INTERVENTION STUDIES

Dietary and nutrition interventions for the therapeutic treatment of chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review

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Introduction

Chronic fatigue syndrome, also known as myalgic encephalomyelitis (CFS/ME), is a chronic, disabling illness characterised by unexplained persistent and debilitating fatigue, and this is accompanied by a diverse but consistent set of symptoms. CFS/ME has an unknown aetiology, as well as no known specific pathogenesis; therefore, there is no diagnostic pathology test. Rather, diagnosis is one of disease exclusion, and is made in accordance with symptom-specific criteria (¹,²). Prior to year 1994, many case definitions were used in research to aid in the diagnosis of this condition, thus limiting comparisons of published studies (³). The Fukuda (1994) criteria was established to overcome inconsistency in the application of case definitions, as well as to assist in defining a distinct group of cases (²), and is now the most frequently used case definition. To meet the Fukuda (²)
criteria, a patient must have debilitating unexplained fati-
gue present for at least 6 months that is not explained by
ongoing exertion or medical or psychiatric conditions,
and is not alleviated by rest. In addition, the fatigue must
be accompanied by four or more of the following symp-
toms: post-exertional malaise, difficulty with short-term
memory or concentration, unrefreshed sleep, sore throat,
muscle and/or joint pain, headaches, and tender lymph
nodes (2). A more recent, and alternative diagnostic crite-
rion for CFS/ME, is the International Consensus Criteria
(ICC) (1), which identifies distinct CFS/ME symptoms
associated with neurological, immunological, gastroin-
testinal and energy production impairments (1).

The current worldwide prevalence of CFS/ME is esti-
lated to be between 0.8% and 3.3% (4). In the USA in
2008, the treatment and management of CFS/ME was esti-
ated to cost US$319 million annually, with a direct cost
of US$7406 per patient (3). This syndrome is heterogeneous
in nature, with CFS/ME patients reporting different accom-
pnying symptoms, at different severities (1), frequency
(continuous or intermittent symptoms) and duration (6).
Many CFS/ME patients experience significant cognitive
and physical impairment and, consequently, a substantial
decline in social, occupational, educational and personal
activity (7). Thus, CFS/ME significantly affects and inter-
ferences with everyday life and patients relationships.

Many CFS/ME patients complain of gastrointestinal
symptoms, including but not limited to early satiety,
abdominal distension and/or pain, nausea, vomiting and
altered bowel habits (8,9). Additionally, irritable bowel syn-
drome (IBS) (8–11), a functional disorder of the gastrointesti-
nal tract, coeliac disease and food intolerance (e.g. wheat
and dairy) (9) are frequently observed in CFS/ME patients.

CFS/ME patients report a high use of nutritional supple-
tments (12,13) and approximately 50% of patients have
reported food intolerances (9–12) and benefit from dietary
modification (12). Therefore, dietary therapy, including diet
modification and/or provision of dietary supplements, may
be beneficial in alleviating symptoms and reducing fatigue in
CFS/ME. The present study aimed to systematically review
original research investigating nutrition interventions in the
symptom management of CFS/ME patients measured using
patient-centred outcomes including fatigue, quality of life,
physical activity and/or psychological wellbeing).

Materials and methods

Literature search
Three databases were utilised: Medline (EBSCOhost),
Cinahl (EBSCO) and Scopus. The following terms were
systematically searched as full-text and Medical Subject
Headings (MeSH) terms (Medline and Cinahl): syn-
drome, chronic fatigue (which includes chronic fatigue
syndrome and myalgic encephalomyelitis) and food, diet,
nutrition therapy, diet therapy, vitamins, minerals,
micronutrients, dietary supplements and/or nutritional
supplements. Search results were limited to English lan-
guage, publication date (year 1994–2016) and humans
(all databases except Scopus). A secondary search was
completed, whereby included studies and review articles
were reviewed for forward citations and to identify other
eligible studies. The final search was completed on 6 May
2016.

