343	1.983	4.402	1.908	2.797	.882	2.934	-2.049	.040*
	Total	3.420	4.283	2.699	4.141	2.155	3.614	1.306	3.004	-4.206	.001***
CDC CFS UnrefreshingSl	Psychology	12.905	6.792	10.788	15.021	10.643	6.698	6.776	14.510	-.802	.422
	Nutrition	12.250	7.088	10.095	14.405	9.444	7.738	6.384	12.505	-1.421	.155

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eep	Combined	12.154	7.147	10.164	14.143	10.161	7.959	7.242	13.080	-1.513	.130
	Total	12.413	6.978	11.238	13.588	9.986	7.557	8.210	11.762	-2.295	.022*
CDC CFS Sleeping Problems	Psychology	9.286	7.658	6.899	11.672	5.286	4.921	2.444	8.127	-1.738	.082
	Nutrition	8.614	7.317	6.389	10.838	9.482	9.200	5.842	13.121	-.190	.849
	Combined	8.904	7.681	6.766	11.042	6.529	6.749	4.053	9.004	-1.794	.073
	Total	8.928	7.509	7.664	10.192	7.394	7.585	5.612	9.177	-1.983	.047*
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	4.357	3.411	2.388	6.326	-1.200	.230
	Nutrition	7.646	7.040	5.506	9.786	5.185	6.294	2.695	7.675	-2.084	.037*
	Combined	6.346	5.857	4.715	7.977	4.050	3.527	2.756	5.343	-2.807	.005**
	Total	6.431	6.200	5.387	7.474	4.535	4.708	3.429	5.642	-3.000	.003**
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.500	3.995	1.193	5.807	-1.965	.049*
	Nutrition	9.409	7.183	7.225	11.593	8.667	7.681	5.628	11.705	-.338	.735
	Combined	8.173	7.610	6.055	10.292	6.148	4.905	4.349	7.947	-1.446	.148
	Total	8.007	6.835	6.857	9.158	6.578	6.189	5.123	8.032	-2.053	.040*
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	5.143	5.559	1.933	8.353	-2.809	.005**
	Nutrition	9.822	7.641	7.499	12.145	7.778	6.941	5.032	10.524	-1.196	.232
	Combined	9.135	6.942	7.202	11.067	6.507	4.843	4.731	8.283	-1.899	.058
	Total	9.161	6.903	7.999	10.323	6.718	5.844	5.345	8.092	-3.440	.001***
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	2.286	2.946	.585	3.987	-.213	.832
	Nutrition	4.769	5.135	3.208	6.330	3.407	5.746	1.134	5.681	-1.686	.092
	Combined	3.327	4.902	1.962	4.692	3.458	3.585	2.144	4.773	-.855	.392
	Total	3.832	4.966	2.996	4.668	3.211	4.396	2.178	4.244	-.584	.559
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	2.786	4.003	.474	5.097	-.343	.732
	Nutrition	5.064	5.165	3.493	6.634	3.593	3.905	2.048	5.137	-1.968	.049*
	Combined	3.750	4.635	2.460	5.041	2.548	2.791	1.524	3.572	-.598	.550

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	Total	3.803	4.535	3.040	4.566	2.986	3.470	2.171	3.801	-1.727	.084
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	2.357	2.437	.950	3.764	-.724	.469
	Nutrition	5.469	6.476	3.500	7.438	4.889	6.104	2.474	7.304	-1.400	.162
	Combined	4.789	6.304	3.034	6.544	3.804	6.710	1.343	6.266	-2.482	.013*
	Total	4.620	5.931	3.622	5.619	3.930	5.882	2.547	5.312	-2.971	.003**
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	1.571	2.209	.296	2.847	-1.556	.120
	Nutrition	3.285	4.090	2.026	4.543	2.407	4.060	.801	4.013	-1.849	.064
	Combined	3.392	4.788	2.046	4.739	2.526	3.631	1.194	3.858	-.976	.329
	Total	3.237	4.365	2.497	3.977	2.296	3.554	1.461	3.131	-2.538	.011*
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	1.214	2.517	-.239	2.668	-1.973	.049*
	Nutrition	5.031	6.097	3.177	6.884	4.111	6.198	1.659	6.563	-2.136	.033*
	Combined	4.481	6.360	2.710	6.251	3.297	5.557	1.259	5.335	-.787	.431
	Total	4.336	5.975	3.330	5.342	3.197	5.419	1.924	4.471	-2.542	.011*
CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	1.571	3.228	-.292	3.435	-1.614	.106
	Nutrition	4.477	5.450	2.821	6.134	3.333	4.883	1.402	5.265	-1.584	.113
	Combined	5.077	5.950	3.420	6.734	2.766	3.324	1.547	3.985	-1.304	.192
	Total	4.544	5.230	3.663	5.424	2.747	3.964	1.815	3.678	-2.297	.022*

[a]*z*-statistic for Wilcoxon Signed-Rank Test

Table 4.Comparisons across time within the secondary outcome measures (psychological)

	Baseline				3-month follow-up				Comparisons	
			95% CI for Mean				95% CI for Mean			
	Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value

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MHLCS Internal	Psychology	.677	.159	.627	.726	.821	.251	.676	.966	-2.983	.003**
	Nutrition	.622	.177	.568	.675	1.193	2.969	.019	2.368	-.687	.492
	Combined	.662	.174	.613	.710	.779	.318	.662	.896	-1.755	.079
	Total	.653	.171	.624	.682	.942	1.822	.514	1.371	-2.962	.003**
MHLCS Chance	Psychology	.368	.156	.320	.417	.351	.152	.263	.439	-2.594	.009**
	Nutrition	.340	.133	.299	.380	.911	3.020	-.284	2.105	-.143	.886
	Combined	.354	.155	.311	.397	.314	.133	.265	.363	-.672	.501
	Total	.354	.148	.329	.379	.545	1.853	.109	.980	-1.552	.121
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.441	.315	.259	.624	.000	1.000
	Nutrition	.418	.141	.374	.460	.804	2.244	-.084	1.691	-1.843	.065
	Combined	.407	.101	.379	.436	.434	.279	.331	.536	-.577	.564
	Total	.409	.124	.388	.430	.574	1.3880	.248	.900	-1.601	.109
MHLCS Doctors	Psychology	.169	.082	.143	.194	.131	.093	.077	.185	-1.122	.262
	Nutrition	.171	.089	.144	.197	.657	2.668	-.398	1.713	-1.686	.092
	Combined	.191	.147	.150	.232	.153	.070	.128	.179	-1.384	.166
	Total	.178	.112	.159	.196	.338	1.635	-.0462	.722	-2.381	.017*
MHLCS Other People	Psychology	.235	.075	.212	.259	.268	.189	.159	.377	-.118	.906
	Nutrition	.264	.129	.225	.304	.739	2.652	-.311	1.788	-1.697	.090
	Combined	.245	.074	.224	.265	.252	.118	.209	.295	-.213	.831
	Total	.248	.095	.232	.264	.438	1.626	.055	.820	-1.186	.236
CDC CFS Maladaptive Stress Index Scale Score	Psychology	94.381	16.836	89.134	99.628	78.571	18.434	67.928	89.215	-3.111	.002**
	Nutrition	96.386	21.946	89.714	103.059	85.259	27.665	74.315	96.203	-3.443	.001***
	Combined	98.269	19.165	92.934	103.605	87.484	22.965	79.060	95.908	-2.215	.027*
	Total	96.486	19.373	93.225	99.747	84.917	24.004	79.276	90.557	-5.123	.001***

[a] *z*-statistic for Wilcoxon Signed-Rank Test

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	9-10

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A preliminary prospective study of nutritional, psychological and combined therapies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) in a private care setting.

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a condition ~~characterised~~characterized by severe and persistent fatigue, neurological disturbances, autonomic and endocrine dysfunctions and sleep difficulties that have a pronounced and significant impact on individuals' lives. Current NICE guidelines within the United Kingdom suggest that this condition should be treated with cognitive ~~behavioural~~behavioral therapy and/or graded exercise therapy where appropriate. There is currently a lack of evidence base concerning other, more integrative interventions that may be beneficial to those with ME/CFS.

Objectives: This study aimed to evaluate whether three patient-centered treatment modalities of psychology, nutrition and combined treatment, influenced symptom report measures in those with ~~reduced symptomatology of~~ ME/CFS over a 3-month time period and whether there were significant differences in these changes between groups.

Design and setting: This is a preliminary prospective~~longitudinal observational~~ study with one follow-up point conducted at a ~~one~~ private secondary health care facility in London, UK.

Participants: One-hundred and thirty-eight individuals (110 females, 79.7%; 42 participants in psychology, 44 in nutrition and 52 in combined) participated at baseline and 72 participants completed the battery of measures at follow-up (52.17% response rate; 14, 27, 31 participants in each group, respectively).

Outcome measures: Self-report measures of ME/CFS symptoms, functional ability, multidimensional fatigue, perceived control and maladaptive stress.

Results: Baseline comparisons showed those in the combined group had higher levels of fatigue. At follow-up, all groups saw improvements in fatigue, functional physical symptomatology and maladaptive stress; those within the psychology group also experienced a shift in perceived control over time. ~~The psychology group demonstrated a significantly greater change in fatigue and perceived control than the combined group; however, the opposite relationship was observed for headaches.~~

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Conclusions: This study provides early evidence that p~~P~~atient-centered techniques for the treatment of ME/CFS may influence ~~appear promising in reducing~~ symptomatology, fatigue, function, perceived control and inappropriate responses to stressors~~, and increasing function and perceived control.~~ However, these results must be viewed with caution as the allocation to groups was not randomized, there was no control group and the study suffered from high drop-out rates. ~~The need for further studies of integrative treatment with robust designs appears warranted.~~

Summary

Article focus

- This preliminary prospective ~~observational~~ study investigated three (psychological, nutritional and combined) tailored patient-centered interventions for ME/CFS over time.
- Differences between the reported changes over time between groups were also assessed.

Key messages

- Patient-centered approaches for the management of ME/CFS ~~reduce symptomatology~~influence symptomatology over time in some individuals with this disorder.
- Self-reported f~~F~~unctional ability~~,~~ (-physical and social)~~,~~ are influenced~~increase with~~ following tailored interventions lasting 3 months~~.~~
- ~~Psychological intervention can help individuals to regain a sense of control over their condition.~~ -
- This study provides preliminary evidence that tailored psychological, nutritional and Combined interventions may be effective treatments for some people with ME/CFS; however, due to the study's methodological limitations, it is important that this potential treatment effect is investigated further in high quality randomized controlled studies.

Strengths and limitations of this study

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- The findings here are an initial step to fill the gap in the extant literature regarding the utility of tailored, multidisciplinary and patient-centered treatments for ME/CFS.
- There is bias in this study as the participants were self-selected in the sense that they chose to attend the clinic and which treatment option they preferred (with advice), i.e. the study was not randomized.
- There were low retention rates in this study which may constitute a bias in that those who remained in the study may have experienced benefits and those who experienced little or no benefits may have dropped out.

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Introduction

Chronic Fatigue Syndrome or myalgic encephalomyelitis (ME/CFS) is a condition characterized by prolonged and debilitating fatigue, although the exact cause of this disorder is still under debate. Due to the lack of a definitive biological marker, diagnosis is made on the basis of the exclusion of other explanatory conditions. The most widely used case definition by the Centers for Disease Control [1] states that there must be at least six months severe fatigue of new and definite onset, not the result of ongoing exertion, not alleviated by rest and resulting in reduced levels of physical activity. The CDC definition also sets out a series of minor complaints that must accompany the fatigue (cognitive impairment, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, headaches of a new type, pattern or severity at onset, unrefreshing sleep and post-exertion malaise), with individuals needing to have the occurrence of four or more symptoms to be diagnosed with

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ME/CFS. Estimates of the prevalence of ME/CFS have been made as low as 3 and as high as 2,800 per 100,000 [2].

The most widely researched strategies for alleviating the symptoms of ME/CFS are Cognitive Behavior Therapy (CBT) and Graded Exercise Therapy (GET). Two reviews of studies on CBT [3,4] found that it significantly improved physical functioning in adult out-patients as compared with medical management, counseling, guided support, education and support or relaxation. ~~However, the longitudinal evidence for CBT is inconsistent and there is a lack of evidence with regard to CBT in combination with other treatments~~[4]. Regarding GET, a systematic review illustrated that this form of therapy was potentially beneficial for people with ME/CFS, especially when combined with a patient education programme[5]. However, drop-out rates were high in the GET groups suggesting that individuals with ME/CFS are a~~d~~verse to this type of therapy. Recently, a large scale, longitudinal study investigating CBT, GET, Adaptive Pacing Therapy (APT) and specialist medical care (SMC) found that CBT and GET (when added to SMC) were moderately effective outpatient treatments for this patient group as opposed to APT or SMC alone [6].

Although CBT and GET studies have shown some promising outcomes, there is no known cure for ME/CFS. Therefore the National Institute for Health and Clinical Excellence (NICE) [7~~6~~] recommends a number of symptom management strategies and interventions aimed at helping individuals to cope with their condition and reduce physical deconditioning brought about by the illness. Pharmacological interventions are, at times, suggested for patients with poor sleep or pain, for instance, low-dose antidepressants, as these have been shown to be effective [8-14~~7-13~~]. However, patient expectations must be realistic as the drugs may help elevate mood and psychological outlook but not reduce fatigue and other symptomatology

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associated with ME/CFS[15,14]. Numerous drugs such as thyroxin, hydrocortisone and antiviral agents are not advised by NICE due to contradictory findings[16,17,15,16].

In terms of function and quality of life management, NICE offers general advice concerning sleep management, appropriate rest periods, and pacing. Sleep hygiene instruction, together with pharmacological treatment tailored to the individual patient can be beneficial in combating fatigue [18,17]. Dietary management may also reduce symptomatology for those with concurrent irritable bowel syndrome (IBS). Management approaches recommended for IBS, such as diet restriction, are thus also recommended for those with ME/CFS[19,18]. Dietary supplementation has been investigated in relation to ME/CFS. Fatty acids [20,19], folic acid [21,20], vitamin C [22,21], co-enzyme Q10 [23,22], magnesium [24,23], multivitamins [25,24] and minerals [26,25] have all been shown to reduce symptomatology in ME/CFS patients. However other studies have shown conflicting findings with regard to nutritional supplementation, therefore it is perhaps wise to treat with supplements on a case-by-case basis[27,28,26,27].

Due to the lack of clear and definitive treatment strategies, individuals often seek out Complementary and Alternative Medicines (CAM). Although NICE does not recommend the use of CAM they do acknowledge that many people with ME/CFS use such therapies and find them beneficial for symptom management. This view is due to the lack of published evidence for the effectiveness of these treatments. Examples of CAM treatments used by individuals with ME/CFS include religious healing, massage therapy, relaxation, meditation, homeopathy, acupuncture, naturopathy and herbal therapies [29,30,28,29]; patient satisfaction with such approaches as CAM has been high, over 80% in some instances [29,28]. A recent systematic review of such interventions identified 70 controlled clinical trials (randomized and non-randomized) and found that 86% of these studies illustrated at least one positive effect, with

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74% showing a decrease of illness-related symptomatology [31~~30~~]. Meditative or mindfulness approaches warranted further investigation based on these results as did supplement programs of magnesium, l-carnitine, and S-adenosylmethionine. A subsequent review based solely on randomized controlled trials (RCTs) of CAM techniques identified 26 such studies and observed that qigong, massage and tuina (approaches based within Chinese Traditional Medicine and based upon relaxation and connection with the body) illustrated positive effects as did supplementation studies utilizing nicotinamide adenine dinucleotide (NADH) and magnesium [32~~31~~]. However, within both reviews it was noted that the methodological quality of reporting was poor and the sample sizes in these studies were small; hence ability to draw strong conclusions on the efficacy of CAM methods is limited. Porter et al. (2010) [31] did note that patient-centered, individualized treatment protocols which include a range of tailored strategies are a promising area for further investigation for this complex, multi-system illness.

Objectives

There is still much debate and uncertainty regarding the most effective treatment for ME/CFS. Recent reviews of CAM techniques highlight the need for further exploration of patient-centered and individually tailored interventions for the alleviation of the condition's often debilitating and intrusive symptomatology. This study therefore aims to provide preliminary evidence for the utility ~~evaluate the effectiveness of three~~of three types of patient-centered approaches to the management of ME/CFS over time (baseline and follow-up) offered at a private health-care center in the UK.

Methods

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Study design and setting

This preliminary prospective ~~a longitudinal observational~~ study ~~which~~ aimed to explore the effectiveness of ~~evaluate~~ three treatment options offered to individuals with ME/CFS. The research was conducted at one private secondary health care facility. All potential ~~prospective~~ patients of the clinic are first asked to complete a comprehensive symptom profile and medical history, including questions relating to triggering factors, psychology sub-types and structural/biological sub-types (this is distinct from the research data collected). Subsequent to this, every individual receives a 15-minute screening with one of the practitioners (please note, this was not either of the authors of the current study) who recommends the best course of action for his/her needs; this will be the psychology-related interventions, nutritional advice and support or a combination of the two.

All individuals requesting treatment at the private care setting were offered the opportunity to participate in the study. Those that expressed an interest (N = 145) were emailed a spreadsheet that contained the questionnaires and asked to complete it at their convenience. Informed consent was obtained prior to the completion of the questionnaires and the study was approved by the University of East London Ethics Committee. Participants were told that they could withdraw from the study at any time and that withdrawal would not affect their care at the clinic. Participants were able to ask questions at any point in the study and no deception was used as the participants were informed of the nature of the research program before they agreed to participate. Subsequently, participants were requested to complete the questionnaire pack on a second occasion, three months from the baseline measures.

Psychology

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The clinic offers a 3-month intervention which consists of a combination of Neuro-linguistic Programming (NLP), Emotional Freedom Technique (EFT), life coaching and hypnotherapy/self-hypnosis constructed in a manner specific to the needs of those with ME/CFS. The primary aim of this approach is to reduce the anxiety that is associated with having a debilitating and unpredictable condition, improve emotional well-being and help individuals slowly manage and increase their activity within their own limits (i.e. pacing). The program is offered as a series of group sessions and the peer support is seen as an important component of the intervention, which is solidified via the use of moderated online support forums, narratives of previous clients' experiences and online materials that can be accessed as often as necessary. In addition to, or as an alternative to this course, individuals receive a series of one-to-one sessions and for the most severely affected ME/CFS patients, telephone sessions are arranged and support materials can be accessed in their own homes.

Over the three-month period of this preliminary study, the participants experienced one of three treatment options. The first option included 13 hours of practitioner contact time in a mix of group training in person, group telephone conference calls and one-to-one telephone sessions, the second option was four hours of one-to-one telephone sessions and the final option was three hours of in person sessions. Participants all had access to various support materials which included CDs and online resources. The amount of time spent on these was patient-led, but was in the region of a further six hours. All the practitioners offering this option are qualified in hypnotherapy, NLP, life coaching and EFT and undergo an intensive period of training in the clinic's own integrative approach (please see Howard and Arroll [33] for more details of this approach) and ongoing supervision (individual and group supervision on a biweekly basis) from the department director, who is the only senior practitioner in the team.

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Nutrition

Tailored nutritional therapy is achieved via one-to-one consultations with individuals. To begin, a very detailed history is taken based upon the information given in the aforementioned symptom profile. Qualified nutritional therapists (who have been given specialist training regarding ME/CFS from the clinic) then suggest tests consistent with symptomatology, for instance the Adrenal Stress Index Test, comprehensive stool analysis/gastro-intestinal function, vitamin & mineral status, etc. Results from these tests are then used to compose an evidence-driven diet and supplement program. As most cases of ME/CFS are complex involving multiple body systems, this process is often iterative and follow-up consultations are necessary to check progress and make alterations to the protocol. The nutritional therapy program consists of an initial one-hour evaluation (which includes the tailored advice) and follow-up approximately every six weeks; therefore, during the course of the present study, the participants received a minimum of two one-hour sessions with email support for any queries and detailed nutritional guidance. All the nutritional therapists are qualified to diploma level and members of (voluntary) regulatory bodies such as the British Association for Applied Nutrition and Nutritional Therapy (BANT) and the Complementary and Natural Healthcare Council (CNHC). Similar to the psychology department, the nutrition department is led by one senior practitioner who supervises the team with individual and group supervisory arrangements.

Combined

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Within the combined program, a multidisciplinary approach is taken with practitioners discussing the patients in case meetings to ensure that the psychological and nutritional aspects complement each other in order to achieve the best outcome. It should be noted that the interventions in the combined program are phased-in as it was found that asking individuals to engage in numerous therapeutic activities at the same time resulted in high drop-out rates.

Primary Outcome Measures

Medical Outcomes Survey Short-Form 36 (SF-36)

This 36-item measure is the short form of the original Medical Outcomes Survey [34~~32~~] to measure functional impairment and contains eight sub-sections: 1) physical activity limitations due to health problems; 2) social activity limitations due to physical or emotional problems; 3) usual role activity limitations due to physical health problems; 4) bodily pain; 5) general mental health; 6) role activity limitations due to emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions [34~~32~~]. The items are scored so that higher scores indicate greater functional ability. In terms of the psychometric properties of this measure, reliability estimates for all sub-scales are good, exceeding a Cronbach's alpha coefficient value of 0.70 [35~~33~~]. In terms of validity, the SF-36 correlates amply, $r \geq 0.40$, with the frequency and severity of numerous symptoms and general health conditions [36;37 ~~34;35~~].

~~*Multidimensional Health Locus of Control Scale (MHLCS)*~~

~~Multidimensional Health Locus of Control [36-38] measures perceived control via three distinct sub-scales: 'internal', 'chance' and 'powerful others' which has two dimensions, that of~~

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~~'doctors' and 'other people'. The instrument contains 18 items in total (six items each for the internal and chance scales and three items for both the powerful others scales) and is scored on a 6 point Likert scale from 'strongly agree' to 'strongly disagree'. Internal reliability of the instrument is good with Cronbach's alpha coefficients ranging from 0.67 for 'powerful others' to 0.77 for 'internal'. The measure correlates positively and significantly with associated scales from Levenson's [39] locus of control measure from which the MHLOC was based upon, which demonstrates good convergent validity [36].~~

Multidimensional Fatigue Inventory (MFI)

This 20-item measure contains five fatigue dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [38,40]. Items such as 'I tire easily' are rated on a 5-point scale (1 = yes, that is true; 5 = no, that is not true) with lower scores reflecting higher levels of fatigue. The MFI has good internal consistency with average Cronbach's alpha coefficient equaling 0.84 across the sub-scales. Convergent validity based on a sample of radiotherapy patients found correlations between the sub-scales and a visual analog fatigue scale to be 0.77 for general fatigue, 0.70 for physical fatigue, 0.61 for reduced activity, 0.56 for reduced motivation (p<0.001) to 0.23 for mental fatigue (p<0.01) [38,40]

Secondary Outcome Measures (ME/CFS-specific)

CDC CFS Symptom Inventory

CDC CFS Symptom Inventory [39,41] was used to measure specific ME/CFS symptoms and confirm diagnosis. This instrument is based upon the CDC case definition [1] and includes a fatigue item and the eight distinct symptoms are also included in the CDC guidelines with an additional ten associated symptoms. The format of this self-report measure is a six-point scale of perceived frequency (0 = absent, 5 = all the time) and severity (0 = none, 5 = very severe). The psychometric properties of this instrument are good: Cronbach's alpha coefficient = 0.88;

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r = .74 convergent validity with the Chalder Fatigue Scale [40,42]; *r* -.68 and -.87 convergent validity with the SF-36 'vitality' and 'bodily pain' sub-scales, respectively.

Secondary Outcome Measures (psychological)

Multidimensional Health Locus of Control Scale (MHLCS)

Multidimensional Health Locus of Control [41-43] measures perceived control via three distinct sub-scales: 'internal', 'chance' and 'powerful others' which has two dimensions, that of 'doctors' and 'other people'. The instrument contains 18 items in total (six items each for the 'internal' and 'chance' scales and three items for both the 'powerful others' scales) and is scored on a 6-point Likert scale from 'strongly agree' to 'strongly disagree'. Internal reliability of the instrument is good with Cronbach's alpha coefficients ranging from 0.67 for 'powerful others' to 0.77 for 'internal'. The measure correlates positively and significantly with associated scales from Levenson's [44] locus of control measure from which the MHLOC was based, which demonstrates good convergent validity [41].

Maladaptive Stress Index

This 32-item measure contains three sub-scales (cognitive/mood, sleep and ME/CFS symptoms) and was designed specifically for this population [45,43]. Items such as 'I constantly replay or pre-empt situations and conversations' are scored on a 5-point scale where 1 = never true and 5 = always true; higher scores illustrate a greater degree of disturbance.

Statistical methods

The data was initially screened for missing data. Four cases contained substantial amounts of missing data; therefore these were excluded from the analysis (one individual from the nutrition group and three from the combined group). Once this was done, all the variables had

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less than 5% missing data, hence mean substitution was carried out in line with guidance [4644]. The baseline data was subsequently of the quality for parametric tests, except for the variables CDC CFS swollen lymph nodes and glands, memory problems, abdominal pain and depression. However, the follow-up data suffered from high levels of skew and kurtosis which was not substantially alleviated by data transformation. This violated a key criterion for parametric testing, that of normality of distribution, so non-parametric tests were selected. In addition, as the sample sizes in each individual treatment group were small, the more conservative non-parametric tests were the preferred choice as even though tests such as analysis of variance are generally robust against non-normality, this does not hold true with small sample sizes. ~~For baseline data,~~ One-way analysis of variance tests and Kruskal-Wallis tests (the former for those variables that met the criteria for parametric tests, and the latter that did not) were used to investigate baseline variation ~~difference between groups, Wilcoxon sign rank tests were employed to look for differences over time (baseline and 3-month follow up)~~ and analysis of covariance (ANCOVA) tests were used to account for this variation and test to for differences between the three groups. ~~Kruskal-Wallis tests were performed to investigate group differences in measures of change as evaluated by mean change scores, with Bonferroni corrected Mann-Whitney tests calculated to identify post hoc differences between groups if the Kruskal-Wallis tests were significant.~~ Wilcoxon sign-rank tests were employed to look for differences over time (baseline and 3-month follow-up) and if differences were significant, percentage change was calculated. Please note, as this is an exploratory study with only one time-point and no control group, any significant findings do not infer clinical significance, rather statistical significance, and as such exact p-values are presented.

