

## INTERVENTION STUDIES

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

N. Campagnolo,<sup>1,2</sup> S. Johnston,<sup>1,2</sup> A. Collatz,<sup>1,2</sup> D. Staines<sup>2</sup> & S. Marshall-Gradisnik<sup>1,2</sup>

<sup>1</sup>School of Medical Science, Griffith University, Gold Coast, QLD, Australia

<sup>2</sup>National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute Queensland, Griffith University, Gold Coast, QLD, Australia

### Keywords

diet therapy, public health, supplements, systematic review, vitamins.

### Correspondence

N. Campagnolo, National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute Queensland, School of Medical Science, Griffith Health Centre (G40), 9.21, Griffith University, Gold Coast, Queensland 4222, Australia.

Tel: +61 (7) 5678 9283

E-mail: nadia.campagnolo@griffithuni.edu.au

### How to cite this article

Campagnolo N., Johnston S., Collatz A., Staines D., & Marshall-Gradisnik S. (2017) Dietary and nutrition interventions for the therapeutic treatment of chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. *J Hum Nutr Diet.* **30**, 247–259  
doi: 10.1111/jhn.12435

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

### 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,

### Abstract

**Background:** Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is characterised by unexplained fatigue for at least 6 months accompanied by a diverse but consistent set of symptoms. Diet modification and nutritional supplements could be used to improve patient outcomes, such as fatigue and quality of life. We reviewed and discussed the evidence for nutritional interventions that may assist in alleviating symptoms of CFS/ME.

**Methods:** Medline, Cinahl and Scopus were systematically searched from 1994 to May 2016. All studies on nutrition intervention were included where CFS/ME patients modified their diet or supplemented their habitual diet on patient-centred outcomes (fatigue, quality of life, physical activity and/or psychological wellbeing).

**Results:** Seventeen studies were included that meet the inclusion criteria. Of these, 14 different interventions were investigated on study outcomes. Many studies did not show therapeutic benefit on CFS/ME. Improvements in fatigue were observed for nicotinamide adenine dinucleotide hydride (NADH), probiotics, high cocoa polyphenol rich chocolate, and a combination of NADH and coenzyme Q10.

**Conclusions:** This review identified insufficient evidence for the use of nutritional supplements and elimination or modified diets to relieve CFS/ME symptoms. Studies were limited by the number of studies investigating the interventions, small sample sizes, study duration, variety of instruments used, and studies not reporting dietary intake method. Further research is warranted in homogeneous CFS/ME populations.

diagnosis is one of disease exclusion, and is made in accordance with symptom-specific criteria<sup>(1,2)</sup>. 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<sup>(3)</sup>. 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<sup>(2)</sup>, and is now the most frequently used case definition. To meet the Fukuda<sup>(2)</sup>

criteria, a patient must have debilitating unexplained fatigue 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 symptoms: post-exertional malaise, difficulty with short-term memory or concentration, unrefreshed sleep, sore throat, muscle and/or joint pain, headaches, and tender lymph nodes<sup>(2)</sup>. A more recent, and alternative diagnostic criteria for CFS/ME, is the International Consensus Criteria (ICC)<sup>(1)</sup>, which identifies distinct CFS/ME symptoms associated with neurological, immunological, gastrointestinal and energy production impairments<sup>(1)</sup>.

The current worldwide prevalence of CFS/ME is estimated to be between 0.8% and 3.3%<sup>(4)</sup>. In the USA in 2008, the treatment and management of CFS/ME was estimated to cost US\$319 million annually, with a direct cost of US\$7406 per patient<sup>(5)</sup>. This syndrome is heterogeneous in nature, with CFS/ME patients reporting different accompanying symptoms, at different severities<sup>(1)</sup>, frequency (continuous or intermittent symptoms) and duration<sup>(6)</sup>. Many CFS/ME patients experience significant cognitive and physical impairment and, consequently, a substantial decline in social, occupational, educational and personal activity<sup>(7)</sup>. Thus, CFS/ME significantly affects and interferes 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<sup>(8,9)</sup>. Additionally, irritable bowel syndrome (IBS)<sup>(8–11)</sup>, a functional disorder of the gastrointestinal tract, coeliac disease and food intolerance (e.g. wheat and dairy)<sup>(9)</sup> are frequently observed in CFS/ME patients.