Inclusion and exclusion criteria

Studies that fulfilled the following criteria were eligible
for inclusion: (i) all studies that were intervention
research, defined as studies that evaluated the effective-
ness of food and/or nutritional supplement on outcome
measures; (ii) CFS/ME diagnosis according to Fukuda (2),
Canadian (2003) (14) or International Consensus Criteria
(ICC) (2011) (1); (iii) adults aged 18 years and over; (iv)
studies that had accessible full-text articles written in En-
lish; (v) year searched 1994 to present to exclude earlier
studies prior to 1994 Fukuda criteria (2,15); and (vi) stud-
ies comprising journal articles based on original research.
The primary outcome of interest for this review was fati-
gue. Secondary outcomes evaluated were quality of life,
physical activity and psychological wellbeing. Studies were
excluded if they explicitly combined CFS/ME with other
patient groups [e.g. CFS/ME and fibromyalgia (FMS)].
Although CFS/ME often co-occurs with FMS and other
disorders such as IBS (1), the co-occurrence of FMS was
excluded to understand the effect of nutrition interven-
tions on outcome measures specifically in CFS/ME. Stud-
ies that used multi-treatments (e.g. nutrition and
pharmaceutical treatment), duplicate studies, case reports/
studies or review articles and studies not meeting the
above inclusion criteria were also excluded.

Selection of studies

Titles and abstracts for each article were initially screened
on the basis of eligibility criteria. Two review authors
independently assessed full-text articles for suitability for
inclusion in this review, and study quality, followed by a
research meeting of all team members that confirm arti-
cles for inclusion in this review.

Data extraction and quality assessment

Eligible studies were read and the relevant data were
extracted (Tables 1–3) including: (i) study design; (ii)
CFS/ME case definition; (iii) country; (iv) sample size;
(v) age of participants (vi) sex, percentage of female
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Dx</th>
<th>Country</th>
<th>Sample (n)</th>
<th>Age (years), mean (SD)</th>
<th>Sex, female %</th>
<th>Illness duration, Mean (SD)</th>
<th>BMI (kg m⁻²), mean (SD)</th>
<th>Weight (kg), mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuda et al. (15)</td>
<td>RCT, PAR</td>
<td>F</td>
<td>Japan</td>
<td>17/14</td>
<td>34.8 (9.36)/39.5 (8.50)</td>
<td>76/86</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
</tr>
<tr>
<td>Fukuda et al. (15) (Pilot)</td>
<td>Cohort, OPT</td>
<td>F</td>
<td>Japan</td>
<td>20 –</td>
<td>36.8 (6.88) –</td>
<td>75 –</td>
<td>123 (64.2) –</td>
<td>NR –</td>
<td>NR –</td>