Results

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Participants

Of the 145 individuals who expressed an interest in the study, 142 time-one questionnaires were returned, equating to a 97.9% response rate at baseline (two participants from the psychology group and one from the combined group dropped out at this stage). Therefore, excluding the four cases deleted due to insufficient data, 138 ~~One hundred and thirty eight~~ cases were used for baseline analysis; ~~individuals completed the questionnaire battery at time one (excluding the four deleted cases);~~ 42 participants in the psychology group, 44 in the nutrition group and 52 in the combined group. There was no significant association between gender and group (χ^2 (2) = 0.179, p = .915 ~~> .05~~), all groups consisting of approximately one-fifth males (Table 1). There was not a significant difference in age (F(2,135) = 0.00~~1~~0, p = 1.000~~> .05~~); in fact group means for age were near identical at 42.881, 42.864 and 42.843 for psychology, nutrition and combined groups, respectively. There was also a non-significant result for illness duration (F(2, 135) = 0.252, p = .778~~> .05~~). Therefore, in terms of demographics, the groups were comparable. With regard to the outcome measures, there were significant differences between the groups in terms of the MFI sub-scale 'general fatigue' (F(2, 135) = 3.219, p = .043~~< .05~~), MFI 'physical fatigue' (F(2, 135) = 3.343, p = .038~~< .05~~) and the CDC CFS symptom 'swollen lymph nodes and glands' (H(2) = 7.161, p = .028~~< .05~~). To investigate the source of these differences, post-hoc tests were conducted (unrelated t-tests for the fatigue variables and Mann-Whitney tests for swollen lymph glands as the former did not meet criteria for parametric tests, all with Bonferroni correction for multiple comparisons). A significant difference was observed between the psychology and combined groups with regards to general fatigue (t(92) = -2.449, p = .016~~< .05~~) and physical fatigue (t(92) = -2.658, p = .009~~< .05~~) and also between the nutrition and psychology group in terms of the degree of lymph node and gland swelling (U = 635.00, p = .009~~< .05~~). Within the fatigue measures, the combined group reported

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significantly higher levels of both general and physical fatigued than the psychology group whereas those undertaking nutritional support stated a higher occurrence of swollen lymph nodes and glands.

Retention analysis

Seventy-two of the original 138 participants (14 participants in the psychology group, 27 in the nutrition group and 31 in the combined group) completed the battery of measures at the 3-month follow-up, resulting in retention rates of ~~(~~52.17% in the study overall, 33.33% in the psychology group, 61.36% in the nutrition group and 59.62% in the combined group~~)~~. To investigate whether the individuals who did not complete the time-two measures were significantly different from those at baseline on demographic and outcome measures, a series of t-tests and Mann-Whitney tests were performed. Those that dropped out of the research (although still receiving treatment at the clinic) differed significantly in terms of age ($t(136) = -2.227$, $p = .028$~~< .05~~) and illness duration ($t(136) = -2.549$, $p = .012$~~< .05~~). Those who remained in the study were of significantly older age (mean age of those that remained in the study = 45.056, SD = 11.535; mean age of drop-outs = 40.400, SD =12.932) and longer illness duration than those who dropped out (mean age of those that remained in the study = 10.836, SD = 7.383; mean illness duration of drop-outs =7.571, SD = 7.472). Individuals who did not remain in the study did not differ significantly in terms of gender (χ^2 (2) = 1.222, p = .269~~> .05~~) or any of the outcome measures.

~~Longitudinal data~~ Comparisons within-groups across time

Primary outcomes

The following percentage change scores represent statistically significant changes, rather than clinically significant shifts, as this was an exploratory study. (Please see Table 2 for the exact

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p-value for each repeated measures comparison.) In the sample as a whole, there were improvements in all areas of the SF-36, with a 5.80% improvement in physical functioning, a 63.32% improvement in role limitations due to physical difficulties, a 5.17% improvement in bodily pain, a 26.17% improvement in social functioning, a 10.58% improvement in role limitations due to emotional difficulties, a 22.30% improvement in vitality, energy or fatigue and a 36.49% improvement in general health perception. When looking at the fatigue sub-scales of the MFI, all five sub-scales showed significant reductions in fatigue; 8.55% in general fatigue, 10.98% in physical fatigue, 8.81% in reduced activity, 12.96% in reduced motivation and 12.79% in mental fatigue.

Within the group of individuals who opted for a purely psychological intervention, improvements were seen in physical functioning (16.75%), role limitations due to physical problems (84.61%), social functioning (37.81%), general mental health (19.15%), vitality, energy or fatigue (49.57%) and general health perceptions (19.01%). Also, all the MFI fatigue scales decreased over a 3-month period, 13.58% in general fatigue, 17.74% in physical fatigue, 23.20% in reduced activity, 11.42% in reduced motivation and 29.66% in mental fatigue.

The nutrition group saw improvements in role limitations due to physical problems (61.05%), social functioning (24.93%), vitality, energy or fatigue (35.35%). and general health perceptions (29.73%). Once again, all the MFI fatigue scales decreased over a 3-month period, 13.39% in general fatigue, 15.00% in physical fatigue, 13.28% in reduced activity, 14.64% in reduced motivation and 12.83% in mental fatigue.

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In terms of general health as evaluated by the SF-36 measure, the group who received both psychological and nutritional intervention reported reductions in role limitations due to physical difficulties (57.02%), social functioning (22.61%), role limitations due to emotional difficulties (29.47%) and general health perceptions (26.45%). In the combined group, only one measure of fatigue, that of physical fatigue, saw significant improvements over time (6.42%).

Secondary outcomes (ME/CFS-specific)

Within the CFS Symptom Inventory, there were improvements in occurrence of sore throats (46.26%), diarrhea (42.47%), fatigue after exertion (16.32%), muscle aches or muscle pains (21.01%), pain in joints (28.32%) chills (37.00%), unrefreshing sleep (19.55%), sleeping problems (17.17%), headaches (29.47%), memory problems (17.86%), difficulty concentrating (26.66%), sinus and nasal symptoms (14.95%), shortness of breath (29.08%), sensitivity to light (26.26%) and depression (39.55%) in the merged sample. Within those taking part in the psychology intervention, ratings of muscle aches or muscle pains (10.34%), chills (23.40%), memory problems (44.73%), difficulty concentrating (39.50%) and sensitivity to light (64.58%) decreased. In the nutrition group, numerous symptom-related indices also showed improvements; sore throat (56.23%), swollen lymph glands (10.09%), fatigue after exertion (13.90%), muscle aches or muscle pains (20.56%), pain in joints (16.40%), chills (40.74%), headaches (32.19%), abdominal pain (29.05%), and sensitivity to light (18.28%). Those in the combined group saw significant reductions over the 3-month interval in diarrhea (47.97%), fatigue after exertion (19.20%), chills (40.23%), headaches (36.18%) and sinus and nasal symptoms (20.56%). (Please see Table 3 for the descriptive and inferential statistics associated with these findings and the exact p-value for each repeated measures comparison.)

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Secondary outcomes (psychological)

There were no significant differences from time-one to time-two in the MHLCS sub-scale of 'chance', 'powerful others' and 'other people', however the MHLCS did illustrate significant increases in internal locus of control (30.67%) and that of doctors (47.49%) in the sample as a whole. Reductions were also observed in the Maladaptive Stress Response (11.99%) in the entire group. In the psychology group, a significant increase of 17.56% was observed in internal locus of control, a decrease of 4.67% in the perception that chance played an influential part in the individuals' lives and a significant reduction in the Maladaptive Stress Response of 16.75%. No significant differences were found from baseline to follow-up in perceived control in the nutrition group, however the way in which the individuals in this group responded to stress also decreased, by 11.54%. No significant differences were found from baseline to follow-up in perceived control as measured by the MHLCS in the combined treatment group although there was a statistically significant difference in the Maladaptive Stress Response (10.98%). (Please see Table 4 for the descriptive and inferential statistics associated with these findings and the exact p-value for each repeated measures comparison.)

~~In the sample as a whole, there were significant differences from baseline to follow-up within the internal and doctors sub-scale of the MHLCS and all the CDC-CFS Symptom Inventory items bar swollen lymph nodes and glands, fever and abdominal pain. There were also significant differences in all areas of the SF-36, all the fatigue sub-scales of the MFI with the five sub-scales illustrating significant reductions in fatigue and, finally, reductions were also observed in the Maladaptive Stress Response.~~

~~Within the psychology group significant differences were also found in the SF-36 sub-scales 'physical functioning', 'role limitations due to physical problem', 'social functioning',~~

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‘general mental health’, ‘vitality, energy or fatigue’ and ‘general health perceptions’. Regarding perceived control, significant differences were found in internal locus of control and the perception that chance played an influential part in the individuals’ lives. Again, all the MFI fatigue scales saw significant decreases over a 3 month period. Regarding ME/CFS specific symptoms, ratings of muscle aches or muscle pains, chills, memory problems, difficulty concentrating and sensitivity to light differed significantly from baseline to follow-up in the expected direction. There was also a significant reduction in the Maladaptive Stress Response over time.

The nutrition group saw significant improvements in role limitations due to physical problems, social functioning, vitality, energy or fatigue and general health perceptions. No significant differences were found from baseline to follow up in perceived control in the nutrition group. Once again, all the MFI fatigue scales decreased over a 3 month period and numerous symptom related indices also showed improvements; sore throat, swollen lymph glands, fatigue after exertion, muscle aches or muscle pains, pain in joints, chills, headaches, abdominal pain and sensitivity to light. The way in which the individuals in this group responded to stress also decreased over the 3 month time period.

In terms of general health as evaluated by the SF 36 measure, the group who received both psychological and nutritional intervention reported reductions in role limitations due to physical difficulties, social functioning, role limitations due to emotional difficulties and general health perceptions. No significant differences were found from baseline to follow up in perceived control as measured by the MHLCS in the combined treatment group. Only one measure of fatigue, that of physical fatigue, saw significant improvements over time. Diarrhea, fatigue after exertion, chills, headaches and sinus and nasal symptoms all illustrated

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~~significant reductions over the 3 month interval, as did the Maladaptive Stress Response. (See Table 2 for descriptive and inferential statistics associated with these findings and Table 3 for percentage of change over time.)~~

Comparisons across groups

With correction for baseline variation, there were no significant differences between the three groups in terms of change scores.

~~As shown in Table 3, three of the outcome measures differed significantly in terms of change from baseline to follow up, namely the MHLCS 'chance' sub scale ($H(2) = 7.674$, $p < .05$), the MFI 'general fatigue' sub scale ($H(2) = 6.790$, $p < .05$) and the CDC CFS symptom 'headaches' ($H(2) = 6.625$, $p < .05$). In terms of perceived control and general fatigue, the psychology group differed significantly as compared to the combined group ($U = 110.500$, $p < .05$) and ($U = 118.000$, $p < .05$), respectively, with the psychology group seeing a greater change over time as compared to the combined group on both measures. Regarding headaches, the combined group ($U = 118.000$, $p < .05$) improved significantly more than the psychology group. No other comparisons reached statistical significance with a Bonferroni correction for multiple comparisons.~~

Discussion

Key results

There was statistically significant (rather than known clinically significant) change over time of numerous measures in all groups investigated. However, this is not to say that these changes were due to the interventions as the design of this study was exploratory, rather than experimental (please see below for a further critique of the design).The psychology group contained the most significant findings, including those concerned with daily functioning,

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fatigue, locus of control, the cognitive CDC CFS specific symptoms and the Maladaptive Stress Response. These findings appear consistent with outcomes from other psychological interventions [3;4;6]. As expected, changes in perceived control were not observed in the nutrition group as this is not an area that is targeted in this program. However, the more immune-type symptoms such as sore throat, swollen lymph nodes or glands and pain in joints did see significant reductions over time as would be envisaged in treatment protocols based upon nutritional expertise. The group that exhibited the least significant findings was the combined group and, as noted below, this may be due to the greater general severity of symptoms in this group and the need for a more lengthy intervention. Nevertheless, considering the small sample sizes in the groups at follow-up, these results are very promising and warrant further attention. ~~In terms of these preliminary findings, the psychology group performed better with regard to lowering the belief that chance influences the course of the condition. This is an important observation as the unpredictable nature of ME/CFS can be one of the most difficult components for individuals to cope with [45] and helping patients gain an improved sense of control over the illness is of great potential benefit. The psychology group also demonstrated a significantly greater change score in general fatigue as compared with the combined group which may infer that in the short term, guiding individuals through the complex nature of the disorder, helping them to understand it and accept that the condition itself gives rise to stresses and psychological distress may be a good starting point for intervention (i.e. a stepped program could be developed).~~

Interpretation

As noted previously [31~~30~~] patient-centered, individualized treatment protocols which include a range of tailored strategies is a favorable direction for dealing with a complex and multi-system disorder such as ME/CFS. The present study has demonstrated that such interventions

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may be ~~are~~ useful in lowering symptomatology, improving functioning and helping individuals gain a greater sense of control over their health status. ~~Considering that the options available on the National Health Service, mainly CBT and GET, are often perceived as coping strategies at best, and physically damaging at worst [46], tailored treatments such as described here may be more palatable, and hence effective.~~

Limitations and Generalisability

This study was a preliminary study in a naturalistic setting and as such did not have a robust design. There was not a~~did not have a~~ control group and the participants were not randomly assigned to groups, therefore ~~so~~ the results should be treated with caution. In order to ascertain whether the changes in symptom and functional reports were due to the interventions, a randomized control trial should be conducted (RCT). ~~Also, the participants were not randomly assigned to groups as this was a naturalistic,observational study.~~ Also, there was a high drop-out rate from time-one to time-two and this rate differed across groups. The highest drop-out rate was in the psychology group; whilst we cannot be sure why this occurred, it is postulated that the retention was poor in the group as the individuals in the psychology program had more activities to engage in and may have felt overburdened with the research questionnaires in addition to their session and homework (this would not be the case in the combined group as the therapeutic activities are phased-in as mentioned above).

In this study, e~~E~~ach individual was guided to appropriate treatment within an initial screening with clinic staff~~,~~ therefore the group was dependent on the nature of the individual's symptoms and their personal choice as the programs on offer were privately funded. ~~However, as can be seen in the baseline comparisons, the groups did not differ in terms of gender, age, illness duration or the majority of outcome measures.~~ Notably, the groups did

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differ in general and physical fatigue with participants in the combined groups reporting greater fatigue than those in the psychology group which suggests that this group's general symptomatology was more severe. The combined group illustrated less change~~improvement~~ over time compared to the psychology and nutrition groups and it is feasible to infer that individuals with a greater number and degree of complaints are referred to the combined group within the clinic. ~~Also, it should be noted that the interventions in the combined program are phasedin as it was found that asking individuals to engage in numerous therapeutic activities resulted in high drop out rates~~. Also, those in the combined group will not experience the intensity of each intervention as this has been demonstrated to result in non-compliance; t~~T~~herefore, changes in outcome measures in this group may not be noted at an interval of three months ~~for that group~~. Further studies underway presently will investigate follow-ups at 6- and 12-months to identify whether the findings here are maintained over time and also whether those with greater symptom severity benefit with a longer intervention. The results from this study will then inform plans for an RCT of the clinic's practices. As the participants were self-selected onto these programs, the findings lack generalizability; future work should sample from the overall ME/CFS population and be randomly-assigned to groups in order to make valid assumptions regarding the illness-group as a whole.

Funding

No external funding was obtained for this research; the work was accomplished in-house at the clinic in question.

Data Sharing

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Dataset available from the corresponding author at m.a.arroll@sa.uel.ac.uk. Consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low.

Contributorship

Alex Howard made substantial contributions to the conception and design and acquisition of data, whilst Megan Arroll made a substantial contribution to the analysis and interpretation of data. Both authors made a substantial contribution to the drafting of the article and revisions for the critical review of important intellectual content. Final approval of the version to be published was also granted by both authors.

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Competing Interests

Alex Howard is the founder and CEO of The Optimum Health Clinic and Megan Arroll is the Director of Research at the Optimum Health Clinic, where this study was conducted.

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List of abbreviations

ME: myalgic encephalomyelitis

CFS: Chronic Fatigue Syndrome

NICE: National Institute for Health and Clinical Excellence

CBT: Cognitive Behavioral Therapy

GET: Graded Exercise Therapy

APT: Adaptive Pacing Therapy

SMC: specialist medical care

CAM: Complementary and Alternative Medicine

NLP: Neuro-linguistic Programming

EFT: Emotional Freedom Technique

SF-36: Medical Outcomes Survey Short-Form 36

MHLCS: Multidimensional Health Locus of Control Scale

MFI: Multidimensional Fatigue Inventory

RCT: randomized controlled trial

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Table 1. Baseline comparisons of sample demographics and outcome variables

				95% CI for Mean		Test	
		Mean	SD	Lower	Upper	statistic	p-value
Gender	Psychology	9 (21.4%)[d]				.179[e]	.915
	Nutrition	8 (18.2%)[d]					
	Combined	11 (21.2%)[d]					
	Total	28 (20.3%)[d]					
Age	Psychology	42.881	13.986	38.523	47.239	.000[a]	1.000
	Nutrition	42.864	12.504	39.062	46.665		
	Combined	42.843	11.125	39.714	45.972		
	Total	42.861	12.406	40.765	44.957		
Illness duration	Psychology	8.874	8.252	6.302	11.445	.252[a]	.778
	Nutrition	10.023	7.375	7.781	12.265		
	Combined	9.625	7.291	7.595	11.655		
	Total	9.523	7.580	8.247	10.800		
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	.319[a]	.727
	Nutrition	47.855	26.226	39.882	55.829		
	Combined	45.299	25.479	38.206	52.393		
	Total	47.344	24.792	43.171	51.517		
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	.281[a]	.755
	Nutrition	7.574	17.500	2.254	12.895		
	Combined	9.774	21.051	3.914	15.635		
	Total	8.272	18.387	5.177	11.367		
SF-36	Psychology	61.548	25.614	53.566	69.530	1.002[a]	.370

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Bodily pain	Nutrition	55.625	30.242	46.431	64.819		
	Combined	53.606	27.019	46.084	61.128		
	Total	56.667	27.683	52.007	61.327		
SF-36	Psychology	37.202	21.824	30.402	44.003	.536[a]	.586
Social functioning	Nutrition	32.671	25.888	24.800	40.541		
	Combined	32.452	24.786	25.552	39.352		
	Total	33.967	24.212	29.892	38.043		
SF-36	Psychology	60.286	19.584	54.183	66.389	.124[a]	.884
General mental health	Nutrition	59.727	19.355	53.843	65.612		
	Combined	58.308	20.948	52.476	64.140		
	Total	59.362	19.911	56.011	62.714		
SF-36	Psychology	55.554	46.368	41.104	70.004	.390[a]	.678
Role limitations emotional	Nutrition	48.482	47.390	34.074	62.890		
	Combined	47.780	43.924	35.551	60.008		
	Total	50.370	45.590	42.695	58.044		
SF-36	Psychology	20.714	16.1386	15.685	25.743	.129[a]	.879
Vitality Energy or Fatigue	Nutrition	20.114	14.570	15.685	24.542		
	Combined	19.039	17.658	14.123	23.955		
	Total	19.891	16.159	17.171	22.611		
SF-36	Psychology	37.024	17.945	31.432	42.616	2.769[a]	.066
General health perceptions	Nutrition	28.636	15.528	23.915	33.357		
	Combined	30.962	17.575	26.069	35.854		
	Total	32.065	17.286	29.156	34.975		
MHLCS Internal	Psychology	.677	.159	.627	.726	1.216[a]	.300
	Nutrition	.622	.177	.568	.675		

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	Combined	.662	.174	.613	.710		
	Total	.653	.171	.625	.682		
MHLCS Chance	Psychology	.368	.156	.320	.417	.395[a]	.674
	Nutrition	.340	.133	.299	.380		
	Combined	.354	.155	.311	.397		
	Total	.354	.148	.329	.379		
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.119[a]	.888
	Nutrition	.417	.141	.374	.460		
	Combined	.407	.101	.379	.436		
	Total	.409	.124	.388	.430		
MHLCS Doctors	Psychology	.169	.082	.143	.194	.575[a]	.564
	Nutrition	.171	.089	.144	.197		
	Combined	.191	.147	.150	.232		
	Total	.178	.112	.159	.196		
MHLCS Other People	Psychology	.235	.075	.212	.259	1.051[a]	.352
	Nutrition	.264	.129	.225	.304		
	Combined	.245	.074	.224	.265		
	Total	.248	.095	.232	.264		
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	3.219[a]	.043*
	Nutrition	16.977	2.601	16.186	17.768		
	Combined	17.327	2.587	16.607	18.047		
	Total	16.797	2.716	16.340	17.254		
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	3.343[a]	.038*
	Nutrition	16.727	3.358	15.707	17.748		
	Combined	17.615	2.823	16.830	18.401		

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	Total	16.819	3.211	16.278	17.359		
MFI Reduced Activity	Psychology	13.857	4.112	12.576	15.138	1.030[a]	.360
	Nutrition	14.136	4.027	12.912	15.361		
	Combined	14.962	3.662	13.942	15.981		
	Total	14.362	3.921	13.702	15.022		
MFI Reduced Motivation	Psychology	10.357	4.287	9.021	11.693	1.324[a]	.270
	Nutrition	10.500	3.474	9.444	11.556		
	Combined	11.462	3.153	10.584	12.339		
	Total	10.819	3.639	10.206	11.431		
MFI Mental Fatigue	Psychology	13.524	4.363	12.164	14.883	.064[a]	.938
	Nutrition	13.682	4.328	12.366	14.998		
	Combined	13.846	4.345	12.637	15.056		
	Total	13.696	4.315	12.969	14.422		
CDC CFS Sore Throat	Psychology	2.571	3.109	1.603	3.540	1.414[a]	.247
	Nutrition	3.977	3.776	2.829	5.125		
	Combined	3.202	4.494	1.951	4.454		
	Total	3.257	3.898	2.601	3.914		
CDC CFS Swollen Lymph nodes Glands	Psychology	1.976	3.382	.922	3.030	7.161[b]	.028*
	Nutrition	5.561	6.491	3.587	7.534		
	Combined	3.462	4.881	2.103	4.820		
	Total	3.679	5.250	2.795	4.563		
CDC CFS DiarrhoeaDiarrhea	Psychology	2.071	3.249	1.059	3.084	.850[a]	.430
	Nutrition	2.841	4.832	1.372	4.310		
	Combined	3.135	3.773	2.084	4.185		
	Total	2.717	3.998	2.044	3.390		

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CDC CFS Fatigue after exertion	Psychology	13.286	6.271	11.331	15.240	.219[a]	.803
	Nutrition	13.722	6.450	11.761	15.682		
	Combined	14.154	6.270	12.408	15.899		
	Total	13.752	6.292	12.693	14.811		
CDC CFS Muscle Aches or Muscle Pains	Psychology	8.286	6.747	6.183	10.388	.166[a]	.847
	Nutrition	9.091	6.383	7.151	11.031		
	Combined	8.519	6.932	6.589	10.449		
	Total	8.630	6.664	7.509	9.752		
CDC CFS Pain In Joints	Psychology	3.476	5.334	1.814	5.138	1.373[a]	.257
	Nutrition	4.696	5.560	3.006	6.386		
	Combined	5.474	6.386	3.696	7.251		
	Total	4.618	5.837	3.635	5.600		
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	.027[a]	.973
	Nutrition	1.394	2.562	.615	2.173		
	Combined	1.333	3.909	.245	2.421		
	Total	1.324	3.106	.801	1.846		
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	.206[a]	.814
	Nutrition	3.750	3.924	2.557	4.943		
	Combined	3.192	4.343	1.983	4.402		
	Total	3.420	4.283	2.699	4.141		
CDC CFS Unrefreshing Sleep	Psychology	12.905	6.792	10.788	15.021	.150[a]	.861
	Nutrition	12.250	7.088	10.095	14.405		
	Combined	12.154	7.147	10.164	14.144		
	Total	12.413	6.978	11.238	13.588		
CDC CFS Sleeping	Psychology	9.286	7.658	6.899	11.672	.085[a]	.918

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Problems	Nutrition	8.614	7.317	6.389	10.838		
	Combined	8.904	7.684	6.766	11.042		
	Total	8.928	7.509	7.664	10.192		
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	1.611[a]	.203
	Nutrition	7.646	7.040	5.506	9.786		
	Combined	6.346	5.857	4.715	7.977		
	Total	6.431	6.200	5.3871	7.474		
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.403[b]	.182
	Nutrition	9.409	7.183	7.225	11.593		
	Combined	8.173	7.610	6.055	10.292		
	Total	8.007	6.835	6.857	9.158		
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	.391[a]	.677
	Nutrition	9.822	7.641	7.499	12.145		
	Combined	9.135	6.942	7.202	11.067		
	Total	9.161	6.903	7.999	10.323		
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	1.162[a]	.316
	Nutrition	4.769	5.135	3.208	6.330		
	Combined	3.327	4.902	1.962	4.692		
	Total	3.832	4.966	2.996	4.668		
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	5.971[b]	.051
	Nutrition	5.064	5.165	3.493	6.634		
	Combined	3.750	4.635	2.460	5.041		
	Total	3.803	4.535	3.040	4.566		
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	1.192[a]	.307
	Nutrition	5.469	6.476	3.500	7.438		