CFS/ME patients report a high use of nutritional supplements<sup>(12,13)</sup> and approximately 50% of patients have reported food intolerances<sup>(9–12)</sup> and benefit from dietary modification<sup>(12)</sup>. 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): syndrome, 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 language, 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 effectiveness of food and/or nutritional supplement on outcome measures; (ii) CFS/ME diagnosis according to Fukuda<sup>(2)</sup>, Canadian (2003)<sup>(14)</sup> or International Consensus Criteria (ICC) (2011)<sup>(1)</sup>; (iii) adults aged 18 years and over; (iv) studies that had accessible full-text articles written in English; (v) year searched 1994 to present to exclude earlier studies prior to 1994 Fukuda criteria<sup>(2,15)</sup>; and (vi) studies comprising journal articles based on original research. The primary outcome of interest for this review was fatigue. 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<sup>(1)</sup>, the co-occurrence of FMS was excluded to understand the effect of nutrition interventions on outcome measures specifically in CFS/ME. Studies 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 articles 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 1** Summary of participant and study characteristics of the included studies

Reference	Study design	Dx	Country	Sample (n)		Age (years), mean (SD)		Sex, female %		Illness duration, Mean (SD)		BMI (kg m <sup>-2</sup> ), mean (SD)		Weight (kg), mean (SD)	
				Tx	Con	Tx	Con	Tx	Con	Tx	Con	Tx	Con	Tx	Con
Fukuda <i>et al.</i> <sup>(15)</sup>	RCT, PAR	F	Japan	17	14	34.8 (9.36)	39.5 (8.50)	76	86	NR	NR	NR	NR	NR	NR
Fukuda <i>et al.</i> <sup>(15)</sup> (Pilot)	Cohort, OPT	F	Japan	20	–	36.8 (6.88)	–	75	–	123 (64.2)	–	NR	–	NR	–
Ostojic <i>et al.</i> <sup>(26)</sup>	RCT, CO	F	Serbia	21	–	39.3 (8.8)	–	100	–	–	–	NR	NR	62.8 (8.5)	–
Castro-Marrero <i>et al.</i> <sup>(21)</sup>	RCT, PAR	F	Spain	39	34	NR	NR	100	100	15.4 (8.9)	14.7 (6.2)	26.7 (5.2)	25.9 (2.4)	68.5 (14.6)	72.1 (13.7)
Witham <i>et al.</i> <sup>(24)</sup>	RCT, PAR	F, C	Scotland	25	25	48.1 (12.0)	50.7 (13.1)	72	80	NR	NR	28.8 (7.9)	29.8 (5.4)	NR	NR
Maric <i>et al.</i> <sup>(30)</sup>	Cohort, PRO	F	Serbia	38	–	NR	–	100	–	NR	–	NR	–	NR	–
Sathyapalan <i>et al.</i> <sup>(32)</sup>	RCP, CO	F	UK	10	–	52 (8)	–	60	–	NR	–	28.3 (2)	–	NR	–
Sullivan <i>et al.</i> <sup>(33)</sup>	Cohort, OPT	F	Sweden	15	–	43	–	67	–	NR	–	NR	–	NR	–
Rao <i>et al.</i> <sup>(31)</sup>	RCP, PAR	Ca	Canada	19	16	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hobday <i>et al.</i> <sup>(27)</sup>	CS, NC	F	UK	25	27	44 (10.2)	42.3 (11.9)	88	78	NR	NR	NR	NR	NR	NR
The <i>et al.</i> <sup>(23)</sup>	RCT, PAR	F	NLD	30	27	40.9 (9.4)	43.4 (11.2)	77	59	NR	NR	NR	NR	NR	NR
McDermott <i>et al.</i> <sup>(22)</sup>	RCT, PAR	F	UK	37	34	42 (15)	43 (12)	76	68	NR	NR	NR	NR	NR	NR
Vermeulen <i>et al.</i> <sup>(28)</sup>	CS, NC	F	AMS	30	30	37 (11)	38 (11)	77	77	5.5 (1–23)*	3.0 (0.5–25)*	NR	NR	NR	NR
				30	30	42 (12)	42 (12)	77	77	6.0 (1.0–21)*	6.0 (1.0–21)*	NR	NR	NR	NR
Brouwers <i>et al.</i> <sup>(20)</sup>	RCT, PAR	F	NLD	27	26	40.0 (9.9)	38.9 (10.9)	74	65	8.0 (2–15)*	4.5 (2–10)*	NR	NR	NR	NR
Ockerman <i>et al.</i> <sup>(25)</sup>	RCT, CO	F	Sweden	22	–	50	–	86	–	NR	–	NR	–	NR	–
Plioplys <i>et al.</i> <sup>(29)</sup>	CS, NC, CO	F	USA	28	–	40 (18–67)*	–	57	–	5.0 (1–20)*	–	NR	–	NR	–
Forsyth <i>et al.</i> <sup>(6)</sup>	RCT, CO	F	USA	26	–	39.6	–	65	–	7.2	–	NR	–	NR	–