</tr>
<tr>
<td>Ostojic et al. (26)</td>
<td>RCT, CO</td>
<td>F</td>
<td>Serbia</td>
<td>21 –</td>
<td>39.3 (8.8) –</td>
<td>100 –</td>
<td>–</td>
<td>NR –</td>
<td>NR –</td>
</tr>
<tr>
<td>Castro-Marrero et al. (21)</td>
<td>RCT, PAR</td>
<td>F</td>
<td>Spain</td>
<td>39/34</td>
<td>NR/ NR</td>
<td>100/100</td>
<td>15.4 (8.9)/14.7 (6.2)</td>
<td>26.7 (5.2)/25.9 (2.4)</td>
<td>68.5 (14.6)/72.1 (13.7)</td>
</tr>
<tr>
<td>Witham et al. (24)</td>
<td>RCT, PAR</td>
<td>F, C</td>
<td>Scotland</td>
<td>25/25</td>
<td>48.1 (12.0)/50.7 (13.1)</td>
<td>72/80</td>
<td>NR/ NR</td>
<td>28.8 (7.9)/29.8 (5.4)</td>
<td>NR/ NR</td>
</tr>
<tr>
<td>Marić et al. (30)</td>
<td>Cohort, PRO</td>
<td>F</td>
<td>Serbia</td>
<td>38 –</td>
<td>NR –</td>
<td>100 –</td>
<td>NR –</td>
<td>NR –</td>
<td>NR –</td>
</tr>
<tr>
<td>Sathyapalan et al. (32)</td>
<td>RCP, CO</td>
<td>F</td>
<td>UK</td>
<td>10 –</td>
<td>52 (8) –</td>
<td>60 –</td>
<td>NR –</td>
<td>NR –</td>
<td>28.3 (2) –</td>
</tr>
<tr>
<td>Rao et al. (31)</td>
<td>RCP, PAR</td>
<td>Ca</td>
<td>Canada</td>
<td>19/16</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
</tr>
<tr>
<td>Hobday et al. (27)</td>
<td>CS, NC</td>
<td>F</td>
<td>UK</td>
<td>25/27</td>
<td>44 (10.2)/42.3 (11.9)</td>
<td>88/78</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
</tr>
<tr>
<td>The et al. (23)</td>
<td>RCT, PAR</td>
<td>F</td>
<td>NLD</td>
<td>30/27</td>
<td>40.9 (9.4)/43.4 (11.2)</td>
<td>77/59</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
</tr>
<tr>
<td>McDermott et al. (22)</td>
<td>RCT, PAR</td>
<td>F</td>
<td>UK</td>
<td>37/34</td>
<td>42 (15)/43 (12)</td>
<td>76/68</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
</tr>
<tr>
<td>Vermeulen et al. (29)</td>
<td>CS, NC</td>
<td>F</td>
<td>AMS</td>
<td>30/30</td>
<td>37 (11)/38 (11)</td>
<td>77/77</td>
<td>5.5 (1-23)<em>/6.0 (1-21)</em></td>
<td>3.0 (0.5-25)<em>/6.0 (1-21)</em></td>
<td>NR/ NR</td>
</tr>
<tr>
<td>Brouwers et al. (20)</td>
<td>RCT, PAR</td>
<td>F</td>
<td>NLD</td>
<td>27/26</td>
<td>40.0 (9.9)/38.9 (10.9)</td>
<td>74/65</td>
<td>8.0 (2-15)/4.5 (2-10)*</td>
<td>NR/ NR</td>
<td>NR/ NR</td>
</tr>
<tr>
<td>Ockerman et al. (25)</td>
<td>RCT, CO</td>
<td>F</td>
<td>Sweden</td>
<td>22 –</td>
<td>50 –</td>
<td>86 –</td>
<td>NR –</td>
<td>NR –</td>
<td>NR –</td>
</tr>
<tr>
<td>Plioplys et al. (29)</td>
<td>CS, NC, CO</td>
<td>F</td>
<td>USA</td>
<td>28 –</td>
<td>40 (18-67)* –</td>
<td>57 –</td>
<td>5.0 (1-20)* –</td>
<td>NR –</td>
<td>NR –</td>
</tr>
<tr>
<td>Forsyth et al. (8)</td>
<td>RCT, CO</td>
<td>F</td>
<td>USA</td>
<td>26 –</td>
<td>39.6 –</td>
<td>65 –</td>
<td>7.2 –</td>
<td>NR –</td>
<td>NR –</td>
</tr>
</tbody>
</table>