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	Combined	4.789	6.304	3.034	6.544		
	Total	4.620	5.932	3.622	5.619		
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	.095[a]	.909
	Nutrition	3.285	4.090	2.026	4.543		
	Combined	3.392	4.788	2.046	4.739		
	Total	3.237	4.365	2.497	3.977		
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	.794[a]	.454
	Nutrition	5.031	6.097	3.177	6.884		
	Combined	4.481	6.360	2.710	6.251		
	Total	4.336	5.975	3.330	5.342		
CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	.160[b]	.923
	Nutrition	4.477	5.450	2.821	6.134		
	Combined	5.077	5.950	3.420	6.734		
	Total	4.544	5.231	3.663	5.424		
CDC CFS Maladaptive Stress Index Scale Score	Psychology	94.381	16.836	89.134	99.628	.465[a]	.629
	Nutrition	96.386	21.946	89.714	103.059		
	Combined	98.269	19.165	92.934	103.605		
	Total	96.486	19.373	93.225	99.747		

[a] *F*-statistic for one-way analysis of variance, d.f = 2,134

[b] *H*-statistic for Kruskal-Wallis test, d.f. = 2

[c] χ^2-statistic for comparison of nominal level data, d.f. = 2

[d] number of males

* test is significant at the $p < .05$ level

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Table 2. Outcome variable comparisons across time

		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	59.267	30.346	41.745	76.788	-2.707	.007**
	Nutrition	47.855	26.226	39.882	55.829	46.706	30.744	34.544	58.868	-1.136	.256
	Combined	45.299	25.479	38.206	52.393	49.288	26.403	39.604	58.973	-1.850	.064
	Total	47.344	24.791	43.171	51.517	50.260	28.818	43.488	57.032	-3.120	.002**
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	46.429	39.048	23.883	68.974	-2.379	.017*
	Nutrition	7.574	17.500	2.254	12.895	19.444	20.016	11.526	27.363	-2.907	.004**
	Combined	9.774	21.051	3.914	15.635	22.742	25.161	13.513	31.971	-2.225	.026*
	Total	8.272	18.387	5.177	11.367	26.111	28.225	19.479	32.744	-4.354	.001***
SF-36 Bodily pain	Psychology	61.548	25.614	53.566	69.530	63.929	29.786	46.731	81.127	-1.196	.232
	Nutrition	55.625	30.242	46.434	64.819	58.889	32.943	45.857	71.921	-1.800	.072
	Combined	53.606	27.019	46.084	61.128	58.629	27.301	48.615	68.643	-1.048	.294
	Total	56.667	27.683	52.007	61.327	59.757	29.649	52.790	66.724	-2.240	.025*
SF-36 Social functioning	Psychology	37.202	21.824	30.402	44.003	59.821	33.318	40.584	79.058	-2.689	.007**
	Nutrition	32.671	25.888	24.800	40.541	43.519	33.679	30.196	56.841	-2.476	.013*
	Combined	32.452	24.786	25.551	39.352	41.936	28.604	31.443	52.428	-2.426	.015*
	Total	33.967	24.212	29.892	38.043	46.007	31.805	38.533	53.481	-4.504	.001***
SF-36 General mental health	Psychology	60.286	19.584	54.183	66.389	74.571	13.276	66.906	82.237	-2.497	.013*
	Nutrition	59.727	19.355	53.843	65.612	64.741	20.548	56.612	72.869	-1.696	.090
	Combined	58.308	20.948	52.476	64.140	64.129	16.637	58.027	70.232	-.524	.600

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	Total	59.362	19.911	56.011	62.714	66.389	17.897	62.183	70.594	-2.665	.008**
SF-36 Role limitations emotional	Psychology	55.554	46.368	41.105	70.004	76.191	33.150	57.051	95.331	-.842	.400
	Nutrition	48.482	47.390	34.074	62.890	55.594	38.130	40.510	70.678	-1.788	.074
	Combined	47.780	43.924	35.551	60.008	67.742	32.756	55.727	79.757	-2.313	.021*
	Total	50.370	45.590	42.695	58.044	64.829	35.335	56.526	73.133	-3.159	.002**
SF-36 Vitality Energy or Fatigue	Psychology	20.714	16.139	15.685	25.743	41.071	20.586	29.186	52.957	-3.066	.002**
	Nutrition	20.114	14.5670	15.685	24.542	31.111	23.588	21.780	40.442	-2.734	.006**
	Combined	19.039	17.658	14.123	23.955	27.097	19.527	19.934	34.259	-1.558	.119
	Total	19.891	16.159	17.171	22.611	31.319	21.657	26.230	36.409	-4.205	.001***
SF-36 General health perceptions	Psychology	37.024	17.945	31.432	42.616	45.714	21.109	33.526	57.903	-2.561	.010*
	Nutrition	28.636	15.528	23.915	33.357	36.482	18.903	29.004	43.959	-2.157	.031*
	Combined	30.962	17.575	26.069	35.854	42.097	21.632	34.162	50.032	-2.423	.015*
	Total	32.065	17.286	29.156	34.975	40.694	20.561	35.863	45.526	-3.996	.001***
MHLCS Internal	Psychology	.677	.159	.627	.726	.821	.251	.676	.966	-2.983	.003**
	Nutrition	.622	.177	.568	.675	1.193	2.969	.019	2.368	-.687	.492
	Combined	.662	.174	.613	.710	.779	.318	.662	.896	-1.755	.079
	Total	.653	.171	.624	.682	.942	1.822	.514	1.371	-2.962	.003**
MHLCS Chance	Psychology	.368	.156	.320	.417	.351	.152	.263	.439	-2.594	.009**
	Nutrition	.340	.133	.299	.380	.911	3.020	-.284	2.105	-.143	.886
	Combined	.354	.155	.311	.397	.314	.133	.265	.363	-.672	.501
	Total	.354	.148	.329	.379	.545	1.853	.109	.980	-1.552	.121
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.441	.315	.259	.624	.000	1.000
	Nutrition	.418	.141	.374	.460	.804	2.244	-.084	1.691	-1.843	.065
	Combined	.407	.101	.379	.436	.434	.279	.331	.536	-.577	.564
	Total	.409	.124	.388	.430	.574	1.3880	.248	.900	-1.601	.109

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MHLCS Doctors	Psychology	.169	.082	.143	.194	.131	.093	.077	.185	-1.122	.262
	Nutrition	.171	.089	.144	.197	.657	2.668	-.398	1.713	-1.686	.092
	Combined	.191	.147	.150	.232	.153	.070	.128	.179	-1.384	.166
	Total	.178	.112	.159	.196	.338	1.635	-.0462	.722	-2.381	.017*
MHLCS Other People	Psychology	.235	.075	.212	.259	.268	.189	.159	.377	-.118	.906
	Nutrition	.264	.129	.225	.304	.739	2.652	-.311	1.788	-1.697	.090
	Combined	.245	.074	.224	.265	.252	.118	.209	.295	-.213	.831
	Total	.248	.095	.232	.264	.438	1.626	.055	.820	-1.186	.236
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	13.786	4.441	11.222	16.350	-2.657	.008**
	Nutrition	16.977	2.601	16.186	17.768	14.704	4.898	12.766	16.641	-2.548	.011*
	Combined	17.327	2.588	16.607	18.047	16.645	2.811	15.614	17.676	-.854	.393
	Total	16.797	2.716	16.340	17.254	15.361	4.136	14.389	16.333	-3.692	.001***
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	13.071	4.632	10.397	15.746	-2.810	.005**
	Nutrition	16.727	3.358	15.707	17.748	14.222	4.987	12.249	16.195	-2.791	.005**
	Combined	17.615	2.823	16.830	18.401	16.484	3.395	15.239	17.729	-2.364	.018*
	Total	16.819	3.211	16.278	17.359	14.972	4.453	13.926	16.019	-4.591	.001***
MFI Reduced Activity	Psychology	13.857	4.112	12.576	15.138	10.643	5.153	7.668	13.618	-2.142	.032*
	Nutrition	14.136	4.027	12.912	15.361	12.259	5.012	10.277	14.242	-2.164	.030*
	Combined	14.962	3.662	13.942	15.981	14.936	3.777	13.550	16.321	-.070	.944
	Total	14.362	3.921	13.702	15.022	13.097	4.798	11.970	14.225	-2.421	.015*
MFI Reduced Motivation	Psychology	10.357	4.287	9.021	11.693	7.286	4.214	4.853	9.719	-2.131	.033*
	Nutrition	10.500	3.474	9.444	11.556	8.963	3.736	7.485	10.441	-1.985	.047*
	Combined	11.462	3.153	10.584	12.339	10.774	3.095	9.639	11.910	-1.082	.279
	Total	10.819	3.639	10.206	11.431	9.417	3.767	8.532	10.302	-2.986	.003**
MFI	Psychology	13.524	4.363	12.164	14.883	10.500	4.468	7.920	13.080	-2.950	.003*

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Mental Fatigue	Nutrition	13.682	4.328	12.366	14.998	11.926	5.334	9.816	14.036	-2.082	.037*
	Combined	13.846	4.345	12.637	15.056	12.613	3.827	11.209	14.017	-1.586	.113
	Total	13.696	4.315	12.969	14.422	11.944	4.568	10.871	13.018	-3.661	.001***
CDC CFS	Psychology	2.571	3.109	1.603	3.540	1.429	2.278	.114	2.744	-1.365	.172
Sore Throat	Nutrition	3.977	3.776	2.829	5.125	1.741	2.087	.915	2.566	-2.211	.027*
	Combined	3.202	4.494	1.951	4.454	1.904	2.821	.870	2.939	-.804	.422
	Total	3.257	3.898	2.601	3.914	1.750	2.437	1.178	2.323	-2.387	.017*
CDC CFS	Psychology	1.976	3.382	.922	3.030	1.786	3.378	-.165	3.736	-.341	.733
Swollen	Nutrition	5.561	6.491	3.587	7.534	5.000	6.760	2.326	7.674	-2.212	.027*
Lymph nodes	Combined	3.462	4.881	2.103	4.820	2.690	4.477	1.0458	4.332	-.725	.468
Glands	Total	3.679	5.250	2.795	4.563	3.380	5.385	2.115	4.646	-1.684	.092
CDC CFS	Psychology	2.071	3.249	1.059	3.084	1.643	2.818	.016	3.270	-.730	.465
DiarrhoeaDiarrhea	Nutrition	2.841	4.832	1.372	4.310	1.444	3.274	.149	2.740	-1.649	.099
	Combined	3.135	3.773	2.084	4.185	1.631	2.483	.720	2.542	-1.996	046*
	Total	2.717	3.998	2.044	3.390	1.563	2.827	.899	2.228	-2.481	.013*
CDC CFS	Psychology	13.286	6.271	11.331	15.240	11.071	6.673	7.218	14.925	-1.550	.121
Fatigue after	Nutrition	13.722	6.450	11.761	15.682	11.815	7.217	8.960	14.670	-2.209	.027*
exertion	Combined	14.154	6.270	12.408	15.899	11.436	6.275	9.134	13.738	-2.392	.017*.
	Total	13.752	6.292	12.693	14.811	11.507	6.629	9.949	13.065	-3.574	.001***
CDC CFS	Psychology	8.286	6.747	6.183	10.388	7.429	6.892	3.450	11.408	-2.145	.032*
Muscle Aches	Nutrition	9.091	6.383	7.151	11.031	7.222	6.278	4.739	9.706	-2.901	.004**
or Muscle	Combined	8.519	6.932	6.589	10.449	6.188	5.528	4.160	8.215	-1.908	.056
Pains	Total	8.630	6.664	7.509	9.752	6.817	6.029	5.400	8.234	-.3995	.001***
CDC CFS	Psychology	3.476	5.334	1.814	5.138	2.786	4.458	.212	5.360	-1.778	.075
Pain In Joints	Nutrition	4.696	5.560	3.006	6.386	3.926	5.099	1.909	5.943	-2.022	.043*

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	Combined	5.474	6.386	3.696	7.251	3.010	4.140	1.492	4.528	-1.840	.066
	Total	4.618	5.837	3.635	5.600	3.310	4.543	2.242	4.377	-3.141	.002**
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	1.643	4.181	-.771	4.057	-.135	.892
	Nutrition	1.394	2.562	.615	2.173	.630	2.041	-.178	1.437	-1.487	.137
	Combined	1.333	3.909	.245	2.421	.378	.709	.118	.638	-1.517	.129
	Total	1.324	3.106	.801	1.846	.718	2.272	.185	1.252	-1.876	.061
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	2.571	4.398	.032	5.111	-1.970	.049*
	Nutrition	3.750	3.924	2.557	4.943	2.222	4.098	.601	3.843	-3.401	.001***
	Combined	3.192	4.343	1.983	4.402	1.908	2.797	.882	2.934	-2.049	.040*
	Total	3.420	4.283	2.699	4.141	2.155	3.614	1.306	3.004	-4.206	.001***
CDC CFS Unrefreshing Sleep	Psychology	12.905	6.792	10.788	15.021	10.643	6.698	6.776	14.510	-.802	.422
	Nutrition	12.250	7.088	10.095	14.405	9.444	7.738	6.384	12.505	-1.421	.155
	Combined	12.154	7.147	10.164	14.143	10.161	7.959	7.242	13.080	-1.513	.130
	Total	12.413	6.978	11.238	13.588	9.986	7.557	8.210	11.762	-2.295	.022*
CDC CFS Sleeping Problems	Psychology	9.286	7.658	6.899	11.672	5.286	4.921	2.444	8.127	-1.738	.082
	Nutrition	8.614	7.317	6.389	10.838	9.482	9.200	5.842	13.121	-.190	.849
	Combined	8.904	7.681	6.766	11.042	6.529	6.749	4.053	9.004	-1.794	.073
	Total	8.928	7.509	7.664	10.192	7.394	7.585	5.612	9.177	-1.983	.047*
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	4.357	3.411	2.388	6.326	-1.200	.230
	Nutrition	7.646	7.040	5.506	9.786	5.185	6.294	2.695	7.675	-2.084	.037*
	Combined	6.346	5.857	4.715	7.977	4.050	3.527	2.756	5.343	-2.807	.005**
	Total	6.431	6.200	5.387	7.474	4.535	4.708	3.429	5.642	-3.000	.003**
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.500	3.995	1.193	5.807	-1.965	.049*
	Nutrition	9.409	7.183	7.225	11.593	8.667	7.681	5.628	11.705	-.338	.735
	Combined	8.173	7.610	6.055	10.292	6.148	4.905	4.349	7.947	-1.446	.148

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	Total	8.007	6.835	6.857	9.158	6.578	6.189	5.123	8.032	-2.053	.040*
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	5.143	5.559	1.933	8.353	-2.809	.005**
	Nutrition	9.822	7.641	7.499	12.145	7.778	6.941	5.032	10.524	-1.196	.232
	Combined	9.135	6.942	7.202	11.067	6.507	4.843	4.731	8.283	-1.899	.058
	Total	9.161	6.903	7.999	10.323	6.718	5.844	5.345	8.092	-3.440	.001***
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	2.286	2.946	.585	3.987	-.213	.832
	Nutrition	4.769	5.135	3.208	6.330	3.407	5.746	1.134	5.681	-1.686	.092
	Combined	3.327	4.902	1.962	4.692	3.458	3.585	2.144	4.773	-.855	.392
	Total	3.832	4.966	2.996	4.668	3.211	4.396	2.178	4.244	-.584	.559
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	2.786	4.003	.474	5.097	-.343	.732
	Nutrition	5.064	5.165	3.493	6.634	3.593	3.905	2.048	5.137	-1.968	.049*
	Combined	3.750	4.635	2.460	5.041	2.548	2.791	1.524	3.572	-.598	.550
	Total	3.803	4.535	3.040	4.566	2.986	3.470	2.171	3.801	-1.727	.084
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	2.357	2.437	.950	3.764	-.724	.469
	Nutrition	5.469	6.476	3.500	7.438	4.889	6.104	2.474	7.304	-1.400	.162
	Combined	4.789	6.304	3.034	6.544	3.804	6.710	1.343	6.266	-2.482	.013*
	Total	4.620	5.931	3.622	5.619	3.930	5.882	2.547	5.312	-2.971	.003**
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	1.571	2.209	.296	2.847	-1.556	.120
	Nutrition	3.285	4.090	2.026	4.543	2.407	4.060	.801	4.013	-1.849	.064
	Combined	3.392	4.788	2.046	4.739	2.526	3.631	1.194	3.858	-.976	.329
	Total	3.237	4.365	2.497	3.977	2.296	3.554	1.461	3.131	-2.538	.011*
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	1.214	2.517	-.239	2.668	-1.973	.049*
	Nutrition	5.031	6.097	3.177	6.884	4.111	6.198	1.659	6.563	-2.136	.033*
	Combined	4.481	6.360	2.710	6.251	3.297	5.557	1.259	5.335	-.787	.431
	Total	4.336	5.975	3.330	5.342	3.197	5.419	1.924	4.471	-2.542	.011*

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CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	1.571	3.228	-.292	3.435	-1.614	.106
	Nutrition	4.477	5.450	2.821	6.134	3.333	4.883	1.402	5.265	-1.584	.113
	Combined	5.077	5.950	3.420	6.734	2.766	3.324	1.547	3.985	-1.304	.192
	Total	4.544	5.230	3.663	5.424	2.747	3.964	1.815	3.678	-2.297	.022*
CDC CFS Maladaptive Stress Index Scale Score	Psychology	94.381	16.836	89.134	99.628	78.571	18.434	67.928	89.215	-3.111	.002**
	Nutrition	96.386	21.946	89.714	103.059	85.259	27.665	74.315	96.203	-3.443	.001***
	Combined	98.269	19.165	92.934	103.605	87.484	22.965	79.060	95.908	-2.215	.027*
	Total	96.486	19.373	93.225	99.747	84.917	24.004	79.276	90.557	-5.123	.001***

[a] z statistic for Wilcoxon Signed Rank Test

Table 3. Change score comparisons between intervention groups

		% change over time for sig. results [a]	Mean	Std. Deviation	Std. Error	95% CI for Mean		*H* [b]	p-value
						Lower	Upper		
SF-36 Physical Functioning	Psychology	16.75	-13.629	14.990	4.006	-22.285	-4.974	3.215	.200
	Nutrition		-.407	19.967	3.843	-8.306	7.492		
	Combined		-6.813	18.242	3.276	-13.505	-.122		
	Total	5.80	-5.736	18.744	2.209	-10.141	-1.332		
SF-36	Psychology	84.61	-33.929	39.960	10.680	-57.001	-10.856	1.558	.459

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Role limitations physical	Nutrition	61.05	-14.509	21.005	4.042	-22.818	-6.199		
	Combined	57.02	-13.871	31.457	5.650	-25.409	-2.333		
	Total	63.32	-18.010	30.564	3.602	-25.192	-10.828		
SF-36	Psychology		-6.071	15.588	4.166	-15.072	2.929	-.163	.922
Bodily pain	Nutrition		-6.574	18.800	3.618	-14.011	.863		
	Combined		-3.387	25.532	4.586	-12.752	5.978		
	Total	5.17	-5.104	21.252	2.505	-10.098	-.110		
SF-36	Psychology	37.81	-24.107	24.741	6.612	-38.392	-9.822	3.301	.192
Social functioning	Nutrition	24.93	-10.648	20.423	3.931	-18.727	-2.569		
	Combined	22.60	-11.290	24.013	4.313	-20.098	-2.482		
	Total	26.17	-13.542	23.149	2.728	-18.981	-8.102		
SF-36	Psychology	19.15	-12.000	14.294	3.820	-20.253	-3.747	4.404	.111
General mental health	Nutrition		-3.259	15.963	3.072	-9.574	3.056		
	Combined		-.645	16.911	3.037	-6.848	5.558		
	Total	10.58	-3.833	16.409	1.934	-7.689	.022		
SF-36	Psychology		-9.527	49.664	13.273	-38.202	19.148	.573	.751
Role limitations	Nutrition		-18.561	55.759	10.731	-40.618	3.497		
emotional	Combined	29.47	-18.284	52.240	9.383	-37.446	.878		
	Total	10.58	-16.685	52.496	6.187	-29.021	-4.349		
SF-36	Psychology	49.57	-17.500	15.902	4.250	-26.682	-8.318	4.988	.083
Vitality Energy or	Nutrition	35.35	-11.482	19.206	3.696	-19.079	-3.884		
Fatigue	Combined		-6.129	17.688	3.177	-12.617	.359		
	Total	22.30	-10.347	18.219	2.147	-14.628	-6.066		
SF-36	Psychology	19.01	-11.429	14.335	3.831	-19.705	-3.152	.627	.731
General health	Nutrition	29.73	-6.852	15.201	2.925	-12.865	-.839		

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perceptions	Combined	26.45	-10.161	22.154	3.97	-18.288	-2.035		
	Total	36.49	-9.167	18.251	2.151	-13.455	-4.878		
MHLCS Internal	Psychology	17.56	-.146	.203	.054	-.263	-.029	3.402	.183
	Nutrition		-.573	3.028	.583	-1.771	.625		
	Combined		-.106	.315	.057	-.222	.010		
	Total	30.67	-.289	1.859	.219	-.726	.148		
MHLCS Chance	Psychology	4.67	.077	.098	.026	.021	.134	7.674	.022*
	Nutrition		-.570	3.019	.581	-1.765	.624		
	Combined		.001	.081	.015	-.029	.031		
	Total		-.198	1.852	.218	-.633	.237		
MHLCS Powerful Others	Psychology		-.054	.284	.076	-.218	.109	1.571	.456
	Nutrition		-.375	2.282	.439	-1.277	.528		
	Combined		-.030	.277	.050	-.132	.072		
	Total		-.164	1.408	.166	-.495	.167		
MHLCS Doctors	Psychology		.020	.058	.0155	-.014	.053	0.076	.963
	Nutrition		-.492	2.678	.515	-1.551	.568		
	Combined		.057	.199	.036	-.016	.130		
	Total	47.49	-.156	1.647	.194	-.543	.231		
MHLCS Other People	Psychology		-.032	.166	.044	-.128	.064	2.479	.290
	Nutrition		-.446	2.692	.518	-1.510	.619		
	Combined		-.012	.096	.017	-.047	.023		
	Total		-.178	1.645	.193	-.565	.208		

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MFI General Fatigue	Psychology	13.58	2.571	2.766	.739	.975	4.168	6.790	.034*
	Nutrition	13.39	2.074	3.842	.740	.554	3.594		
	Combined		.419	2.233	.401	-.400	1.238		
	Total	8.55	1.458	3.126	.368	.724	2.193		
MFI Physical Fatigue	Psychology	17.74	2.857	2.797	.748	1.242	4.472	3.038	.219
	Nutrition	15.00	2.444	4.371	.841	.716	4.173		
	Combined	6.42	1.290	2.735	.491	.287	2.294		
	Total	10.98	2.028	3.468	.409	1.213	2.843		
MFI Reduced Activity	Psychology	23.20	1.857	2.932	.784	.165	3.550	1.734	.420
	Nutrition	13.28	1.148	2.685	.517	.086	2.210		
	Combined		.645	3.189	.572	-.525	1.815		
	Total	8.81	1.069	2.952	.348	.376	1.763		
MFI Reduced Motivation	Psychology	11.42	2.500	3.502	.936	.478	4.522	5.171	.075
	Nutrition	14.64	1.593	3.511	.676	.204	2.982		
	Combined		.129	3.471	.624	-1.144	1.402		
	Total	12.96	1.139	3.570	.421	.300	1.978		
MFI Mental Fatigue	Psychology	29.66	3.571	3.056	.817	1.807	5.336	4.551	.103
	Nutrition	12.83	1.519	3.631	.699	.082	2.955		
	Combined		1.161	4.267	.766	-.404	2.726		
	Total	12.79	1.764	3.880	.457	.852	2.676		
CDC CFS Sore Throat	Psychology		1.429	3.736	.998	-.728	3.586	1.298	.523
	Nutrition	56.23	1.185	2.661	.512	.133	2.238		
	Combined		.500	4.591	.825	-1.184	2.184		
	Total	46.26	.937	3.769	.444	.052	1.823		
CDC CFS Swollen Lymph	Psychology		-.143	2.932	.784	-1.835	1.550	0.462	.794

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nodes Glands	Nutrition	10.09	1.247	2.700	.520	.179	2.316		
	Combined		.794	6.549	1.176	-1.608	3.197		
	Total		.782	4.756	.560	-.336	1.900		
CDC CFS DiarrhoeaDiarrhea	Psychology		-.286	1.490	.398	-1.146	.575	3.619	.164
	Nutrition		.926	2.868	.552	-.209	2.060		
	Combined	47.97	1.272	3.789	.681	-.118	2.662		
	Total	42.47	.839	3.134	.369	.103	1.576		
CDC CFS Fatigue after exertion	Psychology		2.286	4.811	1.286	-.492	5.063	0.379	.827
	Nutrition	13.90	2.593	5.507	1.060	.414	4.771		
	Combined	19.20	2.532	5.578	1.002	.486	4.578		
	Total	16.32	2.507	5.339	.629	1.252	3.761		
CDC CFS Muscle Aches or Muscle Pains	Psychology	10.34	2.500	4.034	1.078	.171	4.829	0.469	.791
	Nutrition	20.56	2.333	3.637	.700	.894	3.772		
	Combined		2.070	5.335	.958	.113	4.027		
	Total	21.01	2.253	4.459	.526	1.205	3.300		
CDC CFS Pain In Joints	Psychology		1.857	4.036	1.079	-.473	4.187	0.054	.973
	Nutrition	16.40	1.393	3.721	.716	-.079	2.865		
	Combined		1.978	5.622	1.010	-.084	4.040		
	Total	28.32	1.735	4.634	.546	.646	2.824		
CDC CFS Fever	Psychology		-.214	1.968	.526	-1.351	.922	0.399	.819
	Nutrition		.604	2.311	.445	-.310	1.519		
	Combined		1.245	4.816	.865	-.521	3.012		
	Total		.721	3.573	.421	-.118	1.561		
CDC CFS Chills	Psychology	23.40	1.571	2.738	.732	-.009	3.152	1.517	.468
	Nutrition	40.74	2.148	3.097	.596	.923	3.373		