AMS, Amsterdam; BMI, body mass index; C, Canadian case definition <sup>(14)</sup>; 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)<sup>(2)</sup>; 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 2** Study intervention characteristic and results for the primary outcome of fatigue

Reference	Duration (weeks)*	Washout period <sup>†</sup>	Treatment intervention	Control intervention	Fatigue outcome	Fatigue result
Fukuda <i>et al.</i> (15)	12	–	Ubiquinol-10 (150 mg day <sup>-1</sup> post meal)	Placebo	Chalder Fatigue Scale	NS
Fukuda <i>et al.</i> (15) (Pilot)	8	–	Ubiquinol-10 (150 mg day <sup>-1</sup> post meal)	–	Chalder Fatigue Scale	NS
Ostojic <i>et al.</i> (26)	3 months	2 months	GAA (2.4 g day <sup>-1</sup> )	Placebo (cellulose)	Multidimensional Fatigue Inventory	NS for general or physical fatigue subscales. Significantly different for mental fatigue, activity and motivation ( $P < 0.05$ ). Decreased ( $P < 0.05$ )
Castro-Marrero <i>et al.</i> (21)	8	–	NADH (200 mg day <sup>-1</sup> ) + CoQ <sub>10</sub> (20 mg day <sup>-1</sup> )	Placebo	Fatigue Index Symptom Questionnaire (FIS-40)	Decreased ( $P = 0.0009$ )
Witham <i>et al.</i> (24)	6 months	–	Vitamin D <sub>3</sub> (100 000 units orally every 2 months)	Placebo	Piper Fatigue Scale	NS
Maric <i>et al.</i> (30)	2 months	–	Multivitamin mineral supplement (Supradyn®)	–	Fibro Fatigue Scale (FFS)	Unclear, inconsistent data reported for total FFS. Fatigue subscale significant ( $P = 0.0009$ ) Decreased ( $P = 0.01$ )
Sathyapalan <i>et al.</i> (32)	8	2 weeks	High cocoa liquor/ polyphenols rich chocolate (85% cocoa solids; 2.28 MJ/100 g; 15 g bar three times daily)	Cocoa liquor free/low polyphenols chocolate (2.29 MJ/100 g; 15 g bar three times daily)	Chalder Fatigue Scale	Decreased ( $P = 0.01$ )
Sullivan <i>et al.</i> (33)	4	–	Probiotic bacteria (2 dl. of Cultura Dofilus natural yogurt twice daily for 30 days. <i>Lactobacillus</i> F19, <i>Lactobacillus acidophilus</i> NCFB 1748 and <i>Bifidobacterium lactis</i> Bb12)	–	Visual analogue Scales for general, muscle and neurocognitive fatigue	NS for general fatigue. Improved neurocognitive function ( $P = 0.040$ )
Rao <i>et al.</i> (31)	8	–	Probiotic bacteria (8 billion cfu of <i>Lactobacillus casei</i> , <i>Shirota</i> )	Placebo	NR	NR
Hobday <i>et al.</i> (27)	24	–	Low sugar low yeast diet + consult at baseline and 24 weeks + phone call monthly	Healthy eating diet <sup>†</sup> + consult at baseline and 24 weeks + phone call monthly	Chalder Fatigue Scale	NS
The <i>et al.</i> (23)	14	–	Aclydline	Placebo	CIS-fatigue Daily Observed Fatigue	NS
McDermott <i>et al.</i> (22)	8	–	BioBran MGN-3 (6 g; 2 g three times per day dissolved in water or milk)	Placebo	Chalder Fatigue Scale	NS