AM5: Amsterdam; BMI: body mass index; C: Canadian case definition; Ca: Carruthers clinical case definition; CO: cross-over design; Con: control group; CS: comparative study design; Dx: case definition for CFS/ME diagnosis; F: Fukuda (1994); NC: no comparative controls; NLD: Netherlands; NR: not reported; OPT: Open labelled pilot trial; PAR: parallel design; PRO: prospective design; RCP: randomised control pilot study; RCT: randomised control study; Tx: treatment group; –: not applicable.

*Median (range) in years.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration (weeks)</th>
<th>Washout period</th>
<th>Treatment intervention</th>
<th>Control intervention</th>
<th>Fatigue outcome</th>
<th>Fatigue result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuda et al. (15)</td>
<td>12</td>
<td>–</td>
<td>Ubiquinol-10 (150 mg day (^{-1}) post meal)</td>
<td>Placebo</td>
<td>Chalder Fatigue Scale</td>
<td>NS</td>
</tr>
<tr>
<td>Fukuda et al. (15) (Pilot)</td>
<td>8</td>
<td>–</td>
<td>Ubiquinol-10 (150 mg day (^{-1}) post meal)</td>
<td>–</td>
<td>Chalder Fatigue Scale</td>
<td>NS</td>
</tr>
<tr>
<td>Ostojic et al. (26)</td>
<td>3 months</td>
<td>2 months</td>
<td>GAA (2.4 g day (^{-1}))</td>
<td>Placebo (cellulose)</td>
<td>Multidimensional Fatigue Inventory</td>
<td>NS for general or physical fatigue subscales. Significantly different for mental fatigue, activity and motivation ((P &lt; 0.05))</td>
</tr>
<tr>
<td>Castro-Marrero et al. (20)</td>
<td>8</td>
<td>–</td>
<td>NADH (200 mg day (^{-1})) + CoQ(_{10}) (20 mg day (^{-1}))</td>
<td>Placebo</td>
<td>Fatigue Index Symptom Questionnaire (FIS-40)</td>
<td>Decreased ((P &lt; 0.05))</td>
</tr>
<tr>
<td>Witham et al. (24)</td>
<td>6 months</td>
<td>–</td>
<td>Vitamin D(_{3}) (100 000 units orally every 2 months)</td>
<td>Placebo</td>
<td>Piper Fatigue Scale</td>
<td>NS</td>
</tr>
<tr>
<td>Maric et al. (30)</td>
<td>2 months</td>
<td>–</td>
<td>Multivitamin mineral supplement (Supradyn(^{9}))</td>
<td>–</td>
<td>Fibro Fatigue Scale (FFS)</td>
<td>Unclear, inconsistent data reported for total FFS. Fatigue subscale significant ((P = 0.0009))</td>
</tr>
<tr>
<td>Sathyapalan et al. (32)</td>
<td>8</td>
<td>2 weeks</td>
<td>High cocoa liquor/ polyphenols rich chocolate (85% cocoa solids; 2.28 MJ/100 g; 15 g bar three times daily)</td>
<td>Cocoa liquor free/low polyphenols chocolate (2.29 MJ/100 g; 15 g bar three times daily)</td>
<td>Chalder Fatigue Scale</td>
<td>Decreased ((P = 0.01))</td>
</tr>
<tr>
<td>Sullivan et al. (33)</td>
<td>4</td>
<td>–</td>
<td>Probiotic bacteria (2 dl of Cultura Dofilus natural yogurt twice daily for 30 days. Lactobacillus F19, Lactobacillus acidophilus NCIB 1748 and Bifidobacterium lactis Bb12)</td>
<td>–</td>
<td>Visual analogue Scales for general, muscle and neurocognitive fatigue</td>
<td>NS for general fatigue. Improved neurocognitive function ((P = 0.040))</td>
</tr>
<tr>
<td>Rao et al. (31)</td>
<td>8</td>
<td>–</td>
<td>Probiotic bacteria (8 billion cfu of Lactobacillus casei, Shirata)</td>
<td>Placebo</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hobday et al. (27)</td>
<td>24</td>
<td>–</td>
<td>Low sugar low yeast diet + consult at baseline and 24 weeks + phone call monthly</td>
<td>Healthy eating diet(^{1}) + consult at baseline and 24 weeks + phone call monthly</td>
<td>Chalder Fatigue Scale</td>
<td>NS</td>
</tr>
<tr>
<td>The et al. (23)</td>
<td>14</td>
<td>–</td>
<td>Acclidine</td>
<td>Placebo</td>
<td>CIS-fatigue Daily Observed Fatigue</td>
<td>NS</td>
</tr>
<tr>
<td>McDermott et al. (22)</td>
<td>8</td>
<td>–</td>
<td>BioBran MGN-3 (6 g; 2 g three times per day dissolved in water or milk)</td>
<td>Placebo</td>
<td>Chalder Fatigue Scale</td>
<td>NS</td>
</tr>
<tr>
<td>Reference</td>
<td>Duration (weeks)*</td>
<td>Washout period</td>
<td>Treatment intervention</td>
<td>Control intervention</td>
<td>Fatigue outcome</td>
<td>Fatigue result</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Vermeulen et al.</td>
<td>24</td>
<td>–</td>
<td>Acetyl-L-carnitine (ALC) (2 g day⁻¹; post BF)</td>
<td>Propionyl-L-carnitine (PLC) (2 g day⁻¹; post BF) OR ALC + PLC (2 g ALC + 2 g PLC day⁻¹; post BF)</td>
<td>Multidimensional Fatigue Inventory</td>
<td>Within group analysis showed that ALC significantly improved mental fatigue (P = 0.015) PLC and ALC + PLC significantly improved general fatigue.</td>
</tr>
<tr>
<td>Brouwers et al.</td>
<td>10</td>
<td>–</td>
<td>Multinutritional supplement, twice daily</td>
<td>Placebo</td>
<td>CIS-fatigue</td>
<td>NS</td>
</tr>
<tr>
<td>Ockerman et al.</td>
<td>3 months</td>
<td>2 weeks</td>
<td>Pollen and pistil extract (Polbax) (7 x tablets in 1 dose at BF)</td>
<td>Placebo</td>
<td>Subjective Symptom</td>
<td>No between group analyses. Decrease in self-reported symptoms in treatment group</td>
</tr>
<tr>
<td>Plioplys et al.</td>
<td>8</td>
<td>2 weeks</td>
<td>L-carnitine (1 g three times daily)</td>
<td>Amantadine² (100 mg once daily (morning) for 4 weeks and then increased to 100 mg twice daily (morning and afternoon)</td>
<td>Fatigue Severity Scale</td>
<td>NS</td>
</tr>
<tr>
<td>Forsyth et al.</td>
<td>4</td>
<td>4 weeks</td>
<td>NADH (10 mg day⁻¹ with water, 45 min before BF, fasted)</td>
<td>Placebo</td>
<td>50 item questionnaire based on CDC criteria for CFS/ME</td>
<td>No between group comparisons. Within group analysis showed that 31% &amp; 8% of patients benefited from NADH versus PBO, respectively (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