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	Combined	40.23	1.447	3.986	.716	-.015	2.909		
	Total	37.00	1.734	3.421	.403	.930	2.538		
CDC CFS Unrefreshing Sleep	Psychology		1.857	6.803	1.818	-2.071	5.785	0.160	.948
	Nutrition		2.148	6.904	1.329	-.583	4.879		
	Combined		1.581	5.726	1.029	-.520	3.681		
	Total	19.55	1.847	6.3123	.744	.364	3.331		
CDC CFS Sleeping Problems	Psychology		2.786	5.352	1.430	-.304	5.876	3.218	.200
	Nutrition		-.222	5.139	.989	-2.255	1.811		
	Combined		1.762	4.871	.875	-.025	3.548		
	Total	17.17	1.217	5.133	.605	.011	2.423		
CDC CFS Headaches	Psychology		-.7143	2.091	.559	-1.922	.493	6.625	.036*
	Nutrition	32.19	1.572	3.507	.675	.184	2.959		
	Combined	36.18	2.467	4.944	.888	.653	4.280		
	Total	29.32	1.512	4.124	.486	.543	2.482		
CDC CFS Memory Problems	Psychology	44.73	2.857	4.655	1.244	.169	5.545	2.316	.314
	Nutrition		-.111	4.925	.947	-2.059	1.837		
	Combined		1.949	6.011	1.080	-.256	4.154		
	Total	17.86	1.353	5.435	.641	.076	2.630		
CDC CFS Difficulty Concentrating	Psychology	39.50	4.643	4.534	1.212	2.025	7.261	5.945	.051
	Nutrition		.815	4.359	.839	-.910	2.539		
	Combined		2.170	5.877	1.056	.015	4.326		
	Total	26.66	2.143	5.217	.615	.917	3.369		
CDC CFS Nausea	Psychology		.143	2.770	.740	-1.456	1.742	4.773	.092
	Nutrition		.660	2.667	.513	-.395	1.716		
	Combined		.251	4.468	.803	-1.388	1.890		

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	Total		.384	3.535	.417	-.447	1.214		
CDC CFS Abdominal Pain	Psychology		.286	1.729	.462	-.713	1.284	1.082	.582
	Nutrition	29.05	.882	2.165	.417	.025	1.738		
	Combined		.839	4.390	.789	-.771	2.449		
	Total		.747	3.234	.381	-.013	1.507		
CDC CFS Sinus Nasal Symptoms	Psychology		.929	3.125	.835	-.876	2.733	1.255	.534
	Nutrition		1.060	4.193	.807	-.599	2.719		
	Combined	20.56	1.906	5.923	1.063	-.267	4.078		
	Total	14.95	1.399	4.822	.568	.266	2.532		
CDC CFS Shortness Of Breath	Psychology		1.500	3.459	.924	-.497	3.497	0.707	.702
	Nutrition	18.28	.779	2.057	.403	-.052	1.609		
	Combined		.690	3.972	.725	-.793	2.173		
	Total	29.08	.885	3.243	.388	.112	1.658		
CDC CFS Sensitivity To Light	Psychology	64.58	1.429	2.472	.661	.001	2.856	0.939	.625
	Nutrition		1.568	3.764	.725	.079	3.057		
	Combined		.961	5.178	.930	-.938	2.860		
	Total	26.26	1.280	4.209	.496	.291	2.269		
CDC CFS Depression	Psychology		1.429	3.502	.936	-.593	3.451	0.490	.783
	Nutrition		.704	3.268	.629	-.589	1.996		
	Combined		1.363	5.345	.960	-.598	3.323		
	Total	39.55	1.129	4.282	.505	.122	2.135		
CDC CFS Maladaptive Stress Index Scale Score	Psychology	16.75	16.286	13.234	3.537	8.645	23.927	4.379	.112
	Nutrition	11.54	12.815	17.802	3.426	5.772	19.857		
	Combined	10.98	9.613	26.424	4.746	.080	19.305		
	Total	11.99	12.111	21.201	2.499	7.129	17.093		

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[a] see table 2 for descriptive and inferential statistics

[b] *H* statistic for Kruskal-Wallis test, d.f. = 2

* significant at the .05 level

Table 1. Demographics for gender, age and illness duration across the three treatment groups

		Mean	SD	95% CI for Mean		Test statistic	p-value
				Lower	Upper		
Gender	Psychology	9 (21.4%)[d]				.179[c]	.915
	Nutrition	8 (18.2%)[d]					
	Combined	11 (21.2%)[d]					
	Total	28 (20.3%)[d]					
Age	Psychology	42.881	13.986	38.523	47.239	.000[a]	1.000
	Nutrition	42.864	12.504	39.062	46.665		
	Combined	42.843	11.125	39.714	45.972		
	Total	42.861	12.406	40.765	44.957		
Illness duration	Psychology	8.874	8.252	6.302	11.445	.252[a]	.778
	Nutrition	10.023	7.375	7.781	12.265		
	Combined	9.625	7.291	7.595	11.655		
	Total	9.523	7.580	8.247	10.800		

Table 2. Comparisons across time within the primary outcome measures

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		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	59.267	30.346	41.745	76.788	-2.707	.007**
	Nutrition	47.855	26.226	39.882	55.829	46.706	30.744	34.544	58.868	-1.136	.256
	Combined	45.299	25.479	38.206	52.393	49.288	26.403	39.604	58.973	-1.850	.064
	Total	47.344	24.791	43.171	51.517	50.260	28.818	43.488	57.032	-3.120	.002**
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	46.429	39.048	23.883	68.974	-2.379	.017*
	Nutrition	7.574	17.500	2.254	12.895	19.444	20.016	11.526	27.363	-2.907	.004**
	Combined	9.774	21.051	3.914	15.635	22.742	25.161	13.513	31.971	-2.225	.026*
	Total	8.272	18.387	5.177	11.367	26.111	28.225	19.479	32.744	-4.354	.001***
SF-36 Bodily pain	Psychology	61.548	25.614	53.566	69.530	63.929	29.786	46.731	81.127	-1.196	.232
	Nutrition	55.625	30.242	46.434	64.819	58.889	32.943	45.857	71.921	-1.800	.072
	Combined	53.606	27.019	46.084	61.128	58.629	27.301	48.615	68.643	-1.048	.294
	Total	56.667	27.683	52.007	61.327	59.757	29.649	52.790	66.724	-2.240	.025*
SF-36 Social functioning	Psychology	37.202	21.824	30.402	44.003	59.821	33.318	40.584	79.058	-2.689	.007**
	Nutrition	32.671	25.888	24.800	40.541	43.519	33.679	30.196	56.841	-2.476	.013*
	Combined	32.452	24.786	25.551	39.352	41.936	28.604	31.443	52.428	-2.426	.015*
	Total	33.967	24.212	29.892	38.043	46.007	31.805	38.533	53.481	-4.504	.001***
SF-36 General mental health	Psychology	60.286	19.584	54.183	66.389	74.571	13.276	66.906	82.237	-2.497	.013*
	Nutrition	59.727	19.355	53.843	65.612	64.741	20.548	56.612	72.869	-1.696	.090
	Combined	58.308	20.948	52.476	64.140	64.129	16.637	58.027	70.232	-.524	.600
	Total	59.362	19.911	56.011	62.714	66.389	17.897	62.183	70.594	-2.665	.008**
SF-36	Psychology	55.554	46.368	41.105	70.004	76.191	33.150	57.051	95.331	-.842	.400

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Role limitations emotional	Nutrition	48.482	47.390	34.074	62.890	55.594	38.130	40.510	70.678	-1.788	.074
	Combined	47.780	43.924	35.551	60.008	67.742	32.756	55.727	79.757	-2.313	.021*
	Total	50.370	45.590	42.695	58.044	64.829	35.335	56.526	73.133	-3.159	.002**
SF-36 Vitality Energy or Fatigue	Psychology	20.714	16.139	15.685	25.743	41.071	20.586	29.186	52.957	-3.066	.002**
	Nutrition	20.114	14.5670	15.685	24.542	31.111	23.588	21.780	40.442	-2.734	.006**
	Combined	19.039	17.658	14.123	23.955	27.097	19.527	19.934	34.259	-1.558	.119
	Total	19.891	16.159	17.171	22.611	31.319	21.657	26.230	36.409	-4.205	.001***
SF-36 General health perceptions	Psychology	37.024	17.945	31.432	42.616	45.714	21.109	33.526	57.903	-2.561	.010*
	Nutrition	28.636	15.528	23.915	33.357	36.482	18.903	29.004	43.959	-2.157	.031*
	Combined	30.962	17.575	26.069	35.854	42.097	21.632	34.162	50.032	-2.423	.015*
	Total	32.065	17.286	29.156	34.975	40.694	20.561	35.863	45.526	-3.996	.001***
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	13.786	4.441	11.222	16.350	-2.657	.008**
	Nutrition	16.977	2.601	16.186	17.768	14.704	4.898	12.766	16.641	-2.548	.011*
	Combined	17.327	2.588	16.607	18.047	16.645	2.811	15.614	17.676	-.854	.393
	Total	16.797	2.716	16.340	17.254	15.361	4.136	14.389	16.333	-3.692	.001***
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	13.071	4.632	10.397	15.746	-2.810	.005**
	Nutrition	16.727	3.358	15.707	17.748	14.222	4.987	12.249	16.195	-2.791	.005**
	Combined	17.615	2.823	16.830	18.401	16.484	3.395	15.239	17.729	-2.364	.018*
	Total	16.819	3.211	16.278	17.359	14.972	4.453	13.926	16.019	-4.591	.001***
MFI Reduced Activity	Psychology	13.857	4.112	12.576	15.138	10.643	5.153	7.668	13.618	-2.142	.032*
	Nutrition	14.136	4.027	12.912	15.361	12.259	5.012	10.277	14.242	-2.164	.030*
	Combined	14.962	3.662	13.942	15.981	14.936	3.777	13.550	16.321	-.070	.944
	Total	14.362	3.921	13.702	15.022	13.097	4.798	11.970	14.225	-2.421	.015*
MFI Reduced	Psychology	10.357	4.287	9.021	11.693	7.286	4.214	4.853	9.719	-2.131	.033*
	Nutrition	10.500	3.474	9.444	11.556	8.963	3.736	7.485	10.441	-1.985	.047*

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Motivation	Combined	11.462	3.153	10.584	12.339	10.774	3.095	9.639	11.910	-1.082	.279
	Total	10.819	3.639	10.206	11.431	9.417	3.767	8.532	10.302	-2.986	.003**
MFI	Psychology	13.524	4.363	12.164	14.883	10.500	4.468	7.920	13.080	-2.950	.003*
Mental Fatigue	Nutrition	13.682	4.328	12.366	14.998	11.926	5.334	9.816	14.036	-2.082	.037*
	Combined	13.846	4.345	12.637	15.056	12.613	3.827	11.209	14.017	-1.586	.113
	Total	13.696	4.315	12.969	14.422	11.944	4.568	10.871	13.018	-3.661	.001***

[a]*z*-statistic for Wilcoxon Signed-Rank Test

Table 3. Comparisons across time within the secondary outcome measures (ME/CFS-specific)

		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value
CDC CFS	Psychology	2.571	3.109	1.603	3.540	1.429	2.278	.114	2.744	-1.365	.172
Sore Throat	Nutrition	3.977	3.776	2.829	5.125	1.741	2.087	.915	2.566	-2.211	.027*
	Combined	3.202	4.494	1.951	4.454	1.904	2.821	.870	2.939	-.804	.422
	Total	3.257	3.898	2.601	3.914	1.750	2.437	1.178	2.323	-2.387	.017*
CDC CFS	Psychology	1.976	3.382	.922	3.030	1.786	3.378	-.165	3.736	-.341	.733
Swollen	Nutrition	5.561	6.491	3.587	7.534	5.000	6.760	2.326	7.674	-2.212	.027*
Lymph nodes	Combined	3.462	4.881	2.103	4.820	2.690	4.477	1.0458	4.332	-.725	.468
Glands	Total	3.679	5.250	2.795	4.563	3.380	5.385	2.115	4.646	-1.684	.092
CDC CFS	Psychology	2.071	3.249	1.059	3.084	1.643	2.818	.016	3.270	-.730	.465

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Diarrhea	Nutrition	2.841	4.832	1.372	4.310	1.444	3.274	.149	2.740	-1.649	.099
	Combined	3.135	3.773	2.084	4.185	1.631	2.483	.720	2.542	-1.996	046*
	Total	2.717	3.998	2.044	3.390	1.563	2.827	.899	2.228	-2.481	.013*
CDC CFS Fatigue after exertion	Psychology	13.286	6.271	11.331	15.240	11.071	6.673	7.218	14.925	-1.550	.121
	Nutrition	13.722	6.450	11.761	15.682	11.815	7.217	8.960	14.670	-2.209	.027*
	Combined	14.154	6.270	12.408	15.899	11.436	6.275	9.134	13.738	-2.392	.017*.
	Total	13.752	6.292	12.693	14.811	11.507	6.629	9.949	13.065	-3.574	.001***
CDC CFS Muscle Aches or Muscle Pains	Psychology	8.286	6.747	6.183	10.388	7.429	6.892	3.450	11.408	-2.145	.032*
	Nutrition	9.091	6.383	7.151	11.031	7.222	6.278	4.739	9.706	-2.901	.004**
	Combined	8.519	6.932	6.589	10.449	6.188	5.528	4.160	8.215	-1.908	.056
	Total	8.630	6.664	7.509	9.752	6.817	6.029	5.400	8.234	-.3995	.001***
CDC CFS Pain In Joints	Psychology	3.476	5.334	1.814	5.138	2.786	4.458	.212	5.360	-1.778	.075
	Nutrition	4.696	5.560	3.006	6.386	3.926	5.099	1.909	5.943	-2.022	.043*
	Combined	5.474	6.386	3.696	7.251	3.010	4.140	1.492	4.528	-1.840	.066
	Total	4.618	5.837	3.635	5.600	3.310	4.543	2.242	4.377	-3.141	.002**
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	1.643	4.181	-.771	4.057	-.135	.892
	Nutrition	1.394	2.562	.615	2.173	.630	2.041	-.178	1.437	-1.487	.137
	Combined	1.333	3.909	.245	2.421	.378	.709	.118	.638	-1.517	.129
	Total	1.324	3.106	.801	1.846	.718	2.272	.185	1.252	-1.876	.061
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	2.571	4.398	.032	5.111	-1.970	.049*
	Nutrition	3.750	3.924	2.557	4.943	2.222	4.098	.601	3.843	-3.401	.001***
	Combined	3.192	4.343	1.983	4.402	1.908	2.797	.882	2.934	-2.049	.040*
	Total	3.420	4.283	2.699	4.141	2.155	3.614	1.306	3.004	-4.206	.001***
CDC CFS UnrefreshingSl	Psychology	12.905	6.792	10.788	15.021	10.643	6.698	6.776	14.510	-.802	.422
	Nutrition	12.250	7.088	10.095	14.405	9.444	7.738	6.384	12.505	-1.421	.155

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eep	Combined	12.154	7.147	10.164	14.143	10.161	7.959	7.242	13.080	-1.513	.130
	Total	12.413	6.978	11.238	13.588	9.986	7.557	8.210	11.762	-2.295	.022*
CDC CFS Sleeping Problems	Psychology	9.286	7.658	6.899	11.672	5.286	4.921	2.444	8.127	-1.738	.082
	Nutrition	8.614	7.317	6.389	10.838	9.482	9.200	5.842	13.121	-.190	.849
	Combined	8.904	7.681	6.766	11.042	6.529	6.749	4.053	9.004	-1.794	.073
	Total	8.928	7.509	7.664	10.192	7.394	7.585	5.612	9.177	-1.983	.047*
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	4.357	3.411	2.388	6.326	-1.200	.230
	Nutrition	7.646	7.040	5.506	9.786	5.185	6.294	2.695	7.675	-2.084	.037*
	Combined	6.346	5.857	4.715	7.977	4.050	3.527	2.756	5.343	-2.807	.005**
	Total	6.431	6.200	5.387	7.474	4.535	4.708	3.429	5.642	-3.000	.003**
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.500	3.995	1.193	5.807	-1.965	.049*
	Nutrition	9.409	7.183	7.225	11.593	8.667	7.681	5.628	11.705	-.338	.735
	Combined	8.173	7.610	6.055	10.292	6.148	4.905	4.349	7.947	-1.446	.148
	Total	8.007	6.835	6.857	9.158	6.578	6.189	5.123	8.032	-2.053	.040*
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	5.143	5.559	1.933	8.353	-2.809	.005**
	Nutrition	9.822	7.641	7.499	12.145	7.778	6.941	5.032	10.524	-1.196	.232
	Combined	9.135	6.942	7.202	11.067	6.507	4.843	4.731	8.283	-1.899	.058
	Total	9.161	6.903	7.999	10.323	6.718	5.844	5.345	8.092	-3.440	.001***
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	2.286	2.946	.585	3.987	-.213	.832
	Nutrition	4.769	5.135	3.208	6.330	3.407	5.746	1.134	5.681	-1.686	.092
	Combined	3.327	4.902	1.962	4.692	3.458	3.585	2.144	4.773	-.855	.392
	Total	3.832	4.966	2.996	4.668	3.211	4.396	2.178	4.244	-.584	.559
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	2.786	4.003	.474	5.097	-.343	.732
	Nutrition	5.064	5.165	3.493	6.634	3.593	3.905	2.048	5.137	-1.968	.049*
	Combined	3.750	4.635	2.460	5.041	2.548	2.791	1.524	3.572	-.598	.550

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	Total	3.803	4.535	3.040	4.566	2.986	3.470	2.171	3.801	-1.727	.084
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	2.357	2.437	.950	3.764	-.724	.469
	Nutrition	5.469	6.476	3.500	7.438	4.889	6.104	2.474	7.304	-1.400	.162
	Combined	4.789	6.304	3.034	6.544	3.804	6.710	1.343	6.266	-2.482	.013*
	Total	4.620	5.931	3.622	5.619	3.930	5.882	2.547	5.312	-2.971	.003**
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	1.571	2.209	.296	2.847	-1.556	.120
	Nutrition	3.285	4.090	2.026	4.543	2.407	4.060	.801	4.013	-1.849	.064
	Combined	3.392	4.788	2.046	4.739	2.526	3.631	1.194	3.858	-.976	.329
	Total	3.237	4.365	2.497	3.977	2.296	3.554	1.461	3.131	-2.538	.011*
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	1.214	2.517	-.239	2.668	-1.973	.049*
	Nutrition	5.031	6.097	3.177	6.884	4.111	6.198	1.659	6.563	-2.136	.033*
	Combined	4.481	6.360	2.710	6.251	3.297	5.557	1.259	5.335	-.787	.431
	Total	4.336	5.975	3.330	5.342	3.197	5.419	1.924	4.471	-2.542	.011*
CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	1.571	3.228	-.292	3.435	-1.614	.106
	Nutrition	4.477	5.450	2.821	6.134	3.333	4.883	1.402	5.265	-1.584	.113
	Combined	5.077	5.950	3.420	6.734	2.766	3.324	1.547	3.985	-1.304	.192
	Total	4.544	5.230	3.663	5.424	2.747	3.964	1.815	3.678	-2.297	.022*

[a]*z*-statistic for Wilcoxon Signed-Rank Test

Table 4.Comparisons across time within the secondary outcome measures (psychological)

	Baseline				3-month follow-up				Comparisons	
			95% CI for Mean				95% CI for Mean			
	Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value

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MHLCS Internal	Psychology	.677	.159	.627	.726	.821	.251	.676	.966	-2.983	.003**
	Nutrition	.622	.177	.568	.675	1.193	2.969	.019	2.368	-.687	.492
	Combined	.662	.174	.613	.710	.779	.318	.662	.896	-1.755	.079
	Total	.653	.171	.624	.682	.942	1.822	.514	1.371	-2.962	.003**
MHLCS Chance	Psychology	.368	.156	.320	.417	.351	.152	.263	.439	-2.594	.009**
	Nutrition	.340	.133	.299	.380	.911	3.020	-.284	2.105	-.143	.886
	Combined	.354	.155	.311	.397	.314	.133	.265	.363	-.672	.501
	Total	.354	.148	.329	.379	.545	1.853	.109	.980	-1.552	.121
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.441	.315	.259	.624	.000	1.000
	Nutrition	.418	.141	.374	.460	.804	2.244	-.084	1.691	-1.843	.065
	Combined	.407	.101	.379	.436	.434	.279	.331	.536	-.577	.564
	Total	.409	.124	.388	.430	.574	1.3880	.248	.900	-1.601	.109
MHLCS Doctors	Psychology	.169	.082	.143	.194	.131	.093	.077	.185	-1.122	.262
	Nutrition	.171	.089	.144	.197	.657	2.668	-.398	1.713	-1.686	.092
	Combined	.191	.147	.150	.232	.153	.070	.128	.179	-1.384	.166
	Total	.178	.112	.159	.196	.338	1.635	-.0462	.722	-2.381	.017*
MHLCS Other People	Psychology	.235	.075	.212	.259	.268	.189	.159	.377	-.118	.906
	Nutrition	.264	.129	.225	.304	.739	2.652	-.311	1.788	-1.697	.090
	Combined	.245	.074	.224	.265	.252	.118	.209	.295	-.213	.831
	Total	.248	.095	.232	.264	.438	1.626	.055	.820	-1.186	.236
CDC CFS Maladaptive Stress Index Scale Score	Psychology	94.381	16.836	89.134	99.628	78.571	18.434	67.928	89.215	-3.111	.002**
	Nutrition	96.386	21.946	89.714	103.059	85.259	27.665	74.315	96.203	-3.443	.001***
	Combined	98.269	19.165	92.934	103.605	87.484	22.965	79.060	95.908	-2.215	.027*
	Total	96.486	19.373	93.225	99.747	84.917	24.004	79.276	90.557	-5.123	.001***

[a] *z*-statistic for Wilcoxon Signed-Rank Test

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Title and Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	9-10

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A preliminary prospective study of nutritional, psychological and combined therapies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) in a private care setting.

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a condition characterized by severe and persistent fatigue, neurological disturbances, autonomic and endocrine dysfunctions and sleep difficulties that have a pronounced and significant impact on individuals' lives. Current NICE guidelines within the United Kingdom suggest that this condition should be treated with cognitive behavioral therapy and/or graded exercise therapy where appropriate. There is currently a lack of evidence base concerning - alternative techniques that may be beneficial to those with ME/CFS.Objectives: This study aimed to investigate whether three modalities of psychology, nutrition and combined treatment, influenced symptom report measures in those with ME/CFS over a 3-month time period and whether there were significant differences in these changes between groups.

Design and setting: This is a preliminary prospective study with one follow-up point conducted at a private secondary health care facility in London, UK.

Participants: One-hundred and thirty-eight individuals (110 females, 79.7%; 42 participants in psychology, 44 in nutrition and 52 in combined) participated at baseline and 72 participants completed the battery of measures at follow-up (52.17% response rate; 14, 27, 31 participants in each group, respectively).

Outcome measures: Self-report measures of ME/CFS symptoms, functional ability, multidimensional fatigue and perceived control.

Results: Baseline comparisons showed those in the combined group had higher levels of fatigue. At follow-up, all groups saw improvements in fatigue, functional physical and symptomatology; those within the psychology group also experienced a shift in perceived control over time.

Conclusions: This study provides early evidence that psychological, nutritional and combined techniques for the treatment of ME/CFS may influence symptomatology, fatigue, function and perceived control. However, these results must be viewed with caution as the allocation

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to groups was not randomized, there was no control group and the study suffered from high drop-out rates.

Summary

Article focus

- This preliminary prospective study investigated three (psychological, nutritional and combined) tailored interventions for ME/CFS over time.
- Differences between the reported changes over time between groups were also assessed.

Key messages

- Psychological, nutritional and combined approaches for the management of ME/CFS influence symptomatology over time in some individuals with this disorder.
- Self-reported functional ability (physical and social) are influenced following tailored interventions lasting 3 months.
- This study provides preliminary evidence that tailored psychological, nutritional and combined interventions may influence self-reported symptomatology in some people with ME/CFS; however due to the study's methodological limitations, it is important that these findings are investigated further in high quality randomized controlled studies.

Strengths and limitations of this study

- The findings here are an initial step to fill the gap in the extant literature regarding the utility of tailored and multidisciplinary (psychological, nutritional and combined) treatments for ME/CFS.
- There is bias in this study as the participants were self-selected in the sense that they chose to attend the clinic and which treatment option they preferred (with advice), i.e. the study was not randomized.

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- There were low retention rates in this study which may constitute a bias in that those who remained in the study may have experienced benefits and those who experienced little or no benefits may have dropped out.

Introduction

Chronic Fatigue Syndrome or myalgic encephalomyelitis (ME/CFS) is a condition characterized by prolonged and debilitating fatigue, although the exact cause of this disorder is still under debate. Due to the lack of a definitive biological marker, diagnosis is made on the basis of the exclusion of other explanatory conditions. The most widely used case definition by the Centers for Disease Control [1] states that there must be at least six months severe fatigue of new and definite onset, not the result of ongoing exertion, not alleviated by rest and resulting in reduced levels of physical activity. The CDC definition also sets out a series of minor complaints that must accompany the fatigue (cognitive impairment, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, headaches of a new type, pattern or severity at onset, unrefreshing sleep and post-exertion malaise), with individuals needing to have the occurrence of four or more symptoms to be diagnosed with ME/CFS. Estimates of the prevalence of ME/CFS have been made as low as 3 and as high as 2,800 per 100,000 [2].

The most widely researched strategies for alleviating the symptoms of ME/CFS are Cognitive Behavior Therapy (CBT) and Graded Exercise Therapy (GET). Two reviews of studies on CBT [3;4] found that it significantly improved physical functioning in adult out-patients as

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compared with medical management, counseling, guided support, education and support or relaxation. Regarding GET, a systematic review illustrated that this form of therapy was potentially beneficial for people with ME/CFS, especially when combined with a patient education programme [5]. However, drop-out rates were higher in the GET groups than control groups suggesting that individuals with ME/CFS are averse to this type of therapy. Recently, a large scale, longitudinal study investigating CBT, GET, Adaptive Pacing Therapy (APT) and specialist medical care (SMC) which had very low drop-out rates, found that CBT and GET (when added to SMC) were moderately effective outpatient treatments for this patient group as opposed to APT or SMC alone [6].