BF, Breakfast; CDC, Centers for Disease Control and Prevention; CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis; CFU, colony-forming units; CIS-Fatigue, Checklist Individual Strength subscale fatigue severity; CoQ10, coenzyme Q10; GAA, guanidinoacetic acid; NADH, nicotinamide adenine dinucleotide hydride; NR, not reported; NS, not significant; PBO, placebo; VAS, Visual Analog Scale.

*Duration reported for cross-over trials is duration of each intervention, excluding washout period.

†Healthy eating diet as per Department of Health guidelines (COMA, 1991) for the general population.

‡Results are outside the scope of this systematic review.

^Washout period between crossover groups.
To evaluate study quality and bias, the Rosendal scale (16), which combines the PEDro scale (17), Jadad scoring system (18) and Delphi List (19), was utilised (see Supporting information, Table S1). Items 15 and 16 of the Rosendal scale were excluded because outcomes associated with exercise performance (e.g. VO₂ max) were not relevant to this review. Item 15 was replaced to include assessment of if an appropriate washout period was used for cross-over trials because of its relevance to nutrition interventions. A Rosendal score cut-off of 60% is classified as excellent methodological quality (16).

### Results

#### Overview of studies and study quality

Figure 1 shows the PRISMA flow diagram with the number of included and excluded studies. Seventeen studies were included in this systematic review of nutrition and psychological wellbeing, quality of life and physical activity level.
dietary interventions in CFS/ME patients. The included studies were six randomised control trial (RCT) parallel designs \cite{15,20-24}; three RCT cross-over designs where patients were their own control \cite{6,25,26}; three comparative studies without concurrent control (two- or three-arm parallel groups) \cite{27-29}; one prospective cohort study (before and after) \cite{30}; and four pilot studies \cite{15,31-33}. All RCT (parallel and cross-over) \cite{6,15,20-26} and two pilot

Figure 1 Flow diagram of database and secondary search for included studies in the review of nutrition intervention on chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) outcomes.
In total, 14 different interventions were evaluated. Studies varied in study quality, with the Rosendal score ranging from 10% to 86%. Eleven of the 17 studies (65% of included studies) had a Rosendal score of >60% (6,15,20–24,26–32) (see Supporting information, Table S1).

Participant characteristics of the included studies are summarised in Table 1. For the diagnosis of CFS/ME, 15 studies used the Fukuda (1994) case definition (6,15,20–23,25–30,32,33), one study used Carruthers (2003) (31) and one combined Fukuda (1994) and the Canadian Clinical Case Definition (24). Two studies also included participants with high fatigue severity measured with subjective fatigue subscale of the Checklist Individual Strength (CIS-fatigue ≥ 40) (20) and Chandler Fatigue Scale (score 10/11) (32). The mean sample size for each study was approximately 24 participants.

All studies, except two, reported fatigue as the primary outcome, and one study did not report fatigue at all (31). Of the 17 studies, five studies used the Chalder Fatigue Scale (15,22,27,32), three studies used an investigator designed symptom questionnaire (6,25,33), two studies used the Multidimensional Fatigue Inventory (26,28) and two studies used both the Checklist Individual Strength Fatigue Subscale and Daily Observed Fatigue (20,23). All other studies used either the Fatigue Index Symptom Questionnaire (FIS-40) (21), Fatigue Severity Scale (29), Fibro Fatigue Subscale and Daily Observed Fatigue (20,23). All other studies used either the Fatigue Index Symptom Questionnaire (FIS-40) (21), Fatigue Severity Scale (29), Fibro Fatigue Subscale and Daily Observed Fatigue (20,23). No trials reported a dietary intake method (diet record or food frequency questionnaires) for measurement at baseline or at the end of the study period to determine whether dietary changes occurred.

Interventions on fatigue

In total, 14 different interventions were evaluated (Table 2). All randomised control trials, including pilot studies, compared a form of nutritional supplement with a placebo control (6,15,20–26,31). One RCT compared the combined effect of nicotinamide adenine dinucleotide hydride (NADH) and coenzyme Q10 (CoQ10) with a placebo, and found a significant reduction of fatigue after 8 weeks of treatment compared to placebo (P < 0.05) (21). Another RCT observed a significant decrease in mental fatigue after guanidinoacetic acid (GAA) supplementation compared to a placebo (26). One RCT tested the effect of pollen and pistil extract and a placebo after 3 months of supplementation on fatigue (25). In the treatment group, a significant decrease in self-reported symptoms was observed, whereas no significant difference was observed for the placebo group from baseline (25). A randomised control pilot study reported a significant decrease in self-reported fatigue after participants consumed high cocoa liquor (polyphenol rich chocolate) compared to iso-caloric chocolate for 8 weeks (P = 0.01) (32). Other RCT either observed no significant difference between the nutrition intervention and placebo control (15,20,22–24) or did not report between group analysis (6,25).

One cohort study observed significant improvement in neurocognitive fatigue (P = 0.040) but not in general fatigue after probiotic bacteria supplementation (33). All other studies reported no difference either compared to a comparative intervention (27) or after the intervention (15,29,30).

Interventions on secondary outcomes

Of the 17 studies, 14 studies evaluated the effect of the nutrition intervention on either quality of life (n = 10) (20,22,23,26–30,32,33), physical activity (n = 3) (20,23,26) and/or psychological wellbeing (n = 8) (15,22,24,27,29,31,32) (Table 3). Three studies observed improvement in psychological wellbeing (29,31,32). One RCT study observed decrease in anxiety but not depression following probiotic supplementation (31). Two comparative studies reported significant improvement in both anxiety and depression after consumption of polyphenol rich chocolate (32) and L-carnitine (29) compared to baseline. Consumption of L-carnitine also improved five other psychometric tests (29). Two RCT observed significant difference in quality of life for supplementation of BioBranTM MGN-3 (Daiva Pharmaceutical, Tokyo, Japan) (social wellbeing subscale only) (22) and guanidinoacetic acid (26). Two comparative studies reported improvement in quality of life after supplementation of acetyl-L-carnitine and propionyl-L-carnitine (28), as well as L-carnitine (29). No studies reported improvement in physical activity level; however, one study reported significant improvement in quadriceps isometric strength and VO2 max after 3 months of supplementation of guanidinoacetic acid in patients compared with controls (26). All other studies observed no difference of the nutrition intervention on any of the secondary outcomes (15,20,23,27,30,33).

Discussion

Elimination diets, dietary restriction and the addition of nutritional supplements to habitual diet are widely reported to be used by CFS/ME patients, and many individuals claim beneficial effects of these dietary interventions in reducing fatigue (12). This systematic review has summarised the available evidence on dietary and nutritional interventions in CFS/ME on patient outcomes, including fatigue, quality of life, psychological wellbeing and physical activity level. Additionally, this review has
updated the literature search according to scientific accepted diagnostic criteria (34). Our study highlights methodological limitations in the evidence and an overall lack of evidence that explores the therapeutic effect of diet and nutritional supplementation in CFS/ME.

Participant and study characteristics

Participants in this review were predominantly female, with a mean age of 35–50 years, residing in Europe. This finding is relatively consistent with epidemiological studies that report a higher prevalence of CFS/ME in females (7,9,35) and individuals aged 35 and 45 years (7,9). However, this sex imbalance may be a consequence of studies recruiting participants from clinics or universities, and men being less likely to engage in help seeking behaviour from a healthcare professional (9).

The majority of studies in this review exclusively used the Fukuda (1994) case definition (2). A common criticisms of this case definition include a combination of broad nonspecific symptoms (1,36), thus being less likely to identify a homogeneous patient population (1,36). This may have contributed to a lack of sensitivity of the studies in this review to detect a beneficial effect of the nutritional treatment. Therefore, it is recommended that future research should employ more specific CFS/ME criteria to classify subgroups with similar symptoms and/or severity to identify those patients who may benefit from therapeutic nutrition treatment and counselling.

A variety of instruments, some validated and nonvalidated, were used to evaluate outcome measures in the included studies, thus highlighting a lack of agreement in the best instrument to measure improvement in CFS/ME symptoms, and limiting future comparisons between current and future studies. Therefore, to improve future intervention research, patient outcomes (e.g. fatigue, quality of life) need to be consistently measured using a single validated instrument for each outcome.