Although CBT and GET studies have shown some promising outcomes, there is no known cure for ME/CFS. Therefore the National Institute for Health and Clinical Excellence (NICE) [7] recommends a number of symptom management strategies and interventions aimed at helping individuals to cope with their condition and reduce physical deconditioning brought about by the illness. Pharmacological interventions are, at times, suggested for patients with poor sleep or pain, for instance, low-dose antidepressants, as these have been shown to be effective [8-14]. However, patient expectations must be realistic as the drugs may help elevate mood and psychological outlook but not reduce fatigue and other symptomatology associated with ME/CFS[15]. Numerous drugs such as thyroxin, hydrocortisone and antiviral agents are not advised by NICE due to contradictory findings[16;17].

In terms of function and quality of life management, NICE offers general advice concerning sleep management, appropriate rest periods, and pacing. Sleep hygiene instruction, together with pharmacological treatment tailored to the individual patient can be beneficial in combating fatigue [18]. Dietary management may also reduce symptomatology for those with

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concurrent irritable bowel syndrome (IBS) [19], although this is not currently recommended by NICE. Dietary supplementation has been investigated in relation to ME/CFS. Fatty acids [20], folic acid [21], vitamin C [22], co-enzyme Q10 [23], magnesium [24], multivitamins [25] and minerals [26] have all been shown to reduce symptomatology in ME/CFS patients. However other studies have shown conflicting findings with regard to nutritional supplementation, therefore it is perhaps wise to treat with supplements on a case-by-case basis [27;28].

Due to the lack of clear and definitive treatment strategies, individuals often seek out Complementary and Alternative Medicines (CAM). Although NICE does not recommend the use of CAM they do acknowledge that many people with ME/CFS use such therapies and find them beneficial for symptom management. This view is due to the lack of published evidence for the effectiveness of these treatments. Examples of CAM treatments used by individuals with ME/CFS include religious healing, massage therapy, relaxation, meditation, homeopathy, acupuncture, naturopathy and herbal therapies [29;30]; patient satisfaction with such approaches as CAM has been high, over 80% in some instances [29]. A recent systematic review of such interventions identified 70 controlled clinical trials (randomized and non-randomized) and found that 86% of these studies illustrated at least one positive effect, with 74% showing a decrease of illness-related symptomatology [31]. Meditative or mindfulness approaches warranted further investigation based on these results as did supplement programs of magnesium, l-carnitine, and S-adenosylmethionine. A subsequent review based solely on randomized controlled trials (RCTs) of CAM techniques identified 26 such studies and observed that qigong, massage and tuina (approaches based within Chinese Traditional Medicine and based upon relaxation and connection with the body) illustrated positive effects as did supplementation studies utilizing nicotinamide adenine dinucleotide (NADH) and magnesium [32]. However, within both reviews it was noted that the methodological quality of

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reporting was poor and the sample sizes in these studies were small; hence ability to draw strong conclusions on the efficacy of CAM methods is limited. Porter et al. (2010) [31] did note that individualized treatment protocols which include a range of tailored strategies are a promising area for further investigation for this complex, multi-system illness.

Objectives

There is still much debate and uncertainty regarding alternative interventions for those with ME/CFS. A recent review of CAM techniques [31] highlight the need for further exploration of individually tailored interventions for the alleviation of the condition's often debilitating and intrusive symptomatology. This study therefore aims to provide preliminary evidence for the utility of three types of approaches (psychological, nutritional and combined) to the management of ME/CFS over time (baseline and follow-up) offered at a private health-care center in the UK.

Methods

Study design and setting

This preliminary prospective study aimed to investigate whether psychological, nutritional and combined approaches to the treatment of ME/CFS influenced symptom report measures over a 3-month time period and whether there were significant differences in these changes between groups. The research was conducted at one private secondary health care facility. All potential patients of the clinic are first asked to complete a comprehensive symptom profile and medical history, including questions relating to triggering factors, psychology sub-types and structural/biological sub-types (this is distinct from the research data collected).

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Subsequent to this, every individual receives a 15-minute screening with one of the practitioners (please note, this was not either of the authors of the current study) who recommends the best course of action for his/her needs; this will be the psychology-related interventions, nutritional advice and support or a combination of the two.

All individuals requesting treatment at the private care setting were offered the opportunity to participate in the study. Those that expressed an interest (N = 145) were emailed a spreadsheet that contained the questionnaires and asked to complete it at their convenience. Informed consent was obtained prior to the completion of the questionnaires and the study was approved by the University of East London Ethics Committee. Participants were told that they could withdraw from the study at any time and that withdrawal would not affect their care at the clinic. Participants were able to ask questions at any point in the study and no deception was used as the participants were informed of the nature of the research program before they agreed to participate. Subsequently, participants were requested to complete the questionnaire pack on a second occasion, three months from the baseline measures.

Psychology

The clinic offers a 3-month intervention which consists of a combination of Neuro-linguistic Programming (NLP), Emotional Freedom Technique (EFT), life coaching and hypnotherapy/self-hypnosis constructed in a manner specific to the needs of those with ME/CFS. The primary aim of this approach is to reduce the anxiety that is associated with having a debilitating and unpredictable condition, improve emotional well-being and help individuals slowly manage and increase their activity within their own limits (i.e. pacing). The program is offered as a series of group sessions and the peer support is seen as an important component of the intervention, which is solidified via the use of moderated online

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support forums, narratives of previous clients' experiences and online materials that can be accessed as often as necessary. In addition to, or as an alternative to this course, individuals receive a series of one-to-one sessions and for the most severely affected ME/CFS patients, telephone sessions are arranged and support materials can be accessed in their own homes.

Over the three-month period of this preliminary study, the participants experienced one of three treatment options. The first option included 13 hours of practitioner contact time in a mix of group training in person, group telephone conference calls and one-to-one telephone sessions, the second option was four hours of one-to-one telephone sessions and the final option was three hours of in person sessions. Participants all had access to various support materials which included CDs and online resources. The amount of time spent on these was patient-led, but was in the region of a further six hours. All the practitioners offering this option are qualified in hypnotherapy, NLP, life coaching and EFT and undergo an intensive period of training in the clinic's own integrative approach (please see Howard and Arroll [33] for more details of this approach) and ongoing supervision (individual and group supervision on a biweekly basis) from the department director, who is the only senior practitioner in the team.

Nutrition

Tailored nutritional therapy is achieved via one-to-one consultations with individuals. To begin, a very detailed history is taken based upon the information given in the aforementioned symptom profile. Qualified nutritional therapists (who have been given specialist training regarding ME/CFS from the clinic) then suggest tests consistent with symptomatology, for instance the Adrenal Stress Index Test, comprehensive stool analysis/gastro-intestinal function, vitamin & mineral status, etc. Results from these tests are then used to compose an evidence-driven diet and supplement program. As most cases of

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ME/CFS are complex involving multiple body systems, this process is often iterative and follow-up consultations are necessary to check progress and make alterations to the protocol. The nutritional therapy program consists of an initial one-hour evaluation (which includes the tailored advice) and follow-up approximately every six weeks; therefore, during the course of the present study, the participants received a minimum of two one-hour sessions with email support for any queries and detailed nutritional guidance. All the nutritional therapists are qualified to diploma level and members of (voluntary) regulatory bodies such as the British Association for Applied Nutrition and Nutritional Therapy (BANT) and the Complementary and Natural Healthcare Council (CNHC). Similar to the psychology department, the nutrition department is led by one senior practitioner who supervises the team with individual and group supervisory arrangements.

Combined

Within the combined program, a multidisciplinary approach is taken with practitioners discussing the patients in case meetings to ensure that the psychological and nutritional aspects complement each other in order to achieve the best outcome. It should be noted that the interventions in the combined program are phased-in as it was found that asking individuals to engage in numerous therapeutic activities at the same time resulted in high drop-out rates.

Primary Outcome Measures

Medical Outcomes Survey Short-Form 36 (SF-36)

This 36-item measure is the short form of the original Medical Outcomes Survey [34] to measure functional impairment and contains eight sub-sections: 1) physical activity limitations due to health problems; 2) social activity limitations due to physical or emotional

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problems; 3) usual role activity limitations due to physical health problems; 4) bodily pain; 5) general mental health; 6) role activity limitations due to emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions [34]. The items are scored so that higher scores indicate greater functional ability. In terms of the psychometric properties of this measure, reliability estimates for all sub-scales are good, exceeding a Cronbach's alpha coefficient value of 0.70 [35]. In terms of validity, the SF-36 correlates amply, $r \geq 0.40$, with the frequency and severity of numerous symptoms and general health conditions [36;37].

Multidimensional Fatigue Inventory (MFI)

This 20-item measure contains five fatigue dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [38]. Items such as 'I tire easily' are rated on a 5-point scale (1 = yes, that is true; 5 = no, that is not true) with lower scores reflecting higher levels of fatigue. The MFI has good internal consistency with average Cronbach's alpha coefficient equaling 0.84 across the sub-scales. Convergent validity based on a sample of radiotherapy patients found correlations between the sub-scales and a visual analog fatigue scale to be 0.77 for general fatigue, 0.70 for physical fatigue, 0.61 for reduced activity, 0.56 for reduced motivation ($p<0.001$) to 0.23 for mental fatigue ($p<0.01$) [38].

Secondary Outcome Measures

CDC CFS Symptom Inventory

CDC CFS Symptom Inventory [39] was used to measure specific ME/CFS symptoms and confirm diagnosis. This instrument is based upon the CDC case definition [1] and includes a fatigue item and the eight distinct symptoms are also included in the CDC guidelines with an additional ten associated symptoms. The format of this self-report measure is a six-point scale of perceived frequency (0 = absent, 5 = all the time) and severity (0 = none, 5 = very severe).

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The psychometric properties of this instrument are good: Cronbach's alpha coefficient = 0.88; r = .74 convergent validity with the Chalder Fatigue Scale [40]; r -.68 and -.87 convergent validity with the SF-36 'vitality' and 'bodily pain' sub-scales, respectively.

Multidimensional Health Locus of Control Scale (MHLCS)

Multidimensional Health Locus of Control [41-43] measures perceived control via three distinct sub-scales: 'internal', 'chance' and 'powerful others' which has two dimensions, that of 'doctors' and 'other people'. The instrument contains 18 items in total (six items each for the 'internal' and 'chance' scales and three items for both the 'powerful others' scales) and is scored on a 6-point Likert scale from 'strongly agree' to 'strongly disagree'. Internal reliability of the instrument is good with Cronbach's alpha coefficients ranging from 0.67 for 'powerful others' to 0.77 for 'internal'. The measure correlates positively and significantly with associated scales from Levenson's [44] locus of control measure from which the MHLOC was based, which demonstrates good convergent validity [41].

Statistical methods

The data was initially screened for missing data. Four cases contained substantial amounts of missing data; therefore these were excluded from the analysis (one individual from the nutrition group and three from the combined group). Subsequent analyses were conducted on complete date only. . The baseline data was subsequently of the quality for parametric tests, except for the variables CDC CFS swollen lymph nodes and glands, memory problems, abdominal pain and depression. However, the follow-up data suffered from high levels of skew and kurtosis which was not substantially alleviated by data transformation. This violated a key criterion for parametric testing, that of normality of distribution, so non-

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parametric tests were selected. In addition, as the sample sizes in each individual treatment group were small, the more conservative non-parametric tests were the preferred choice as even though tests such as analysis of variance are generally robust against non-normality, this does not hold true with small sample sizes. One-way analysis of variance tests and Kruskal-Wallis tests (the former for those variables that met the criteria for parametric tests, and the latter that did not) were used to investigate baseline variation and analysis of covariance (ANCOVA) tests were used to account for this variation and test to for differences between the three groups. Wilcoxon sign-rank tests were employed to look for differences over time (baseline and 3-month follow-up) and if differences were significant, percentage change was calculated. Please note, as this is an exploratory study with only one time-point and no control group, any significant findings do not infer clinical significance, rather statistical significance, and as such exact p-values are presented.

Results

Participants

Of the 145 individuals who expressed an interest in the study, 142 time-one questionnaires were returned, equating to a 97.9% response rate at baseline (two participants from the psychology group and one from the combined group dropped out at this stage). Therefore, excluding the four cases deleted due to insufficient data, 138 cases were used for baseline analysis; 42 participants in the psychology group, 44 in the nutrition group and 52 in the combined group. There was no significant association between gender and group (χ^2 (2) = 0.179, p = .915), all groups consisting of approximately one-fifth males (Table 1). There was not a significant difference in age (F(2,135) = 0.001, p = 1.000); in fact group means for age were near identical at 42.881, 42.864 and 42.843 for psychology, nutrition and combined groups, respectively. There was also a non-significant result for illness duration (F(2, 135) =

0.252, p = .778). Therefore, in terms of demographics, the groups were comparable. With regard to the outcome measures, there were significant differences between the groups in terms of the MFI sub-scale 'general fatigue' (F(2, 135) = 3.219, p = .043), MFI 'physical fatigue' (F(2, 135) = 3.343, p = .038) and the CDC CFS symptom 'swollen lymph nodes and glands' (H(2) = 7.161, p = .028). To investigate the source of these differences, post-hoc tests were conducted (unrelated t-tests for the fatigue variables and Mann-Whitney tests for swollen lymph glands as the former did not meet criteria for parametric tests, all with Bonferroni correction for multiple comparisons). A significant difference was observed between the psychology and combined groups with regards to general fatigue (t(92) = -2.449, p = .016) and physical fatigue (t(92) = -2.658, p = .009) and also between the nutrition and psychology group in terms of the degree of lymph node and gland swelling (U = 635.00, p = .009). Within the fatigue measures, the combined group reported significantly higher levels of both general and physical fatigued than the psychology group whereas those undertaking nutritional support stated a higher occurrence of swollen lymph nodes and glands.

Retention analysis

Seventy-two of the original 138 participants (14 participants in the psychology group, 27 in the nutrition group and 31 in the combined group) completed the battery of measures at the 3-month follow-up, resulting in retention rates of 52.17% in the study overall, 33.33% in the psychology group, 61.36% in the nutrition group and 59.62% in the combined group. To investigate whether the individuals who did not complete the time-two measures were significantly different from those at baseline on demographic and outcome measures, a series of t-tests and Mann-Whitney tests were performed. Those that dropped out of the research (although still receiving treatment at the clinic) differed significantly in terms of age (t(136) = -2.227, p = .028) and illness duration (t(136) = -2.549, p = .012). Those who remained in the

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study were of significantly older age (mean age of those that remained in the study = 45.056, SD = 11.535; mean age of drop-outs = 40.400, SD =12.932) and longer illness duration than those who dropped out (mean age of those that remained in the study = 10.836, SD = 7.383; mean illness duration of drop-outs =7.571, SD = 7.472). Individuals who did not remain in the study did not differ significantly in terms of gender (χ^2 (2) = 1.222, p = .269) or any of the outcome measures.

Comparisons within-groups across time

Overall sample

Primary outcomes

The following percentage change scores represent statistically significant changes, rather than clinically significant shifts, as this was an exploratory study. In the sample as a whole, there were improvements in all areas of the SF-36 (Table 2), with a 5.80% improvement in physical functioning, a 68.98% improvement in role limitations due to physical difficulties, a 5.17% improvement in bodily pain, a 26.17% improvement in social functioning, a 5.77% improvement in general mental health, a 10.58% improvement in role limitations due to emotional difficulties, a 22.30% improvement in vitality, energy or fatigue and a 36.49% improvement in general health perception. When looking at the fatigue sub-scales of the MFI, all five sub-scales showed significant reductions in fatigue; 8.55% in general fatigue, 10.98% in physical fatigue, 8.81% in reduced activity, 12.96% in reduced motivation and 12.79% in mental fatigue.

Secondary outcomes

Within the CFS Symptom Inventory (Table 3), there were improvements in occurrence of sore throats (34.48%), diarrhea (42.47%), fatigue after exertion (16.32%), muscle aches or

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muscle pains (21.01%), pain in joints (34.55%) chills (37.00%), unrefreshing sleep (19.55%), sleeping problems (17.17%), headaches (24.94%), memory problems (17.86%), difficulty concentrating (26.66%), sinus and nasal symptoms (26.38%), shortness of breath (29.28%), sensitivity to light (28.62%) and depression (39.55%). There were no significant differences from time-one to time-two in the MHLCS sub-scale of 'chance', 'powerful others' and 'other people' (Table 3), however the MHLCS did illustrate significant increases in internal locus of control (30.67%) and that of doctors (47.49%).

Psychology group

Primary outcomes

Within the group of individuals who opted for a purely psychological intervention, improvements were seen in physical functioning (16.75%), role limitations due to physical problems (84.61%), social functioning (37.81%), general mental health (19.15%), vitality, energy or fatigue (49.57%) and general health perceptions (19.01%). Also, all the MFI fatigue scales decreased over a 3-month period, 13.58% in general fatigue, 17.74% in physical fatigue, 23.20% in reduced activity, 11.42% in reduced motivation and 29.66% in mental fatigue (Table 4).

Secondary outcomes

Within those taking part in the psychology intervention, ratings of muscle aches or muscle pains (10.34%), chills (23.40%), memory problems (44.73%), difficulty concentrating (39.50%) and sensitivity to light (64.58%) decreased (Table 5). A significant increase of 17.56% was observed in internal locus of control, a decrease of 4.67% in the perception that chance played an influential part in the individuals' lives (Table 5).

Nutrition group

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Primary outcomes

The nutrition group saw improvements in role limitations due to physical problems (75.28%), social functioning (24.93%), vitality, energy or fatigue (35.35%). and general health perceptions (29.73%). Once again, all the MFI fatigue scales decreased over a 3-month period, 13.39% in general fatigue, 15.00% in physical fatigue, 13.28% in reduced activity, 14.64% in reduced motivation and 12.83% in mental fatigue (Table 6).

Secondary outcomes

In the nutrition group, numerous symptom-related indices also showed improvements (Table 7); sore throat (56.23%), swollen lymph glands (21.21%), fatigue after exertion (13.90%), muscle aches or muscle pains (20.56%), chills (40.74%), nausea (16.42%) and abdominal pain (20.16%). No significant differences were found from baseline to follow-up in perceived control (Table 7).

Combined group

Primary outcomes

In terms of general health as gauged by the SF-36 measure, the group who received both psychological and nutritional intervention reported reductions in role limitations due to physical difficulties (57.02%), social functioning (22.61%), role limitations due to emotional difficulties (29.47%) and general health perceptions (26.45%). Only one measure of fatigue, that of physical fatigue, saw significant improvements over time (6.42%) in the combined group (Table 8).

Secondary outcomes

Those in the combined group saw significant reductions over the 3-month interval in diarrhea (47.97%), fatigue after exertion (19.20%), chills (40.23%), headaches (36.18%) and sinus and nasal symptoms (20.56%) (Table 9). No significant differences were found from baseline to

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follow-up in perceived control as measured by the MHLCS in the combined treatment group (Table 9).

Comparisons across groups

With correction for baseline variation, there were no significant differences between the three groups in terms of change scores.

Discussion

Key results

There was statistically significant (rather than known clinically significant) change over time of numerous measures in all groups investigated. However, this is not to say that these changes were due to the interventions as the design of this study was exploratory, rather than experimental (please see below for a further critique of the design).The psychology group contained the most significant findings, including those concerned with daily functioning, fatigue, locus of control and cognitive CDC CFS specific symptoms. These findings appear consistent with outcomes from other psychological interventions [3;4;6]. As expected, changes in perceived control were not observed in the nutrition group as this is not an area that is targeted in this program. However, the more immune-type symptoms such as sore throat and swollen lymph nodes or glands did see significant reductions over time as would be envisaged in treatment protocols based upon nutritional expertise. The group that exhibited the least significant findings was the combined group and, as noted below, this may be due to

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the greater general severity of symptoms in this group and the need for a more lengthy intervention. Nevertheless, considering the small sample sizes in the groups at follow-up, these results are very promising and warrant further attention.

Interpretation

As noted previously [31] individualized treatment protocols which include a range of tailored strategies is a favorable direction for dealing with a complex and multi-system disorder such as ME/CFS. The present study has demonstrated that such interventions may be useful in lowering symptomatology, improving functioning and helping individuals gain a greater sense of control over their health status.

Limitations and Generalisability

This study was a preliminary study in a naturalistic setting and as such did not have a robust design. There was not a control group and the participants were not randomly assigned to groups, therefore the results should be treated with caution. In order to ascertain whether the changes in symptom and functional reports were due to the interventions, a randomized control trial should be conducted (RCT). Also, there was a high drop-out rate from time-one to time-two and this rate differed across groups. The highest drop-out rate was in the psychology group; whilst we cannot be sure why this occurred, it is postulated that the retention was poor in the group as the individuals in the psychology program had more activities to engage in and may have felt overburdened with the research questionnaires in addition to their session and homework (this would not be the case in the combined group as the therapeutic activities are phased-in as mentioned above).

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In this study, each individual was guided to appropriate treatment within an initial screening with clinic staff; therefore the group was dependent on the nature of the individual's symptoms and their personal choice as the programs on offer were privately funded. Notably, the groups did differ in general and physical fatigue with participants in the combined groups reporting greater fatigue than those in the psychology group which suggests that this group's general symptomatology was more severe. The combined group illustrated less change over time compared to the psychology and nutrition groups and it is feasible to infer that individuals with a greater number and degree of complaints are referred to the combined group within the clinic. Also, those in the combined group will not experience the intensity of each intervention as this has been demonstrated to result in non-compliance; therefore, changes in outcome measures in this group may not be noted at an interval of three months. Further studies underway presently will investigate follow-ups at 6- and 12-months to identify whether the findings here are maintained over time and also whether those with greater symptom severity benefit with a longer intervention. The results from this study will then inform plans for an RCT of the clinic's practices. As the participants were self-selected onto these programs, the findings lack generalizability; future work should sample from the overall ME/CFS population and be randomly-assigned to groups in order to make valid assumptions regarding the illness-group as a whole.

Funding

No external funding was obtained for this research; the work was accomplished in-house at the clinic in question.

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Data Sharing

Dataset available from the corresponding author at drarroll@theoptimumhealthclinic.com. Consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low.

Contributorship

Alex Howard made substantial contributions to the conception and design and acquisition of data, whilst Megan Arroll made a substantial contribution to the analysis and interpretation of data. Both authors made a substantial contribution to the drafting of the article and revisions for the critical review of important intellectual content. Final approval of the version to be published was also granted by both authors.

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Competing Interests

Alex Howard is the founder and CEO of The Optimum Health Clinic and Megan Arroll is the Director of Research at the Optimum Health Clinic, where this study was conducted.