Additionally, many of the studies procedures indirectly excluded CFS/ME patients who were house and/or bed bound (i.e. severely affected patients) as a result of their inability to attend a clinic, hospital or university for screening and/or follow-up. Consequently, sampling bias is likely confounding results, and limits the results to CFS/ME patients with a mild severity of symptoms who have the ability to leave their home. Therefore, future research needs to consider the fluctuating nature and different severities of CFS/ME and thus design flexible protocols that are delivered in a variety of settings (e.g. in clinic or patient’s homes) over the telephone or via the post. This will distinguish the effect of different dietary therapies, and identify whether patients with different severity of symptoms respond differently to the intervention.

Nutrition interventions

The aetiology of CFS/ME remains unclear; however, research suggests that this heterogeneous condition is likely a multisystem disorder involving the immune, gastrointestinal, neurological and metabolic systems (1). A majority of the studies in this review investigated the effect of nutritional supplementation to initiate and promote ATP production with respect to reducing patient fatigue and cognitive dysfunction (6,15,21,29). NADH alone (6) and in combination with CoQ10 (21) was observed to reduce fatigue in CFS/ME patients. Despite beneficial effects being observed, neither study reported a dietary intake method at baseline or at conclusion of the study to determine whether dietary changes occurred and potentially influenced the results. Furthermore, both studies are limited by small sample sizes and the duration of therapeutic treatment (4 and 8 weeks, respectively). Therefore, longitudinal studies with larger sample sizes are needed to determine whether NADH with and without CoQ10 has a prolonged therapeutic effect on CFS/ME patients. Furthermore, the study by Forsyth et al. (6) is also limited by the use of an investigator-developed questionnaire to measure symptom outcomes. Despite reproducibility testing being completed, it remains unclear whether this questionnaire was able to identify CFS/ME symptoms. It is recommended that future research uses validated instruments to enable confidence when interpreting results, and to allow comparison between studies.

Ubiquinol-10 (also known as coenzyme Q10) is an important nutrient for cellular energy production and for its antioxidant function (37). Reduced levels of CoQ10 have been reported in CFS/ME patients compared to healthy controls (38). Only one RCT has investigated supplementation of Ubiquinol-10 for 12 week in CFS/ME patients (15). Despite no improvement in fatigue, measured with Chandler’s Fatigue Scale, Ubiquinol-10 supplementation improved several other CFS/ME symptoms (e.g. night-time awakenings), which may have a longer-term effect on reducing fatigue in CFS/ME patients. To evaluate and demonstrate the benefits of ubiquinol-10 supplementation, longer-term controlled studies are needed.

Cocoa and dark chocolate consumption are known to have a number of positive health effect on chronic diseases (39–41). This review has identified one randomised control cross-over study that investigated the therapeutic effect of cocoa with respect to decreasing fatigue and improving residual functions, as accessed by the London Handicap Scale, compared to when patients consumed an iso-caloric low polyphenol chocolate in CFS/ME patients (32). Despite this positive result, the study is
limited by the small sample size \((n = 10)\), treatment duration, and a lack of information on dietary habits and intake during the trial. Thus, it is unclear whether energy intake and the micro- and macronutrient composition of the diet influenced the result. Furthermore, long-term observational prospective research and well-designed RCTs are needed to confirm the clinical effects of cocoa in CFS/ME patients, as well as to understand the mechanism of different types of chocolate in this patient population.

Altered intestinal microbiota may contribute to pathogenesis of CFS/ME \((42-44)\). It has been postulated that the administration of probiotics may have therapeutic value in CFS/ME patients by decreasing pro-inflammatory cytokines and improving gut microbiota and mucosal barrier function \((45)\). This review identified two pilot studies each investigating different outcomes. These studies suggest that probiotic bacteria may improve neurocognitive function \((33)\) and anxiety \((31)\). Furthermore, Sullivan et al. \((33)\) observed individual differences regarding improvement in fatigue and physical activity, with patients reporting improvement in one or both areas. This provides further support for stratifying subgroups of CFS/ME patients likely to respond to a therapeutic nutrition treatment. As a result of the individual and preliminary benefits observed in these studies, the future research of probiotics is warranted in a larger homogeneous population.

Previous research suggests that oxidative stress results in CFS/ME patients as a result of diminished antioxidant capacity and/or reduced antioxidant enzymes activity \((1,46)\). The therapeutic treatment with antioxidants in CFS/ME is limited \((20,25,30)\). The studies identified in the present review suggest that the provision of pollen extract may improve CFS/ME symptoms and patients overall wellbeing \((25)\). However, no therapeutic benefits were observed in CFS/ME patients after multinutritional supplementation \((20,30)\). The results reported by Ockerman \((25)\) are limited by a small sample size \((n = 22)\) and an improvement in certain self-reported symptoms; thus, the reliability of results remains unclear.