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List of abbreviations

ME: myalgic encephalomyelitis

CFS: Chronic Fatigue Syndrome

NICE: National Institute for Health and Clinical Excellence

CBT: Cognitive Behavioral Therapy

GET: Graded Exercise Therapy

APT: Adaptive Pacing Therapy

SMC: specialist medical care

CAM: Complementary and Alternative Medicine

NLP: Neuro-linguistic Programming

EFT: Emotional Freedom Technique

SF-36: Medical Outcomes Survey Short-Form 36

MHLCS: Multidimensional Health Locus of Control Scale

MFI: Multidimensional Fatigue Inventory

RCT: randomized controlled trial

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Table 1. Demographics for gender, age and illness duration across the three treatment groups

		Mean	SD	95% CI for Mean Lower	95% CI for Mean Upper	Test statistic	p-value
Gender	Psychology	9 (21.4%)[d]				.179[c]	.915
	Nutrition	8 (18.2%)[d]					
	Combined	11 (21.2%)[d]					
	Total	28 (20.3%)[d]					
Age	Psychology	42.881	13.986	38.523	47.239	.000[a]	1.000
	Nutrition	42.864	12.504	39.062	46.665		
	Combined	42.843	11.125	39.714	45.972		
	Total	42.861	12.406	40.765	44.957		
Illness duration	Psychology	8.874	8.252	6.302	11.445	.252[a]	.778
	Nutrition	10.023	7.375	7.781	12.265		
	Combined	9.625	7.291	7.595	11.655		
	Total	9.523	7.580	8.247	10.800		

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Table 2. Comparisons across time within the primary outcome measures within the overall sample

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	72	18.075	41.644	66.667	25.694	47.222	77.583	-3.120	.002**
SF-36 Role limitations physical	71	0	0	0	0	25	50	-4.321	.001***
SF-36 Bodily pain	72	32.5	56.25	79.375	32.500	67.500	90	-2.240	.025*
SF-36 Social functioning	72	12.5	25	50	12.500	50	75	-4.504	.001***
SF-36 General mental health	72	53	60	75	57	68	80	-2.665	.008**
SF-36 Role limitations emotional	72	0	33.317	100	41.667	66.670	100	-3.159	.002**
SF-36 Vitality Energy or Fatigue	72	10	15	35	11.250	30	45	-4.205	.001***
SF-36 General health perceptions	72	20	30	40	25	40	50	-3.996	.001***
MFI General Fatigue	72	15	18	19	12	16	19	-3.692	.001***
MFI Physical Fatigue	72	15	18	20	12	16	19	-4.591	.001***
MFI Reduced Activity	72	11	15	18	9	14	17	-2.421	.015*
MFI Reduced Motivation	72	8	10	13.750	7	9	12	-2.986	.003**
MFI Mental Fatigue	72	11	14	18	8.250	12.500	15	-3.661	.001***

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Table 3. Comparisons across time within the secondary outcome measures within the overall sample

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
CDC CFS Sore throat	70	0	1.5	4	0	1	2	-2.257	.024*
CDC CFS Swollen lymph nodes/glands	71	0	2	6	0	1	4	-1.567	.115
CDC CFS Diarrhea	72	0	1	4	0	0	2	-2.481	.013*
CDC CFS Fatigue after exertion	72	9	15	20	6.500	12	16	-3.574	.001***
CDC CFS Muscle aches/pains	72	4	9	12	1.250	6	12	-3.995	.001***
CDC CFS Pain in joints	70	0	4	9	0	1	6	-2.908	.004**
CDC CFS Fever	70	0	0	1	0	0	0	-1.667	.095
CDC CFS Chills	72	0	2	6	0	0	2.113	-4.206	.001***
CDC CFS Unrefreshing sleep	72	6	12	16	4	6	16	-2.295	.022*
CDC CFS Sleeping problems	72	2	8	12	2	4	12	-1.983	.047*
CDC CFS Headaches	71	1	6	9	1	6	11.250	-2.850	.004**

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CDC CFS Memory Problems	72	2	6	12	1	6	11.250	-2.053	.040*
CDC CFS Difficulty Concentrating	72	2.500	8.500	12	1	6	12	-3.440	.001***
CDC CFS Nausea	71	0	1	4	0	2	6	-0.898	.369
CDC CFS Abdominal Pain	71	0	2	6	0	2	6	-1.932	.053
CDC CFS Sinus nasal symptoms	71	1	4	6	0	1	6	-2.862	.004**
CDC CFS Shortness of breath	69	0	2	4	0	1	4	-2.402	.016*
CDC CFS Sensitivity to light	71	0	2	6	0	1	4	-2.388	.017*
CDC CFS Depression	72	0	2	6	0	1	4	-2.297	.022*
MHLCS Internal	72	0.528	0.681	0.799	0.611	0.722	0.889	-2.962	.003**
MHLCS Chance	72	0.222	0.344	0.417	0.201	0.320	0.444	-1.552	.121
MHLCS Powerful Others	72	0.333	0.389	0.500	0.306	0.361	0.500	-1.601	.109
MHLCS Doctors	72	0.0833	0.139	0.222	0.083	0.111	0.194	-2.381	.017*
MHLCS Other People	72	0.194	0.250	0.3056	0.174	0.250	0.278	-1.186	.236

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Table 4. Comparisons across time within the primary outcome measures within the psychology group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	14	25.008	44.444	58.367	27.083	69.450	84.700	-2.707	.007**
SF-36 Role limitations physical	14	0	0	25	0	50	81.250	-2.379	.017*
SF-36 Bodily pain	14	39.375	57.500	80.625	32.500	72.500	90	-1.195	.232
SF-36 Social functioning	14	25	37.500	50	34.375	56.250	90.625	-2.689	.007**
SF-36 General mental health	14	47	62	80	67	76	88	-2.497	.013*
SF-36 Role limitations emotional	14	24.974	100	100	58.336	100	100	-.842	.400
SF-36 Vitality Energy or Fatigue	14	10	20	40	28.750	45	52.500	-3.066	.002**
SF-36 General health perceptions	14	23.750	30	41.250	31.250	40	63.750	-2.561	.010*
MFI General Fatigue	14	14	16.500	18.500	9.750	13.500	18.500	-2.657	.008**
MFI Physical Fatigue	14	13.750	16	19.250	8.750	13	16.750	-2.810	.005**
MFI Reduced Activity	14	9.750	12.500	18.250	7	9	14.500	-2.142	.032*

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MFI Reduced Motivation	14	5.750	8	11.750	4.750	5.500	8.250	-2.131	.033*
MFI Mental Fatigue	14	11.750	15.500	18	6.500	9.500	15	-2.950	.003*

Table 5. Comparisons across time within the secondary outcome measures within the psychology group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
CDC CFS Sore throat	14	0	2	6	0	0	2.500	-1.365	.172
CDC CFS Swollen lymph nodes/glands	14	0	0.5	2.5	0	0	4	-.341	.733
CDC CFS Diarrhea	14	0	0	2	0	0	2.500	-.730	.465
CDC CFS Fatigue after exertion	14	9	12	20	7.750	9	14	-1.550	.121
CDC CFS Muscle aches/pains	14	4	9	15.25	1.750	9	14	-2.145	.032*
CDC CFS Pain in joints	14	0	2.5	9	0	0.500	4.500	-1.778	.075
CDC CFS Fever	14	0	0	1.5	0	0	0.500	-.135	.892
CDC CFS Chills	14	0	1	6.75	0	0	4.500	-1.970	.049*
CDC CFS Unrefreshing sleep	14	9	12	15.25	5.500	9	16	-.802	.422

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CDC CFS Sleeping problems	14	2.75	7	12	1	3	9.750	-1.738	.082
CDC CFS Headaches	14	1	2.5	6	0.750	1	6.750	-1.200	.230
CDC CFS Memory Problems	14	1	6	9	0.750	1	6.750	-1.965	.049*
CDC CFS Difficulty Concentrating	14	3.5	9	17	1	5	6.750	-2.809	.005**
CDC CFS Nausea	14	0	0	4.25	0	1	4.500	-.213	.832
CDC CFS Abdominal Pain	14	0	2	5.25	0	0	6	-.343	.732
CDC CFS Sinus nasal symptoms	14	1	3.5	4.5	0	1.500	4.500	-.724	.469
CDC CFS Shortness of breath	14	0	1.5	4.5	0	0.500	2.50	-1.556	.120
CDC CFS Sensitivity to light	14	0	1	4.5	0	0	1.250	-1.973	.049*
CDC CFS Depression	14	0	1.5	6	0	0	2	-1.614	.106
MHLCS Internal	14	0.556	0.653	0.840	0.611	0.872	0.923	-2.983	.003**
MHLCS Chance	14	0.326	0.417	0.535	0.167	0.361	0.451	-2.594	.009**
MHLCS Powerful Others	14	0.319	0.375	0.451	0.299	0.356	0.431	.000	1.000
MHLCS Doctors	14	0.083	0.125	0.194	0.083	0.083	0.174	-1.122	.262
MHLCS Other People	14	0.194	0.236	0.285	0.194	0.222	0.257	-.118	.906

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Table 6. Comparisons across time within the primary outcome measures within the nutrition group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	27	16.7	44.444	77.778	16.700	38.889	77.778	-1.136	.256
SF-36 Role limitations physical	26	0	0	0	0	25	25	-2.878	.004**
SF-36 Bodily pain	27	32.5	45	67.5	35.200	67.500	90	-1.800	.072
SF-36 Social functioning	27	0	25	50	12.500	37.500	75	-2.476	.013*
SF-36 General mental health	27	52	60	72	52	64	80	-1.696	.090
SF-36 Role limitations emotional	27	0	0	100	0	66.670	100	-1.788	.074
SF-36 Vitality Energy or Fatigue	27	5	15	35	15	25	45	-2.734	.006**
SF-36 General health perceptions	27	20	25	35	25	35	45	-2.157	.031*
MFI General Fatigue	27	15	18	19	12	15	19	-2.548	.011*
MFI Physical Fatigue	27	14	18	19	11	16	19	-2.791	.005**
MFI Reduced Activity	27	10	14	18	8	13	16	-2.164	.030*
MFI Reduced Motivation	27	8	10	12	6	8	12	-1.985	.047*

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MFI Mental Fatigue	27	11	13	16	8	13	15	-2.082	.037*

Table 7. Comparisons across time within the secondary outcome measures within the nutrition group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
CDC CFS Sore throat	27	8	1	2	0	1	2	-2.211	.027*
CDC CFS Swollen lymph nodes/glands	26	20	0	5	0	1	12	-2.051	.040*
CDC CFS Diarrhea	27	16	0	1	0	0	1	-1.649	.099
CDC CFS Fatigue after exertion	27	25	9	16	4	12	20	-2.209	.027*
CDC CFS Muscle aches/pains	27	20	4	9	2	6	12	-2.901	.004**
CDC CFS Pain in joints	26	20	0.750	4	0	1	6	-1.827	.068
CDC CFS Fever	26	9	0	0	0	0	0	-1.254	.210
CDC CFS Chills	27	12	1	3	0	0	1	-3.401	.001***
CDC CFS Unrefreshing sleep	27	25	6	12	4	6	16	-1.421	.155
CDC CFS Sleeping problems	27	25	1	9	2	4	16	-0.190	.849

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CDC CFS Headaches	26	25	0.750	6	1	3	6	-1.895	.058
CDC CFS Memory Problems	27	25	2	6	2	6	12	-0.338	.735
CDC CFS Difficulty Concentrating	27	25	2	6	4	6	12	-1.196	.232
CDC CFS Nausea	26	25	0	2	0	1	6	-2.407	.016*
CDC CFS Abdominal Pain	26	16	0.750	3	0	3	6	-2.322	.020*
CDC CFS Sinus nasal symptoms	26	20	1	3.500	0	1	9	-1.244	.213
CDC CFS Shortness of breath	25	20	0	2	0	1	3	-1.651	.099
CDC CFS Sensitivity to light	26	25	0	4	0	2	6	-1.890	.059
CDC CFS Depression	27	20	0	4	0	2	4	-1.584	.113
MHLCS Internal	27	0.944	0.528	0.667	0.528	0.639	0.778	-.687	.492
MHLCS Chance	27	0.694	0.222	0.333	0.222	0.333	0.472	-.143	.886
MHLCS Powerful Others	27	0.694	0.333	0.389	0.278	0.361	0.528	-1.843	.065
MHLCS Doctors	27	0.417	0.0833	0.139	0.083	0.139	0.222	-1.686	.092
MHLCS Other People	27	0.833	0.222	0.278	0.167	0.250	0.306	-1.697	.090

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Table 8. Comparisons across time within the primary outcome measures within the combined group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	31	22.200	33.333	61.111	27.778	55.556	72.222	-1.850	.064
SF-36 Role limitations physical	31	0	0	0	0	25	25	-2.225	.026*
SF-36 Bodily pain	31	32.500	45	80	32.500	57.500	80	-1.048	.294
SF-36 Social functioning	31	12.500	25	37.500	12.500	37.500	62.500	-2.426	.015*
SF-36 General mental health	31	56	60	72	56	68	76	-0.524	.600
SF-36 Role limitations emotional	31	0	33.333	100	66.667	66.670	100	-2.313	.021*
SF-36 Vitality Energy or Fatigue	31	10	15	30	10	25	40	-1.558	.119
SF-36 General health perceptions	31	20	30	40	25	40	55	-2.423	.015*
MFI General Fatigue	31	16	18	19	14	17	19	-0.854	.393
MFI Physical Fatigue	31	15	19	20	13	17	20	-2.364	.018*

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MFI Reduced Activity	31	12	16	18	11	16	18	-0.070	.944
MFI Reduced Motivation	31	9	11	14	8	10	13	-1.082	.279
MFI Mental Fatigue	31	10	14	18	11	13	16	-1.586	.113

Table 9. Comparisons across time within the secondary outcome measures within the combined group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
CDC CFS Sore throat	29	0	0	3.500	0	1	2.030	-0.567	.571
CDC CFS Swollen lymph nodes/glands	31	0	2	4	0	1	3	-0.725	.468
CDC CFS Diarrhea	31	0	2	4	0	0	2	-1.996	046*
CDC CFS Fatigue after exertion	31	8	15	20	6	12	16	-2.392	.017*
CDC CFS Muscle aches/pains	31	2	6	12	1	6	9	-1.908	.056
CDC CFS Pain in joints	30	0	1.500	8	0	1	4	-1.680	.093
CDC CFS Fever	30	0	0	1	0	0	0.720	-1.383	.167
CDC CFS Chills	31	0	2	6	0	1	2.150	-2.049	.040*

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CDC CFS Unrefreshing sleep	31	6	12	16	4	9	16	-1.513	.130
CDC CFS Sleeping problems	31	1	6	12	2	4	9	-1.794	.073
CDC CFS Headaches	31	2	6	9	1	3	6	-2.807	.005**
CDC CFS Memory Problems	31	2	6	12	1	3	9	-1.446	.148
CDC CFS Difficulty Concentrating	31	2	8	12	1	6	12	-1.899	.058
CDC CFS Nausea	31	0	1	6	0	2	6	-0.855	.392
CDC CFS Abdominal Pain	31	0	1	6	0	2	4	-0.598	.550
CDC CFS Sinus nasal symptoms	31	0	5	8	0	1	4	-2.482	.013*
CDC CFS Shortness of breath	30	0	2	6	0	1	4	-0.976	.329
CDC CFS Sensitivity to light	31	0	1	6	0	1	4	-0.787	.431
CDC CFS Depression	31	0	2	6	0	1	6	-1.304	.192
MHLCS Internal	31	0.556	0.694	0.861	0.639	0.750	0.889	-1.755	.079
MHLCS Chance	31	0.222	0.333	0.361	0.167	0.306	0.417	-0.672	.501
MHLCS Powerful Others	31	0.333	0.389	0.500	0.333	0.389	0.500	-0.577	.564
MHLCS Doctors	31	0.111	0.167	0.222	0.083	0.139	0.500	-1.384	.166
MHLCS Other People	31	0.167	0.250	0.278	0.194	0.250	0.306	-0.213	.831

*** significant at .05 level**
**** significant at .01 level**

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*** significant at .001 level

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a condition characterized by severe and persistent fatigue, neurological disturbances, autonomic and endocrine dysfunctions and sleep difficulties that have a pronounced and significant impact on individuals' lives. Current NICE guidelines within the United Kingdom suggest that this condition should be treated with cognitive behavioral therapy and/or graded exercise therapy where appropriate. There is currently a lack of evidence base concerning ~~other, more integrative interventions~~ alternative techniques that may be beneficial to those with ME/CFS.

Objectives: This study aimed to investigate ~~evaluate~~ whether three ~~patient-centered treatment~~ modalities of psychology, nutrition and combined treatment, influenced symptom report measures in those with ME/CFS over a 3-month time period and whether there were significant differences in these changes between groups.

Design and setting: This is a preliminary prospective study with one follow-up point conducted at a private secondary health care facility in London, UK.

Participants: One-hundred and thirty-eight individuals (110 females, 79.7%; 42 participants in psychology, 44 in nutrition and 52 in combined) participated at baseline and 72 participants completed the battery of measures at follow-up (52.17% response rate; 14, 27, 31 participants in each group, respectively).

Outcome measures: Self-report measures of ME/CFS symptoms, functional ability, multidimensional fatigue~~,~~ and perceived control ~~and maladaptive stress~~.

Results: Baseline comparisons showed those in the combined group had higher levels of fatigue. At follow-up, all groups saw improvements in fatigue, functional physical and symptomatology ~~and maladaptive stress~~; those within the psychology group also experienced a shift in perceived control over time.

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Conclusions: This study provides early evidence that psychological, nutritional and combined ~~patient centered~~ techniques for the treatment of ME/CFS may influence symptomatology, fatigue, function~~,~~ and perceived control ~~and inappropriate responses to stressors~~. However, these results must be viewed with caution as the allocation to groups was not randomized, there was no control group and the study suffered from high drop-out rates.

Summary

Article focus

- This preliminary prospective study investigated three (psychological, nutritional and combined) tailored ~~patient centered~~ interventions for ME/CFS over time.
- Differences between the reported changes over time between groups were also assessed.

Key messages

- Psychological, nutritional and combined ~~Patient centered~~ approaches for the management of ME/CFS influence symptomatology over time in some individuals with this disorder.
- Self-reported functional ability (physical and social) are influenced following tailored interventions lasting 3 months.
- This study provides preliminary evidence that tailored psychological, nutritional and combined interventions ~~may be effective treatments for~~may influence self-reported symptomatology in some people with ME/CFS; however due to the study's methodological limitations, it is important that these findings~~is potential treatment effect is~~ are investigated further in high quality randomized controlled studies.

Strengths and limitations of this study

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- The findings here are an initial step to fill the gap in the extant literature regarding the utility of tailored and, multidisciplinary (psychological, nutritional and combined) and patient centered treatments for ME/CFS.
- There is bias in this study as the participants were self-selected in the sense that they chose to attend the clinic and which treatment option they preferred (with advice), i.e. the study was not randomized.
- There were low retention rates in this study which may constitute a bias in that those who remained in the study may have experienced benefits and those who experienced little or no benefits may have dropped out.

Introduction

Chronic Fatigue Syndrome or myalgic encephalomyelitis (ME/CFS) is a condition characterized by prolonged and debilitating fatigue, although the exact cause of this disorder is still under debate. Due to the lack of a definitive biological marker, diagnosis is made on the basis of the exclusion of other explanatory conditions. The most widely used case definition by the Centers for Disease Control [1] states that there must be at least six months severe fatigue of new and definite onset, not the result of ongoing exertion, not alleviated by rest and resulting in reduced levels of physical activity. The CDC definition also sets out a series of minor complaints that must accompany the fatigue (cognitive impairment, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, headaches of a new type, pattern or severity at onset, unrefreshing sleep and post-exertion malaise), with individuals needing to have the occurrence of four or more symptoms to be diagnosed with

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ME/CFS. Estimates of the prevalence of ME/CFS have been made as low as 3 and as high as 2,800 per 100,000 [2].

The most widely researched strategies for alleviating the symptoms of ME/CFS are Cognitive Behavior Therapy (CBT) and Graded Exercise Therapy (GET). Two reviews of studies on CBT [3;4] found that it significantly improved physical functioning in adult out-patients as compared with medical management, counseling, guided support, education and support or relaxation. Regarding GET, a systematic review illustrated that this form of therapy was potentially beneficial for people with ME/CFS, especially when combined with a patient education programme [5]. However, drop-out rates were higher in the GET groups than control groups suggesting that individuals with ME/CFS are averse to this type of therapy. Recently, a large scale, longitudinal study investigating CBT, GET, Adaptive Pacing Therapy (APT) and specialist medical care (SMC) which had very low drop-out rates, found that CBT and GET (when added to SMC) were moderately effective outpatient treatments for this patient group as opposed to APT or SMC alone [6].

Although CBT and GET studies have shown some promising outcomes, there is no known cure for ME/CFS. Therefore the National Institute for Health and Clinical Excellence (NICE) [7] recommends a number of symptom management strategies and interventions aimed at helping individuals to cope with their condition and reduce physical deconditioning brought about by the illness. Pharmacological interventions are, at times, suggested for patients with poor sleep or pain, for instance, low-dose antidepressants, as these have been shown to be effective [8-14]. However, patient expectations must be realistic as the drugs may help elevate mood and psychological outlook but not reduce fatigue and other symptomatology associated

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with ME/CFS[15]. Numerous drugs such as thyroxin, hydrocortisone and antiviral agents are not advised by NICE due to contradictory findings[16;17].

In terms of function and quality of life management, NICE offers general advice concerning sleep management, appropriate rest periods, and pacing. Sleep hygiene instruction, together with pharmacological treatment tailored to the individual patient can be beneficial in combating fatigue [18]. Dietary management may also reduce symptomatology for those with concurrent irritable bowel syndrome (IBS). ~~Management approaches recommended for IBS, such as diet restriction, are thus also recommended for those with ME/CFS~~ [19], although this is not currently recommended by NICE. Dietary supplementation has been investigated in relation to ME/CFS. Fatty acids [20], folic acid [21], vitamin C [22], co-enzyme Q10 [23], magnesium [24], multivitamins [25] and minerals [26] have all been shown to reduce symptomatology in ME/CFS patients. However other studies have shown conflicting findings with regard to nutritional supplementation, therefore it is perhaps wise to treat with supplements on a case-by-case basis [27;28].

Due to the lack of clear and definitive treatment strategies, individuals often seek out Complementary and Alternative Medicines (CAM). Although NICE does not recommend the use of CAM they do acknowledge that many people with ME/CFS use such therapies and find them beneficial for symptom management. This view is due to the lack of published evidence for the effectiveness of these treatments. Examples of CAM treatments used by individuals with ME/CFS include religious healing, massage therapy, relaxation, meditation, homeopathy, acupuncture, naturopathy and herbal therapies [29;30]; patient satisfaction with such approaches as CAM has been high, over 80% in some instances [29]. A recent systematic review of such interventions identified 70 controlled clinical trials (randomized and non-

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randomized) and found that 86% of these studies illustrated at least one positive effect, with 74% showing a decrease of illness-related symptomatology [31]. Meditative or mindfulness approaches warranted further investigation based on these results as did supplement programs of magnesium, l-carnitine, and S-adenosylmethionine. A subsequent review based solely on randomized controlled trials (RCTs) of CAM techniques identified 26 such studies and observed that qigong, massage and tuina (approaches based within Chinese Traditional Medicine and based upon relaxation and connection with the body) illustrated positive effects as did supplementation studies utilizing nicotinamide adenine dinucleotide (NADH) and magnesium [32]. However, within both reviews it was noted that the methodological quality of reporting was poor and the sample sizes in these studies were small; hence ability to draw strong conclusions on the efficacy of CAM methods is limited. Porter et al. (2010) [31] did note that ~~patient centered,~~ individualized treatment protocols which include a range of tailored strategies are a promising area for further investigation for this complex, multi-system illness.

Objectives

There is still much debate and uncertainty regarding alternative interventions ~~the most effective treatment for~~ for those with ~~-~~ME/CFS. A r~~R~~ecent review~~s~~ of CAM techniques [31] highlight the need for further exploration of ~~patient centered and~~ individually tailored interventions for the alleviation of the condition's often debilitating and intrusive symptomatology. This study therefore aims to provide preliminary evidence for the utility of three types of ~~patient centered~~ approaches (psychological, nutritional and combined) to the management of ME/CFS over time (baseline and follow-up) offered at a private health-care center in the UK.

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Methods

Study design and setting

This preliminary prospective study aimed to investigate whether psychological, nutritional and combined approaches to the ~~explore the effectiveness of three~~ treatment of ~~options offered to individuals with~~ ME/CFS influenced symptom report measures over a 3-month time period and whether there were significant differences in these changes between groups. The research was conducted at one private secondary health care facility. All potential patients of the clinic are first asked to complete a comprehensive symptom profile and medical history, including questions relating to triggering factors, psychology sub-types and structural/biological sub-types (this is distinct from the research data collected). Subsequent to this, every individual receives a 15-minute screening with one of the practitioners (please note, this was not either of the authors of the current study) who recommends the best course of action for his/her needs; this will be the psychology-related interventions, nutritional advice and support or a combination of the two.

All individuals requesting treatment at the private care setting were offered the opportunity to participate in the study. Those that expressed an interest (N = 145) were emailed a spreadsheet that contained the questionnaires and asked to complete it at their convenience. Informed consent was obtained prior to the completion of the questionnaires and the study was approved by the University of East London Ethics Committee. Participants were told that they could withdraw from the study at any time and that withdrawal would not affect their care at the clinic. Participants were able to ask questions at any point in the study and no deception was used as the participants were informed of the nature of the research program

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before they agreed to participate. Subsequently, participants were requested to complete the questionnaire pack on a second occasion, three months from the baseline measures.

Psychology

The clinic offers a 3-month intervention which consists of a combination of Neuro-linguistic Programming (NLP), Emotional Freedom Technique (EFT), life coaching and hypnotherapy/self-hypnosis constructed in a manner specific to the needs of those with ME/CFS. The primary aim of this approach is to reduce the anxiety that is associated with having a debilitating and unpredictable condition, improve emotional well-being and help individuals slowly manage and increase their activity within their own limits (i.e. pacing). The program is offered as a series of group sessions and the peer support is seen as an important component of the intervention, which is solidified via the use of moderated online support forums, narratives of previous clients' experiences and online materials that can be accessed as often as necessary. In addition to, or as an alternative to this course, individuals receive a series of one-to-one sessions and for the most severely affected ME/CFS patients, telephone sessions are arranged and support materials can be accessed in their own homes.

Over the three-month period of this preliminary study, the participants experienced one of three treatment options. The first option included 13 hours of practitioner contact time in a mix of group training in person, group telephone conference calls and one-to-one telephone sessions, the second option was four hours of one-to-one telephone sessions and the final option was three hours of in person sessions. Participants all had access to various support materials which included CDs and online resources. The amount of time spent on these was patient-led, but was in the region of a further six hours. All the practitioners offering this option are qualified in hypnotherapy, NLP, life coaching and EFT and undergo an intensive period of training in the clinic's own integrative approach (please see Howard and Arroll [33]

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for more details of this approach) and ongoing supervision (individual and group supervision on a biweekly basis) from the department director, who is the only senior practitioner in the team.

Nutrition

Tailored nutritional therapy is achieved via one-to-one consultations with individuals. To begin, a very detailed history is taken based upon the information given in the aforementioned symptom profile. Qualified nutritional therapists (who have been given specialist training regarding ME/CFS from the clinic) then suggest tests consistent with symptomatology, for instance the Adrenal Stress Index Test, comprehensive stool analysis/gastro-intestinal function, vitamin & mineral status, etc. Results from these tests are then used to compose an evidence-driven diet and supplement program. As most cases of ME/CFS are complex involving multiple body systems, this process is often iterative and follow-up consultations are necessary to check progress and make alterations to the protocol. The nutritional therapy program consists of an initial one-hour evaluation (which includes the tailored advice) and follow-up approximately every six weeks; therefore, during the course of the present study, the participants received a minimum of two one-hour sessions with email support for any queries and detailed nutritional guidance. All the nutritional therapists are qualified to diploma level and members of (voluntary) regulatory bodies such as the British Association for Applied Nutrition and Nutritional Therapy (BANT) and the Complementary and Natural Healthcare Council (CNHC). Similar to the psychology department, the nutrition department is led by one senior practitioner who supervises the team with individual and group supervisory arrangements.

Combined

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Within the combined program, a multidisciplinary approach is taken with practitioners discussing the patients in case meetings to ensure that the psychological and nutritional aspects complement each other in order to achieve the best outcome. It should be noted that the interventions in the combined program are phased-in as it was found that asking individuals to engage in numerous therapeutic activities at the same time resulted in high drop-out rates.

Primary Outcome Measures

Medical Outcomes Survey Short-Form 36 (SF-36)

This 36-item measure is the short form of the original Medical Outcomes Survey [34] to measure functional impairment and contains eight sub-sections: 1) physical activity limitations due to health problems; 2) social activity limitations due to physical or emotional problems; 3) usual role activity limitations due to physical health problems; 4) bodily pain; 5) general mental health; 6) role activity limitations due to emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions [34]. The items are scored so that higher scores indicate greater functional ability. In terms of the psychometric properties of this measure, reliability estimates for all sub-scales are good, exceeding a Cronbach's alpha coefficient value of 0.70 [35]. In terms of validity, the SF-36 correlates amply, $r \geq 0.40$, with the frequency and severity of numerous symptoms and general health conditions [36;37].

Multidimensional Fatigue Inventory (MFI)

This 20-item measure contains five fatigue dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [38]. Items such as 'I tire easily' are rated on a 5-point scale (1 = yes, that is true; 5 = no, that is not true) with lower scores reflecting higher levels of fatigue. The MFI has good internal consistency with average

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Cronbach's alpha coefficient equaling 0.84 across the sub-scales. Convergent validity based on a sample of radiotherapy patients found correlations between the sub-scales and a visual analog fatigue scale to be 0.77 for general fatigue, 0.70 for physical fatigue, 0.61 for reduced activity, 0.56 for reduced motivation (p<0.001) to 0.23 for mental fatigue (p<0.01) [38].

Secondary Outcome Measures ~~(ME/CFS specific)~~

CDC CFS Symptom Inventory

CDC CFS Symptom Inventory [39] was used to measure specific ME/CFS symptoms and confirm diagnosis. This instrument is based upon the CDC case definition [1] and includes a fatigue item and the eight distinct symptoms are also included in the CDC guidelines with an additional ten associated symptoms. The format of this self-report measure is a six-point scale of perceived frequency (0 = absent, 5 = all the time) and severity (0 = none, 5 = very severe). The psychometric properties of this instrument are good: Cronbach's alpha coefficient = 0.88; r = .74 convergent validity with the Chalder Fatigue Scale [40]; r -.68 and -.87 convergent validity with the SF-36 'vitality' and 'bodily pain' sub-scales, respectively.

~~Secondary Outcome Measures (psychological)~~

Multidimensional Health Locus of Control Scale (MHLCS)

Multidimensional Health Locus of Control [41-43] measures perceived control via three distinct sub-scales: 'internal', 'chance' and 'powerful others' which has two dimensions, that of 'doctors' and 'other people'. The instrument contains 18 items in total (six items each for the 'internal' and 'chance' scales and three items for both the 'powerful others' scales) and is scored on a 6-point Likert scale from 'strongly agree' to 'strongly disagree'. Internal reliability of the instrument is good with Cronbach's alpha coefficients ranging from 0.67 for 'powerful others' to 0.77 for 'internal'. The measure correlates positively and significantly

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with associated scales from Levenson's [44] locus of control measure from which the MHLOC was based, which demonstrates good convergent validity [41].

~~*Maladaptive Stress Index*~~

~~This 32 item measure contains three sub scales (cognitive/mood, sleep and ME/CFS symptoms) and was designed specifically for this population [45]. Items such as 'I constantly replay or pre empt situations and conversations' are scored on a 5 point scale where 1 = never true and 5 = always true; higher scores illustrate a greater degree of disturbance.~~

Statistical methods

The data was initially screened for missing data. Four cases contained substantial amounts of missing data; therefore these were excluded from the analysis (one individual from the nutrition group and three from the combined group). Subsequent analyses were conducted on complete date only. ~~Once this was done, all the variables had less than 5% missing data, hence mean substitution was carried out in line with guidance [46]~~. The baseline data was subsequently of the quality for parametric tests, except for the variables CDC CFS swollen lymph nodes and glands, memory problems, abdominal pain and depression. However, the follow-up data suffered from high levels of skew and kurtosis which was not substantially alleviated by data transformation. This violated a key criterion for parametric testing, that of normality of distribution, so non-parametric tests were selected. In addition, as the sample sizes in each individual treatment group were small, the more conservative non-parametric tests were the preferred choice as even though tests such as analysis of variance are generally robust against non-normality, this does not hold true with small sample sizes. One-way analysis of variance tests and Kruskal-Wallis tests (the former for those variables that met the criteria for parametric tests, and the latter that did not) were used to investigate baseline

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variation and analysis of covariance (ANCOVA) tests were used to account for this variation and test to for differences between the three groups. Wilcoxon sign-rank tests were employed to look for differences over time (baseline and 3-month follow-up) and if differences were significant, percentage change was calculated. Please note, as this is an exploratory study with only one time-point and no control group, any significant findings do not infer clinical significance, rather statistical significance, and as such exact p-values are presented.

Results

Participants

Of the 145 individuals who expressed an interest in the study, 142 time-one questionnaires were returned, equating to a 97.9% response rate at baseline (two participants from the psychology group and one from the combined group dropped out at this stage). Therefore, excluding the four cases deleted due to insufficient data, 138 cases were used for baseline analysis; 42 participants in the psychology group, 44 in the nutrition group and 52 in the combined group. There was no significant association between gender and group (χ^2 (2) = 0.179, p = .915), all groups consisting of approximately one-fifth males (Table 1). There was not a significant difference in age (F(2,135) = 0.001, p = 1.000); in fact group means for age were near identical at 42.881, 42.864 and 42.843 for psychology, nutrition and combined groups, respectively. There was also a non-significant result for illness duration (F(2, 135) = 0.252, p = .778). Therefore, in terms of demographics, the groups were comparable. With regard to the outcome measures, there were significant differences between the groups in terms of the MFI sub-scale 'general fatigue' (F(2, 135) = 3.219, p = .043), MFI 'physical fatigue' (F(2, 135) = 3.343, p = .038) and the CDC CFS symptom 'swollen lymph nodes and glands' (H(2) = 7.161, p = .028). To investigate the source of these differences, post-hoc tests

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were conducted (unrelated t-tests for the fatigue variables and Mann-Whitney tests for swollen lymph glands as the former did not meet criteria for parametric tests, all with Bonferroni correction for multiple comparisons). A significant difference was observed between the psychology and combined groups with regards to general fatigue ($t(92) = -2.449$, $p = .016$) and physical fatigue ($t(92) = -2.658$, $p = .009$) and also between the nutrition and psychology group in terms of the degree of lymph node and gland swelling ($U = 635.00$, $p = .009$). Within the fatigue measures, the combined group reported significantly higher levels of both general and physical fatigued than the psychology group whereas those undertaking nutritional support stated a higher occurrence of swollen lymph nodes and glands.

Retention analysis

Seventy-two of the original 138 participants (14 participants in the psychology group, 27 in the nutrition group and 31 in the combined group) completed the battery of measures at the 3-month follow-up, resulting in retention rates of 52.17% in the study overall, 33.33% in the psychology group, 61.36% in the nutrition group and 59.62% in the combined group. To investigate whether the individuals who did not complete the time-two measures were significantly different from those at baseline on demographic and outcome measures, a series of t-tests and Mann-Whitney tests were performed. Those that dropped out of the research (although still receiving treatment at the clinic) differed significantly in terms of age ($t(136) = -2.227$, $p = .028$) and illness duration ($t(136) = -2.549$, $p = .012$). Those who remained in the study were of significantly older age (mean age of those that remained in the study = 45.056, SD = 11.535; mean age of drop-outs = 40.400, SD =12.932) and longer illness duration than those who dropped out (mean age of those that remained in the study = 10.836, SD = 7.383; mean illness duration of drop-outs =7.571, SD = 7.472). Individuals who did not remain in

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the study did not differ significantly in terms of gender (χ^2 (2) = 1.222, p = .269) or any of the outcome measures.

Comparisons within-groups across time

Overall sample

Primary outcomes

The following percentage change scores represent statistically significant changes, rather than clinically significant shifts, as this was an exploratory study. ~~(Please see Table 2 for the exact p value for each repeated measures comparison.)~~ In the sample as a whole, there were improvements in all areas of the SF-36 (Table 2), with a 5.80% improvement in physical functioning, a 68.98~~63.32~~% improvement in role limitations due to physical difficulties, a 5.17% improvement in bodily pain, a 26.17% improvement in social functioning, a 5.77% improvement in general mental health, a 10.58% improvement in role limitations due to emotional difficulties, a 22.30% improvement in vitality, energy or fatigue and a 36.49% improvement in general health perception. When looking at the fatigue sub-scales of the MFI, all five sub-scales showed significant reductions in fatigue; 8.55% in general fatigue, 10.98% in physical fatigue, 8.81% in reduced activity, 12.96% in reduced motivation and 12.79% in mental fatigue.

Secondary outcomes

Within the CFS Symptom Inventory (Table 3), there were improvements in occurrence of sore throats (34.48%), diarrhea (42.47%), fatigue after exertion (16.32%), muscle aches or muscle pains (21.01%), pain in joints (34.55%) chills (37.00%), unrefreshing sleep (19.55%), sleeping problems (17.17%), headaches (24.94%), memory problems (17.86%), difficulty concentrating (26.66%), sinus and nasal symptoms (26.38%), shortness of breath (29.28%),

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sensitivity to light (28.62%) and depression (39.55%). There were no significant differences from time-one to time-two in the MHLCS sub-scale of 'chance', 'powerful others' and 'other people' (Table 3), however the MHLCS did illustrate significant increases in internal locus of control (30.67%) and that of doctors (47.49%).

Psychology group

Primary outcomes

Within the group of individuals who opted for a purely psychological intervention, improvements were seen in physical functioning (16.75%), role limitations due to physical problems (84.61%), social functioning (37.81%), general mental health (19.15%), vitality, energy or fatigue (49.57%) and general health perceptions (19.01%). Also, all the MFI fatigue scales decreased over a 3-month period, 13.58% in general fatigue, 17.74% in physical fatigue, 23.20% in reduced activity, 11.42% in reduced motivation and 29.66% in mental fatigue (Table 4).

Secondary outcomes

Within those taking part in the psychology intervention, ratings of muscle aches or muscle pains (10.34%), chills (23.40%), memory problems (44.73%), difficulty concentrating (39.50%) and sensitivity to light (64.58%) decreased (Table 5). A significant increase of 17.56% was observed in internal locus of control, a decrease of 4.67% in the perception that chance played an influential part in the individuals' lives (Table 5).

Nutrition group

Primary outcomes

The nutrition group saw improvements in role limitations due to physical problems (75.2861.05%), social functioning (24.93%), vitality, energy or fatigue (35.35%). and general

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health perceptions (29.73%). Once again, all the MFI fatigue scales decreased over a 3-month period, 13.39% in general fatigue, 15.00% in physical fatigue, 13.28% in reduced activity, 14.64% in reduced motivation and 12.83% in mental fatigue (Table 6).

Secondary outcomes

In the nutrition group, numerous symptom-related indices also showed improvements (Table 7); sore throat (56.23%), swollen lymph glands (21.21%), fatigue after exertion (13.90%), muscle aches or muscle pains (20.56%), chills (40.74%), nausea (16.42%) and abdominal pain (20.16%). No significant differences were found from baseline to follow-up in perceived control (Table 7).

Combined group

Primary outcomes

In terms of general health as ~~evaluated~~ gauged by the SF-36 measure, the group who received both psychological and nutritional intervention reported reductions in role limitations due to physical difficulties (57.02%), social functioning (22.61%), role limitations due to emotional difficulties (29.47%) and general health perceptions (26.45%). ~~In the combined group, O~~only one measure of fatigue, that of physical fatigue, saw significant improvements over time (6.42%)~~.~~ in the combined group (Table 8).

Secondary outcomes

Those in the combined group saw significant reductions over the 3-month interval in diarrhea (47.97%), fatigue after exertion (19.20%), chills (40.23%), headaches (36.18%) and sinus and nasal symptoms (20.56%) (Table 9). No significant differences were found from baseline to follow-up in perceived control as measured by the MHLCS in the combined treatment group (Table 9).

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Secondary outcomes (ME/CFS specific)

Within the CFS Symptom Inventory, there were improvements in occurrence of sore throats (46.26%), diarrhea (42.47%), fatigue after exertion (16.32%), muscle aches or muscle pains (21.01%), pain in joints (28.32%) chills (37.00%), unrefreshing sleep (19.55%), sleeping problems (17.17%), headaches (29.47%), memory problems (17.86%), difficulty concentrating (26.66%), sinus and nasal symptoms (14.95%), shortness of breath (29.08%), sensitivity to light (26.26%) and depression (39.55%) in the merged sample. Within those taking part in the psychology intervention, ratings of muscle aches or muscle pains (10.34%), chills (23.40%), memory problems (44.73%), difficulty concentrating (39.50%) and sensitivity to light (64.58%) decreased. In the nutrition group, numerous symptom related indices also showed improvements; sore throat (56.23%), swollen lymph glands (10.09%), fatigue after exertion (13.90%), muscle aches or muscle pains (20.56%), pain in joints (16.40%), chills (40.74%), headaches (32.19%), abdominal pain (29.05%), and sensitivity to light (18.28%). Those in the combined group saw significant reductions over the 3 month interval in diarrhea (47.97%), fatigue after exertion (19.20%), chills (40.23%), headaches (36.18%) and sinus and nasal symptoms (20.56%). (Please see Table 3 for the descriptive and inferential statistics associated with these findings and the exact p value for each repeated measures comparison.)

Secondary outcomes (psychological)

There were no significant differences from time one to time two in the MHLCS sub scale of 'chance', 'powerful others' and 'other people', however the MHLCS did illustrate significant increases in internal locus of control (30.67%) and that of doctors (47.49%) in the sample as a whole. Reductions were also observed in the Maladaptive Stress Response (11.99%) in the entire group. In the psychology group, a significant increase of 17.56% was observed in

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~~internal locus of control, a decrease of 4.67% in the perception that chance played an influential part in the individuals' lives and a significant reduction in the Maladaptive Stress Response of 16.75%. No significant differences were found from baseline to follow up in perceived control in the nutrition group, however the way in which the individuals in this group responded to stress also decreased, by 11.54%. No significant differences were found from baseline to follow up in perceived control as measured by the MHLCS in the combined treatment group although there was a statistically significant difference in the Maladaptive Stress Response (10.98%). (Please see Table 4 for the descriptive and inferential statistics associated with these findings and the exact p value for each repeated measures comparison.)~~

Comparisons across groups

With correction for baseline variation, there were no significant differences between the three groups in terms of change scores.

Discussion

Key results

There was statistically significant (rather than known clinically significant) change over time of numerous measures in all groups investigated. However, this is not to say that these changes were due to the interventions as the design of this study was exploratory, rather than experimental (please see below for a further critique of the design).The psychology group contained the most significant findings, including those concerned with daily functioning, fatigue, locus of control~~,~~ and ~~the~~ cognitive CDC CFS specific symptoms ~~and the Maladaptive Stress Response~~. These findings appear consistent with outcomes from other psychological interventions [3;4;6]. As expected, changes in perceived control were not observed in the nutrition group as this is not an area that is targeted in this program. However, the more

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immune-type symptoms such as sore throat and, swollen lymph nodes or glands and pain in joints did see significant reductions over time as would be envisaged in treatment protocols based upon nutritional expertise. The group that exhibited the least significant findings was the combined group and, as noted below, this may be due to the greater general severity of symptoms in this group and the need for a more lengthy intervention. Nevertheless, considering the small sample sizes in the groups at follow-up, these results are very promising and warrant further attention.

Interpretation

As noted previously [31] patient centered, individualized treatment protocols which include a range of tailored strategies is a favorable direction for dealing with a complex and multi-system disorder such as ME/CFS. The present study has demonstrated that such interventions may be useful in lowering symptomatology, improving functioning and helping individuals gain a greater sense of control over their health status.

Limitations and Generalisability

This study was a preliminary study in a naturalistic setting and as such did not have a robust design. There was not a control group and the participants were not randomly assigned to groups, therefore the results should be treated with caution. In order to ascertain whether the changes in symptom and functional reports were due to the interventions, a randomized control trial should be conducted (RCT). Also, there was a high drop-out rate from time-one to time-two and this rate differed across groups. The highest drop-out rate was in the psychology group; whilst we cannot be sure why this occurred, it is postulated that the retention was poor in the group as the individuals in the psychology program had more activities to engage in and may have felt overburdened with the research questionnaires in

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addition to their session and homework (this would not be the case in the combined group as the therapeutic activities are phased-in as mentioned above).

In this study, each individual was guided to appropriate treatment within an initial screening with clinic staff; therefore the group was dependent on the nature of the individual's symptoms and their personal choice as the programs on offer were privately funded. Notably, the groups did differ in general and physical fatigue with participants in the combined groups reporting greater fatigue than those in the psychology group which suggests that this group's general symptomatology was more severe. The combined group illustrated less change over time compared to the psychology and nutrition groups and it is feasible to infer that individuals with a greater number and degree of complaints are referred to the combined group within the clinic. Also, those in the combined group will not experience the intensity of each intervention as this has been demonstrated to result in non-compliance; therefore, changes in outcome measures in this group may not be noted at an interval of three months. Further studies underway presently will investigate follow-ups at 6- and 12-months to identify whether the findings here are maintained over time and also whether those with greater symptom severity benefit with a longer intervention. The results from this study will then inform plans for an RCT of the clinic's practices. As the participants were self-selected onto these programs, the findings lack generalizability; future work should sample from the overall ME/CFS population and be randomly-assigned to groups in order to make valid assumptions regarding the illness-group as a whole.

Funding

No external funding was obtained for this research; the work was accomplished in-house at the clinic in question.

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Data Sharing

Dataset available from the corresponding author at drarroll@theoptimumhealthclinic.com. Consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low.

Contributorship

Alex Howard made substantial contributions to the conception and design and acquisition of data, whilst Megan Arroll made a substantial contribution to the analysis and interpretation of data. Both authors made a substantial contribution to the drafting of the article and revisions for the critical review of important intellectual content. Final approval of the version to be published was also granted by both authors.

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Competing Interests

Alex Howard is the founder and CEO of The Optimum Health Clinic and Megan Arroll is the Director of Research at the Optimum Health Clinic, where this study was conducted.

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List of abbreviations

ME: myalgic encephalomyelitis

CFS: Chronic Fatigue Syndrome

NICE: National Institute for Health and Clinical Excellence

CBT: Cognitive Behavioral Therapy

GET: Graded Exercise Therapy

APT: Adaptive Pacing Therapy

SMC: specialist medical care

CAM: Complementary and Alternative Medicine

NLP: Neuro-linguistic Programming

EFT: Emotional Freedom Technique

SF-36: Medical Outcomes Survey Short-Form 36

MHLCS: Multidimensional Health Locus of Control Scale

MFI: Multidimensional Fatigue Inventory

RCT: randomized controlled trial

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Table 1. Demographics for gender, age and illness duration across the three treatment groups

		Mean	SD	95% CI for Mean Lower	95% CI for Mean Upper	Test statistic	p-value
Gender	Psychology	9 (21.4%)[d]				.179[c]	.915
	Nutrition	8 (18.2%)[d]					
	Combined	11 (21.2%)[d]					
	Total	28 (20.3%)[d]					
Age	Psychology	42.881	13.986	38.523	47.239	.000[a]	1.000
	Nutrition	42.864	12.504	39.062	46.665		
	Combined	42.843	11.125	39.714	45.972		
	Total	42.861	12.406	40.765	44.957		
Illness duration	Psychology	8.874	8.252	6.302	11.445	.252[a]	.778
	Nutrition	10.023	7.375	7.781	12.265		
	Combined	9.625	7.291	7.595	11.655		
	Total	9.523	7.580	8.247	10.800		

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Table 2. Comparisons across time within the primary outcome measures within the overall sample

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	72	18.075	41.644	66.667	25.694	47.222	77.583	-3.120	.002**
SF-36 Role limitations physical	71	0	0	0	0	25	50	-4.321	.001***
SF-36 Bodily pain	72	32.5	56.25	79.375	32.500	67.500	90	-2.240	.025*
SF-36 Social functioning	72	12.5	25	50	12.500	50	75	-4.504	.001***
SF-36 General mental health	72	53	60	75	57	68	80	-2.665	.008**
SF-36 Role limitations emotional	72	0	33.317	100	41.667	66.670	100	-3.159	.002**
SF-36 Vitality Energy or Fatigue	72	10	15	35	11.250	30	45	-4.205	.001***
SF-36 General health perceptions	72	20	30	40	25	40	50	-3.996	.001***
MFI General Fatigue	72	15	18	19	12	16	19	-3.692	.001***
MFI Physical Fatigue	72	15	18	20	12	16	19	-4.591	.001***
MFI Reduced Activity	72	11	15	18	9	14	17	-2.421	.015*
MFI Reduced Motivation	72	8	10	13.750	7	9	12	-2.986	.003**
MFI Mental Fatigue	72	11	14	18	8.250	12.500	15	-3.661	.001***

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Table 3. Comparisons across time within the secondary outcome measures within the overall sample

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
CDC CFS Sore throat	70	0	1.5	4	0	1	2	-2.257	.024*
CDC CFS Swollen lymph nodes/glands	71	0	2	6	0	1	4	-1.567	.115
CDC CFS Diarrhea	72	0	1	4	0	0	2	-2.481	.013*
CDC CFS Fatigue after exertion	72	9	15	20	6.500	12	16	-3.574	.001***
CDC CFS Muscle aches/pains	72	4	9	12	1.250	6	12	-3.995	.001***
CDC CFS Pain in joints	70	0	4	9	0	1	6	-2.908	.004**
CDC CFS Fever	70	0	0	1	0	0	0	-1.667	.095
CDC CFS Chills	72	0	2	6	0	0	2.113	-4.206	.001***
CDC CFS Unrefreshing sleep	72	6	12	16	4	6	16	-2.295	.022*
CDC CFS Sleeping problems	72	2	8	12	2	4	12	-1.983	.047*
CDC CFS Headaches	71	1	6	9	1	6	11.250	-2.850	.004**

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CDC CFS Memory Problems	72	2	6	12	1	6	11.250	-2.053	.040*
CDC CFS Difficulty Concentrating	72	2.500	8.500	12	1	6	12	-3.440	.001***
CDC CFS Nausea	71	0	1	4	0	2	6	-0.898	.369
CDC CFS Abdominal Pain	71	0	2	6	0	2	6	-1.932	.053
CDC CFS Sinus nasal symptoms	71	1	4	6	0	1	6	-2.862	.004**
CDC CFS Shortness of breath	69	0	2	4	0	1	4	-2.402	.016*
CDC CFS Sensitivity to light	71	0	2	6	0	1	4	-2.388	.017*
CDC CFS Depression	72	0	2	6	0	1	4	-2.297	.022*
MHLCS Internal	72	0.528	0.681	0.799	0.611	0.722	0.889	-2.962	.003**
MHLCS Chance	72	0.222	0.344	0.417	0.201	0.320	0.444	-1.552	.121
MHLCS Powerful Others	72	0.333	0.389	0.500	0.306	0.361	0.500	-1.601	.109
MHLCS Doctors	72	0.0833	0.139	0.222	0.083	0.111	0.194	-2.381	.017*
MHLCS Other People	72	0.194	0.250	0.3056	0.174	0.250	0.278	-1.186	.236

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Table 4. Comparisons across time within the primary outcome measures within the psychology group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	14	25.008	44.444	58.367	27.083	69.450	84.700	-2.707	.007**
SF-36 Role limitations physical	14	0	0	25	0	50	81.250	-2.379	.017*
SF-36 Bodily pain	14	39.375	57.500	80.625	32.500	72.500	90	-1.195	.232
SF-36 Social functioning	14	25	37.500	50	34.375	56.250	90.625	-2.689	.007**
SF-36 General mental health	14	47	62	80	67	76	88	-2.497	.013*
SF-36 Role limitations emotional	14	24.974	100	100	58.336	100	100	-.842	.400
SF-36 Vitality Energy or Fatigue	14	10	20	40	28.750	45	52.500	-3.066	.002**
SF-36 General health perceptions	14	23.750	30	41.250	31.250	40	63.750	-2.561	.010*
MFI General Fatigue	14	14	16.500	18.500	9.750	13.500	18.500	-2.657	.008**
MFI Physical Fatigue	14	13.750	16	19.250	8.750	13	16.750	-2.810	.005**
MFI Reduced Activity	14	9.750	12.500	18.250	7	9	14.500	-2.142	.032*

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MFI Reduced Motivation	14	5.750	8	11.750	4.750	5.500	8.250	-2.131	.033*
MFI Mental Fatigue	14	11.750	15.500	18	6.500	9.500	15	-2.950	.003*

Table 5. Comparisons across time within the secondary outcome measures within the psychology group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
CDC CFS Sore throat	14	0	2	6	0	0	2.500	-1.365	.172
CDC CFS Swollen lymph nodes/glands	14	0	0.5	2.5	0	0	4	-.341	.733
CDC CFS Diarrhea	14	0	0	2	0	0	2.500	-.730	.465
CDC CFS Fatigue after exertion	14	9	12	20	7.750	9	14	-1.550	.121
CDC CFS Muscle aches/pains	14	4	9	15.25	1.750	9	14	-2.145	.032*
CDC CFS Pain in joints	14	0	2.5	9	0	0.500	4.500	-1.778	.075
CDC CFS Fever	14	0	0	1.5	0	0	0.500	-.135	.892
CDC CFS Chills	14	0	1	6.75	0	0	4.500	-1.970	.049*
CDC CFS Unrefreshing sleep	14	9	12	15.25	5.500	9	16	-.802	.422

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CDC CFS Sleeping problems	14	2.75	7	12	1	3	9.750	-1.738	.082
CDC CFS Headaches	14	1	2.5	6	0.750	1	6.750	-1.200	.230
CDC CFS Memory Problems	14	1	6	9	0.750	1	6.750	-1.965	.049*
CDC CFS Difficulty Concentrating	14	3.5	9	17	1	5	6.750	-2.809	.005**
CDC CFS Nausea	14	0	0	4.25	0	1	4.500	-.213	.832
CDC CFS Abdominal Pain	14	0	2	5.25	0	0	6	-.343	.732
CDC CFS Sinus nasal symptoms	14	1	3.5	4.5	0	1.500	4.500	-.724	.469
CDC CFS Shortness of breath	14	0	1.5	4.5	0	0.500	2.50	-1.556	.120
CDC CFS Sensitivity to light	14	0	1	4.5	0	0	1.250	-1.973	.049*
CDC CFS Depression	14	0	1.5	6	0	0	2	-1.614	.106
MHLCS Internal	14	0.556	0.653	0.840	0.611	0.872	0.923	-2.983	.003**
MHLCS Chance	14	0.326	0.417	0.535	0.167	0.361	0.451	-2.594	.009**
MHLCS Powerful Others	14	0.319	0.375	0.451	0.299	0.356	0.431	.000	1.000
MHLCS Doctors	14	0.083	0.125	0.194	0.083	0.083	0.174	-1.122	.262
MHLCS Other People	14	0.194	0.236	0.285	0.194	0.222	0.257	-.118	.906