CFS/ME is a complex condition with many symptoms, some of which may be related to the food and beverages consumed. This review identified only one study that evaluated an elimination diet in response to food sensitivities \((27)\). Therefore, future research may consider eliminating potential trigger foods in CFS/ME \((e.g. \text{alcohol, caffeine, fat, milk and dairy, gluten})\), followed by challenges to identify potential problem foods.

Quality assessment

Many of the studies included in this review were of high quality \((\text{Rosendal score} > 60\%; \text{Table S1})\), despite not reporting all methods \((e.g. \text{method of blinding, pre-trial conditions and method for assessing adverse effects})\). Those studies that received poorer quality scores were pilot or cohort or comparative studies and/or lacked full details of the methods. Future research should describe pretrial conditions and the method for evaluating blinding and accessing adverse effects, as well as the method of dietary assessment at baseline and at the trial conclusion.

Conclusions

Nutrition interventions may be used, in some chronic diseases \((e.g. \text{diabetes, cardiovascular disease, obesity})\), to manage or to minimise the progression of these conditions. Therefore, it is reasonable to suggest that nutrition interventions may also improve patient outcomes, such as fatigue and quality of life, in CFS/ME patients. The conclusion of this review supports the current guidelines in that there is insufficient evidence for the use of nutritional supplements and elimination and modified diets with respect to relieving CFS/ME symptoms \((47)\). Therefore, the general prescription of supplements and long-term elimination diets is not recommended. Rather, recommendations are to eat a balanced diet and a variety of nutritious foods from the basic food groups \((47)\) in accordance with the dietary guidelines for healthy people. However, supplementations may be considered as indicated \((47)\); for example, where CFS/ME patients have diagnoses of irritable bowel syndrome, lactose or gluten intolerance or coeliac disease; or have suspected inadequate nutrient intake; or in cases where nutrient deficiencies are identified via pathology tests.

Studies investigating nutritional interventions in CFS/ME remain very limited, with most interventions being evaluated in a single study. Furthermore, the present review emphasise that the interventions investigated have only been conducted in small sample sizes, and also lacked long-term follow-up \((>6 \text{ months})\). Despite relative consistency in case definition, the studies differed with regard to inclusion and exclusion criteria and the reporting of participant characteristics \((e.g. \text{illness duration, BMI, weight})\). This heterogeneity in study design presents challenges when aiming to apply findings in the clinical environment. Therefore, longer-term randomised control trials in homogeneous populations that use more specific criteria are warranted.

Common comorbidities in CFS/ME include FMS and IBS \((1)\). The results of the present study are directly related to CFS/ME only because it did not assess effects on specific comorbid groups. Nutrition interventions targeted toward alleviating symptoms of FMS and IBS, for example, may also reduce the overall functional impact of CFS/ME. Hence, this is an important consideration for
future research to inform the dietetic practice, given the high prevalence of comorbidities among CFS/ME patients.

Dietary assessment methods and analysis were not described in any of the studies in the present review. Therefore, dietary variables, other than those being examined, may have confounded the results. The method of dietary assessment for future studies may be derived from a checklist devised by Nelson et al. to adequately describe robust methodological approaches.

Furthermore, to control for dietary variables, it is recommended that future research: (i) assess the intervention for energy and nutrient content and (ii) assess habitual diet at baseline and study conclusion, as well as randomly throughout the trial. This will monitor compliance and minimise diet as a confounding factor in the interpretation of the results. Similarly, to control for physical activity, future research should also consider the use of wearable technology to monitor physical activity levels for the duration of the study.

From a clinical perspective, case studies derived from research with accredited dietitians may also provide additional evidence of benefits to specific cases of CFS/ME, as well as support patients with the dietary regime and fluctuating nature of CFS/ME symptoms.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained. The reporting of this work is compliant with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

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NC designed the study and search strategy, and also performed primary and secondary searches, title and abstract screening, full-text screening, analysis, quality assessment, and wrote the draft and final manuscript. SJ provided consultation on the study design and data collection and critically reviewed the draft and final manuscript. AC performed the full-text screening and quality assessment, and also contributed to the final manuscript. DS supervised the study design and critically reviewed and contributed to the final manuscript. SMG supervised the study design and analysis and critically reviewed the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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**Supporting information**

Additional Supporting Information may be found online in the supporting information tab for this article: Table S1. Methodology quality assessment summary and Rosendal score of studies included in the present systematic review.