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Table 6. Comparisons across time within the primary outcome measures within the nutrition group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	27	16.7	44.444	77.778	16.700	38.889	77.778	-1.136	.256
SF-36 Role limitations physical	26	0	0	0	0	25	25	-2.878	.004**
SF-36 Bodily pain	27	32.5	45	67.5	35.200	67.500	90	-1.800	.072
SF-36 Social functioning	27	0	25	50	12.500	37.500	75	-2.476	.013*
SF-36 General mental health	27	52	60	72	52	64	80	-1.696	.090
SF-36 Role limitations emotional	27	0	0	100	0	66.670	100	-1.788	.074
SF-36 Vitality Energy or Fatigue	27	5	15	35	15	25	45	-2.734	.006**
SF-36 General health perceptions	27	20	25	35	25	35	45	-2.157	.031*
MFI General Fatigue	27	15	18	19	12	15	19	-2.548	.011*
MFI Physical Fatigue	27	14	18	19	11	16	19	-2.791	.005**
MFI Reduced Activity	27	10	14	18	8	13	16	-2.164	.030*
MFI Reduced Motivation	27	8	10	12	6	8	12	-1.985	.047*

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MFI Mental Fatigue	27	11	13	16	8	13	15	-2.082	.037*

Table 7. Comparisons across time within the secondary outcome measures within the nutrition group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
CDC CFS Sore throat	27	8	1	2	0	1	2	-2.211	.027*
CDC CFS Swollen lymph nodes/glands	26	20	0	5	0	1	12	-2.051	.040*
CDC CFS Diarrhea	27	16	0	1	0	0	1	-1.649	.099
CDC CFS Fatigue after exertion	27	25	9	16	4	12	20	-2.209	.027*
CDC CFS Muscle aches/pains	27	20	4	9	2	6	12	-2.901	.004**
CDC CFS Pain in joints	26	20	0.750	4	0	1	6	-1.827	.068
CDC CFS Fever	26	9	0	0	0	0	0	-1.254	.210
CDC CFS Chills	27	12	1	3	0	0	1	-3.401	.001***
CDC CFS Unrefreshing sleep	27	25	6	12	4	6	16	-1.421	.155
CDC CFS Sleeping problems	27	25	1	9	2	4	16	-0.190	.849

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CDC CFS Headaches	26	25	0.750	6	1	3	6	-1.895	.058
CDC CFS Memory Problems	27	25	2	6	2	6	12	-0.338	.735
CDC CFS Difficulty Concentrating	27	25	2	6	4	6	12	-1.196	.232
CDC CFS Nausea	26	25	0	2	0	1	6	-2.407	.016*
CDC CFS Abdominal Pain	26	16	0.750	3	0	3	6	-2.322	.020*
CDC CFS Sinus nasal symptoms	26	20	1	3.500	0	1	9	-1.244	.213
CDC CFS Shortness of breath	25	20	0	2	0	1	3	-1.651	.099
CDC CFS Sensitivity to light	26	25	0	4	0	2	6	-1.890	.059
CDC CFS Depression	27	20	0	4	0	2	4	-1.584	.113
MHLCS Internal	27	0.944	0.528	0.667	0.528	0.639	0.778	-.687	.492
MHLCS Chance	27	0.694	0.222	0.333	0.222	0.333	0.472	-.143	.886
MHLCS Powerful Others	27	0.694	0.333	0.389	0.278	0.361	0.528	-1.843	.065
MHLCS Doctors	27	0.417	0.0833	0.139	0.083	0.139	0.222	-1.686	.092
MHLCS Other People	27	0.833	0.222	0.278	0.167	0.250	0.306	-1.697	.090

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Table 8. Comparisons across time within the primary outcome measures within the combined group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
SF-36 Physical Functioning	31	22.200	33.333	61.111	27.778	55.556	72.222	-1.850	.064
SF-36 Role limitations physical	31	0	0	0	0	25	25	-2.225	.026*
SF-36 Bodily pain	31	32.500	45	80	32.500	57.500	80	-1.048	.294
SF-36 Social functioning	31	12.500	25	37.500	12.500	37.500	62.500	-2.426	.015*
SF-36 General mental health	31	56	60	72	56	68	76	-0.524	.600
SF-36 Role limitations emotional	31	0	33.333	100	66.667	66.670	100	-2.313	.021*
SF-36 Vitality Energy or Fatigue	31	10	15	30	10	25	40	-1.558	.119
SF-36 General health perceptions	31	20	30	40	25	40	55	-2.423	.015*
MFI General Fatigue	31	16	18	19	14	17	19	-0.854	.393
MFI Physical Fatigue	31	15	19	20	13	17	20	-2.364	.018*

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MFI Reduced Activity	31	12	16	18	11	16	18	-0.070	.944
MFI Reduced Motivation	31	9	11	14	8	10	13	-1.082	.279
MFI Mental Fatigue	31	10	14	18	11	13	16	-1.586	.113

Table 9. Comparisons across time within the secondary outcome measures within the combined group

	N	Baseline			3-month follow-up			Comparisons	
		Percentiles			Percentiles				
		Lower	Mdn	Upper	Lower	Mdn	Upper	*z*-statistic	*p*-value
CDC CFS Sore throat	29	0	0	3.500	0	1	2.030	-0.567	.571
CDC CFS Swollen lymph nodes/glands	31	0	2	4	0	1	3	-0.725	.468
CDC CFS Diarrhea	31	0	2	4	0	0	2	-1.996	046*
CDC CFS Fatigue after exertion	31	8	15	20	6	12	16	-2.392	.017*
CDC CFS Muscle aches/pains	31	2	6	12	1	6	9	-1.908	.056
CDC CFS Pain in joints	30	0	1.500	8	0	1	4	-1.680	.093
CDC CFS Fever	30	0	0	1	0	0	0.720	-1.383	.167
CDC CFS Chills	31	0	2	6	0	1	2.150	-2.049	.040*

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CDC CFS Unrefreshing sleep	31	6	12	16	4	9	16	-1.513	.130
CDC CFS Sleeping problems	31	1	6	12	2	4	9	-1.794	.073
CDC CFS Headaches	31	2	6	9	1	3	6	-2.807	.005**
CDC CFS Memory Problems	31	2	6	12	1	3	9	-1.446	.148
CDC CFS Difficulty Concentrating	31	2	8	12	1	6	12	-1.899	.058
CDC CFS Nausea	31	0	1	6	0	2	6	-0.855	.392
CDC CFS Abdominal Pain	31	0	1	6	0	2	4	-0.598	.550
CDC CFS Sinus nasal symptoms	31	0	5	8	0	1	4	-2.482	.013*
CDC CFS Shortness of breath	30	0	2	6	0	1	4	-0.976	.329
CDC CFS Sensitivity to light	31	0	1	6	0	1	4	-0.787	.431
CDC CFS Depression	31	0	2	6	0	1	6	-1.304	.192
MHLCS Internal	31	0.556	0.694	0.861	0.639	0.750	0.889	-1.755	.079
MHLCS Chance	31	0.222	0.333	0.361	0.167	0.306	0.417	-0.672	.501
MHLCS Powerful Others	31	0.333	0.389	0.500	0.333	0.389	0.500	-0.577	.564
MHLCS Doctors	31	0.111	0.167	0.222	0.083	0.139	0.500	-1.384	.166
MHLCS Other People	31	0.167	0.250	0.278	0.194	0.250	0.306	-0.213	.831

*** significant at .05 level**
**** significant at .01 level**

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*** significant at .001 level

Table 2. Comparisons across time within the primary outcome measures

		Baseline				3 month follow up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z* statistic	*p* value
SF-36 Physical Functioning	Psychology	49.339	22.698	42.266	56.413	59.267	30.346	41.745	76.788	-2.707	.007**
	Nutrition	47.855	26.226	39.882	55.829	46.706	30.744	34.544	58.868	-1.136	.256
	Combined	45.299	25.479	38.206	52.393	49.288	26.403	39.604	58.973	-1.850	.064
	Total	47.344	24.791	43.171	51.517	50.260	28.818	43.488	57.032	-3.120	.002**
SF-36 Role limitations physical	Psychology	7.143	15.894	2.190	12.096	46.429	39.048	23.883	68.974	-2.379	.017*
	Nutrition	7.574	17.500	2.254	12.895	19.444	20.016	11.526	27.363	-2.907	.004**
	Combined	9.774	21.051	3.914	15.635	22.742	25.161	13.513	31.971	-2.225	.026*
	Total	8.272	18.387	5.177	11.367	26.111	28.225	19.479	32.744	-4.354	.001***
SF-36 Bodily pain	Psychology	61.548	25.614	53.566	69.530	63.929	29.786	46.731	81.127	-1.196	.232
	Nutrition	55.625	30.242	46.434	64.819	58.889	32.943	45.857	71.921	-1.800	.072
	Combined	53.606	27.019	46.084	61.128	58.629	27.301	48.615	68.643	-1.048	.294
	Total	56.667	27.683	52.007	61.327	59.757	29.649	52.790	66.724	-2.240	.025*
SF-36 Social functioning	Psychology	37.202	21.824	30.402	44.003	59.821	33.318	40.584	79.058	-2.689	.007**
	Nutrition	32.671	25.888	24.800	40.541	43.519	33.679	30.196	56.841	-2.476	.013*
	Combined	32.452	24.786	25.551	39.352	41.936	28.604	31.443	52.428	-2.426	.015*
	Total	33.967	24.212	29.892	38.043	46.007	31.805	38.533	53.481	-4.504	.001***
SF-36	Psychology	60.286	19.584	54.183	66.389	74.571	13.276	66.906	82.237	-2.497	.013*

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General mental health	Nutrition	59.727	19.355	53.843	65.612	64.741	20.548	56.612	72.869	-1.696	.090
	Combined	58.308	20.948	52.476	64.140	64.129	16.637	58.027	70.232	-.524	.600
	Total	59.362	19.911	56.011	62.714	66.389	17.897	62.183	70.594	-2.665	.008**
SF-36 Role limitations emotional	Psychology	55.554	46.368	41.105	70.004	76.191	33.150	57.051	95.331	-.842	.400
	Nutrition	48.482	47.390	34.074	62.890	55.594	38.130	40.510	70.678	-1.788	.074
	Combined	47.780	43.924	35.551	60.008	67.742	32.756	55.727	79.757	-2.313	.021*
	Total	50.370	45.590	42.695	58.044	64.829	35.335	56.526	73.133	-3.159	.002**
SF-36 Vitality Energy or Fatigue	Psychology	20.714	16.139	15.685	25.743	41.071	20.586	29.186	52.957	-3.066	.002**
	Nutrition	20.114	14.5670	15.685	24.542	31.111	23.588	21.780	40.442	-2.734	.006**
	Combined	19.039	17.658	14.123	23.955	27.097	19.527	19.934	34.259	-1.558	.119
	Total	19.891	16.159	17.171	22.611	31.319	21.657	26.230	36.409	-4.205	.001***
SF-36 General health perceptions	Psychology	37.024	17.945	31.432	42.616	45.714	21.109	33.526	57.903	-2.561	.010*
	Nutrition	28.636	15.528	23.915	33.357	36.482	18.903	29.004	43.959	-2.157	.031*
	Combined	30.962	17.575	26.069	35.854	42.097	21.632	34.162	50.032	-2.423	.015*
	Total	32.065	17.286	29.156	34.975	40.694	20.561	35.863	45.526	-3.996	.001***
MFI General Fatigue	Psychology	15.952	2.845	15.066	16.839	13.786	4.441	11.222	16.350	-2.657	.008**
	Nutrition	16.977	2.601	16.186	17.768	14.704	4.898	12.766	16.641	-2.548	.011*
	Combined	17.327	2.588	16.607	18.047	16.645	2.811	15.614	17.676	-.854	.393
	Total	16.797	2.716	16.340	17.254	15.361	4.136	14.389	16.333	-3.692	.001***
MFI Physical Fatigue	Psychology	15.929	3.331	14.891	16.966	13.071	4.632	10.397	15.746	-2.810	.005**
	Nutrition	16.727	3.358	15.707	17.748	14.222	4.987	12.249	16.195	-2.791	.005**
	Combined	17.615	2.823	16.830	18.401	16.484	3.395	15.239	17.729	-2.364	.018*
	Total	16.819	3.211	16.278	17.359	14.972	4.453	13.926	16.019	-4.591	.001***
MFI Reduced	Psychology	13.857	4.112	12.576	15.138	10.643	5.153	7.668	13.618	-2.142	.032*
	Nutrition	14.136	4.027	12.912	15.361	12.259	5.012	10.277	14.242	-2.164	.030*

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Activity	Combined	14.962	3.662	13.942	15.981	14.936	3.777	13.550	16.321	-.070	.944
	Total	14.362	3.921	13.702	15.022	13.097	4.798	11.970	14.225	-2.421	.015*
MFI	Psychology	10.357	4.287	9.021	11.693	7.286	4.214	4.853	9.719	-2.131	.033*
Reduced	Nutrition	10.500	3.474	9.444	11.556	8.963	3.736	7.485	10.441	-1.985	.047*
Motivation	Combined	11.462	3.153	10.584	12.339	10.774	3.095	9.639	11.910	-1.082	.279
	Total	10.819	3.639	10.206	11.431	9.417	3.767	8.532	10.302	-2.986	.003**
MFI	Psychology	13.524	4.363	12.164	14.883	10.500	4.468	7.920	13.080	-2.950	.003*
Mental Fatigue	Nutrition	13.682	4.328	12.366	14.998	11.926	5.334	9.816	14.036	-2.082	.037*
	Combined	13.846	4.345	12.637	15.056	12.613	3.827	11.209	14.017	-1.586	.113
	Total	13.696	4.315	12.969	14.422	11.944	4.568	10.871	13.018	-3.661	.001***

[a] *z*-statistic for Wilcoxon Signed-Rank Test

Table 3. Comparisons across time within the secondary outcome measures (ME/CFS-specific)

		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z*-statistic	*p*-value
CDC CFS	Psychology	2.571	3.109	1.603	3.540	1.429	2.278	.114	2.744	-1.365	.172
Sore Throat	Nutrition	3.977	3.776	2.829	5.125	1.741	2.087	.915	2.566	-2.211	.027*
	Combined	3.202	4.494	1.951	4.454	1.904	2.821	.870	2.939	-.804	.422
	Total	3.257	3.898	2.601	3.914	1.750	2.437	1.178	2.323	-2.387	.017*
CDC CFS	Psychology	1.976	3.382	.922	3.030	1.786	3.378	-.165	3.736	-.341	.733

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Swollen Lymph nodes Glands	Nutrition	5.561	6.491	3.587	7.534	5.000	6.760	2.326	7.674	-2.212	.027*
	Combined	3.462	4.881	2.103	4.820	2.690	4.477	1.0458	4.332	-.725	.468
	Total	3.679	5.250	2.795	4.563	3.380	5.385	2.115	4.646	-1.684	.092
CDC CFS Diarrhea	Psychology	2.071	3.249	1.059	3.084	1.643	2.818	.016	3.270	-.730	.465
	Nutrition	2.841	4.832	1.372	4.310	1.444	3.274	.149	2.740	-1.649	.099
	Combined	3.135	3.773	2.084	4.185	1.631	2.483	.720	2.542	-1.996	046*
	Total	2.717	3.998	2.044	3.390	1.563	2.827	.899	2.228	-2.481	.013*
CDC CFS Fatigue after exertion	Psychology	13.286	6.271	11.331	15.240	11.071	6.673	7.218	14.925	-1.550	.121
	Nutrition	13.722	6.450	11.761	15.682	11.815	7.217	8.960	14.670	-2.209	.027*
	Combined	14.154	6.270	12.408	15.899	11.436	6.275	9.134	13.738	-2.392	.017*.
	Total	13.752	6.292	12.693	14.811	11.507	6.629	9.949	13.065	-3.574	.001***
CDC CFS Muscle Aches or Muscle Pains	Psychology	8.286	6.747	6.183	10.388	7.429	6.892	3.450	11.408	-2.145	.032*
	Nutrition	9.091	6.383	7.151	11.031	7.222	6.278	4.739	9.706	-2.901	.004**
	Combined	8.519	6.932	6.589	10.449	6.188	5.528	4.160	8.215	-1.908	.056
	Total	8.630	6.664	7.509	9.752	6.817	6.029	5.400	8.234	-.3995	.001***
CDC CFS Pain In Joints	Psychology	3.476	5.334	1.814	5.138	2.786	4.458	.212	5.360	-1.778	.075
	Nutrition	4.696	5.560	3.006	6.386	3.926	5.099	1.909	5.943	-2.022	.043*
	Combined	5.474	6.386	3.696	7.251	3.010	4.140	1.492	4.528	-1.840	.066
	Total	4.618	5.837	3.635	5.600	3.310	4.543	2.242	4.377	-3.141	.002**
CDC CFS Fever	Psychology	1.238	2.516	.454	2.022	1.643	4.181	-.771	4.057	-.135	.892
	Nutrition	1.394	2.562	.615	2.173	.630	2.041	-.178	1.437	-1.487	.137
	Combined	1.333	3.909	.245	2.421	.378	.709	.118	.638	-1.517	.129
	Total	1.324	3.106	.801	1.846	.718	2.272	.185	1.252	-1.876	.061
CDC CFS Chills	Psychology	3.357	4.637	1.912	4.802	2.571	4.398	.032	5.111	-1.970	.049*
	Nutrition	3.750	3.924	2.557	4.943	2.222	4.098	.601	3.843	-3.401	.001***

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	Combined	3.192	4.343	1.983	4.402	1.908	2.797	.882	2.934	-2.049	.040*
	Total	3.420	4.283	2.699	4.141	2.155	3.614	1.306	3.004	-4.206	.001***
CDC CFS UnrefreshingSleep	Psychology	12.905	6.792	10.788	15.021	10.643	6.698	6.776	14.510	-.802	.422
	Nutrition	12.250	7.088	10.095	14.405	9.444	7.738	6.384	12.505	-1.421	.155
	Combined	12.154	7.147	10.164	14.143	10.161	7.959	7.242	13.080	-1.513	.130
	Total	12.413	6.978	11.238	13.588	9.986	7.557	8.210	11.762	-2.295	.022*
CDC CFS Sleeping Problems	Psychology	9.286	7.658	6.899	11.672	5.286	4.921	2.444	8.127	-1.738	.082
	Nutrition	8.614	7.317	6.389	10.838	9.482	9.200	5.842	13.121	-.190	.849
	Combined	8.904	7.681	6.766	11.042	6.529	6.749	4.053	9.004	-1.794	.073
	Total	8.928	7.509	7.664	10.192	7.394	7.585	5.612	9.177	-1.983	.047*
CDC CFS Headaches	Psychology	5.262	5.548	3.533	6.991	4.357	3.411	2.388	6.326	-1.200	.230
	Nutrition	7.646	7.040	5.506	9.786	5.185	6.294	2.695	7.675	-2.084	.037*
	Combined	6.346	5.857	4.715	7.977	4.050	3.527	2.756	5.343	-2.807	.005**
	Total	6.431	6.200	5.387	7.474	4.535	4.708	3.429	5.642	-3.000	.003**
CDC CFS Memory Problems	Psychology	6.333	4.996	4.777	7.890	3.500	3.995	1.193	5.807	-1.965	.049*
	Nutrition	9.409	7.183	7.225	11.593	8.667	7.681	5.628	11.705	-.338	.735
	Combined	8.173	7.610	6.055	10.292	6.148	4.905	4.349	7.947	-1.446	.148
	Total	8.007	6.835	6.857	9.158	6.578	6.189	5.123	8.032	-2.053	.040*
CDC CFS Difficulty Concentrating	Psychology	8.500	6.094	6.601	10.399	5.143	5.559	1.933	8.353	-2.809	.005**
	Nutrition	9.822	7.641	7.499	12.145	7.778	6.941	5.032	10.524	-1.196	.232
	Combined	9.135	6.942	7.202	11.067	6.507	4.843	4.731	8.283	-1.899	.058
	Total	9.161	6.903	7.999	10.323	6.718	5.844	5.345	8.092	-3.440	.001***
CDC CFS Nausea	Psychology	3.476	4.845	1.966	4.986	2.286	2.946	.585	3.987	-.213	.832
	Nutrition	4.769	5.135	3.208	6.330	3.407	5.746	1.134	5.681	-1.686	.092
	Combined	3.327	4.902	1.962	4.692	3.458	3.585	2.144	4.773	-.855	.392

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	Total	3.832	4.966	2.996	4.668	3.211	4.396	2.178	4.244	-.584	.559
CDC CFS Abdominal Pain	Psychology	2.548	3.270	1.529	3.567	2.786	4.003	.474	5.097	-.343	.732
	Nutrition	5.064	5.165	3.493	6.634	3.593	3.905	2.048	5.137	-1.968	.049*
	Combined	3.750	4.635	2.460	5.041	2.548	2.791	1.524	3.572	-.598	.550
	Total	3.803	4.535	3.040	4.566	2.986	3.470	2.171	3.801	-1.727	.084
CDC CFS Sinus Nasal Symptoms	Psychology	3.524	4.702	2.059	4.989	2.357	2.437	.950	3.764	-.724	.469
	Nutrition	5.469	6.476	3.500	7.438	4.889	6.104	2.474	7.304	-1.400	.162
	Combined	4.789	6.304	3.034	6.544	3.804	6.710	1.343	6.266	-2.482	.013*
	Total	4.620	5.931	3.622	5.619	3.930	5.882	2.547	5.312	-2.971	.003**
CDC CFS Shortness Of Breath	Psychology	3.000	4.191	1.694	4.306	1.571	2.209	.296	2.847	-1.556	.120
	Nutrition	3.285	4.090	2.026	4.543	2.407	4.060	.801	4.013	-1.849	.064
	Combined	3.392	4.788	2.046	4.739	2.526	3.631	1.194	3.858	-.976	.329
	Total	3.237	4.365	2.497	3.977	2.296	3.554	1.461	3.131	-2.538	.011*
CDC CFS Sensitivity To Light	Psychology	3.429	5.347	1.762	5.095	1.214	2.517	-.239	2.668	-1.973	.049*
	Nutrition	5.031	6.097	3.177	6.884	4.111	6.198	1.659	6.563	-2.136	.033*
	Combined	4.481	6.360	2.710	6.251	3.297	5.557	1.259	5.335	-.787	.431
	Total	4.336	5.975	3.330	5.342	3.197	5.419	1.924	4.471	-2.542	.011*
CDC CFS Depression	Psychology	3.952	3.938	2.725	5.180	1.571	3.228	-.292	3.435	-1.614	.106
	Nutrition	4.477	5.450	2.821	6.134	3.333	4.883	1.402	5.265	-1.584	.113
	Combined	5.077	5.950	3.420	6.734	2.766	3.324	1.547	3.985	-1.304	.192
	Total	4.544	5.230	3.663	5.424	2.747	3.964	1.815	3.678	-2.297	.022*

[a] *z*-statistic for Wilcoxon Signed-Rank Test

Table 4.Comparisons across time within the secondary outcome measures (psychological)

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		Baseline				3-month follow-up				Comparisons	
				95% CI for Mean				95% CI for Mean			
		Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	*z* statistic	*p* value
MHLCS Internal	Psychology	.677	.159	.627	.726	.821	.251	.676	.966	-2.983	.003**
	Nutrition	.622	.177	.568	.675	1.193	2.969	.019	2.368	-.687	.492
	Combined	.662	.174	.613	.710	.779	.318	.662	.896	-1.755	.079
	Total	.653	.171	.624	.682	.942	1.822	.514	1.371	-2.962	.003**
MHLCS Chance	Psychology	.368	.156	.320	.417	.351	.152	.263	.439	-2.594	.009**
	Nutrition	.340	.133	.299	.380	.911	3.020	-.284	2.105	-.143	.886
	Combined	.354	.155	.311	.397	.314	.133	.265	.363	-.672	.501
	Total	.354	.148	.329	.379	.545	1.853	.109	.980	-1.552	.121
MHLCS Powerful Others	Psychology	.404	.134	.362	.446	.441	.315	.259	.624	.000	1.000
	Nutrition	.418	.141	.374	.460	.804	2.244	-.084	1.691	-1.843	.065
	Combined	.407	.101	.379	.436	.434	.279	.331	.536	-.577	.564
	Total	.409	.124	.388	.430	.574	1.3880	.248	.900	-1.601	.109
MHLCS Doctors	Psychology	.169	.082	.143	.194	.131	.093	.077	.185	-1.122	.262
	Nutrition	.171	.089	.144	.197	.657	2.668	-.398	1.713	-1.686	.092
	Combined	.191	.147	.150	.232	.153	.070	.128	.179	-1.384	.166
	Total	.178	.112	.159	.196	.338	1.635	-.0462	.722	-2.381	.017*
MHLCS Other People	Psychology	.235	.075	.212	.259	.268	.189	.159	.377	-.118	.906
	Nutrition	.264	.129	.225	.304	.739	2.652	-.311	1.788	-1.697	.090
	Combined	.245	.074	.224	.265	.252	.118	.209	.295	-.213	.831
	Total	.248	.095	.232	.264	.438	1.626	.055	.820	-1.186	.236
CDC CFS	Psychology	94.381	16.836	89.134	99.628	78.571	18.434	67.928	89.215	-3.111	.002**

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Maladaptive	Nutrition	96.386	21.946	89.714	103.059	85.259	27.665	74.315	96.203	-3.443	.001***
Stress Index	Combined	98.269	19.165	92.934	103.605	87.484	22.965	79.060	95.908	-2.215	.027*
Scale Score	Total	96.486	19.373	93.225	99.747	84.917	24.004	79.276	90.557	-5.123	.001***

[a]z-statistic for Wilcoxon Signed-Rank Test

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10-12*
Bias	9	Describe any efforts to address potential sources of bias	20-21
Study size	10	Explain how the study size was arrived at	13-14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	12-13
		(*c*) Explain how missing data were addressed	12
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	12 & 14

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14-15
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14 & Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	15-17
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2-9 (IQR)
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	19-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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