Table 2. Continued

Reference	Duration (weeks)*	Washout period <sup>†</sup>	Treatment intervention	Control intervention	Fatigue outcome	Fatigue result
Vermeulen <i>et al.</i> <sup>(28)</sup>	24	–	Acetyl-L-carnitine (ALC) (2 g day <sup>-1</sup> ; post BF)	Propionyl-L-carnitine (PLC) (2 g day <sup>-1</sup> ; post BF) OR ALC + PLC (2 g ALC + 2 g PLC day <sup>-1</sup> ; post BF)	Multidimensional Fatigue Inventory	Within group analysis showed that ALC significantly improved mental fatigue ( $P = 0.015$ ) PLC and ALC + PLC significantly improved general fatigue.
Brouwers <i>et al.</i> <sup>(20)</sup>	10	–	Multinutritional supplement, twice daily	Placebo	CIS-fatigue Daily Observed Fatigue	NS
Ockerman <i>et al.</i> <sup>(25)</sup>	3 months	2 weeks	Pollen and pistil extract (Polbax) (7 × tablets in 1 dose at BF)	Placebo	Subjective Symptom	No between group analyses. Decrease in self-reported symptoms in treatment group
Pliophlys <i>et al.</i> <sup>(29)</sup>	8	2 weeks	L-carnitine (1 g three times daily)	Amantadine <sup>‡</sup> (100 mg once daily (morning) for 4 weeks and then increased to 100 mg twice daily (morning and afternoon))	Fatigue Severity Scale	NS
Forsyth <i>et al.</i> <sup>(6)</sup>	4	4 weeks	NADH (10 mg day <sup>-1</sup> with water, 45 min before BF, fasted)	Placebo	50 item questionnaire based on CDC criteria for CFS/ME	No between group comparisons. Within group analysis showed that 31% & 8% of patients benefited from NADH versus PBO, respectively ( $P < 0.05$ )

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.

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

<sup>‡</sup>Results are outside the scope of this systematic review.

<sup>§</sup>Washout period between crossover groups.

**Table 3** Secondary outcome measure of psychological wellbeing, quality of life and physical activity level

Reference	Secondary outcome measure(s)	Results
<b>Psychological wellbeing</b>		
Fukuda <i>et al.</i> <sup>(15)</sup>	CES-D	NS
Fukuda <i>et al.</i> <sup>(15)</sup> (Pilot)	CES-D	NS
		Improvement in depressive symptoms was dependant on increase in total plasma CoQ10 levels
Witham <i>et al.</i> <sup>(24)</sup>	HADS	NS
Sathyapalan <i>et al.</i> <sup>(32)</sup>	HADS	Significant decrease in anxiety and depression ( $P = 0.01$ )
Rao <i>et al.</i> <sup>(31)</sup>	Beck Depression Inventory	NS
	Beck Anxiety Inventory	Significant decrease in anxiety symptoms ( $P = 0.01$ )
Hobday <i>et al.</i> <sup>(27)</sup>	HADS	NS
McDermott <i>et al.</i> <sup>(22)</sup>	HADS	NS
Plioplys <i>et al.</i> <sup>(29)</sup>	Beck Depression Inventory	Significant decrease in depression at 8 weeks ( $P = 0.22$ )
	Symptom Checklist 90-R	Significant decrease in somatisation ( $P = 0.012$ ), obsessive-compulsive ( $P = 0.036$ ), anxiety ( $P = 0.006$ ) and depression ( $P = 0.006$ ) subscale; and all summary scales including GSI ( $P = 0.007$ ), PSDI ( $P = 0.000$ ) and PSTI ( $P = 0.038$ ) at 8 weeks
<b>Quality of life</b>		
Ostojic <i>et al.</i> <sup>(26)</sup>	SF-36	Significant improvement in physical ( $P = 0.04$ ) and mental common scores ( $P = 0.00$ )
Maric <i>et al.</i> <sup>(30)</sup>	SF-36	NS
Sathyapalan <i>et al.</i> <sup>(32)</sup>	London Handicap Scale	Significant increase in residual function ( $P = 0.01$ )
Sullivan <i>et al.</i> <sup>(33)</sup>	SF-12 Health Survey	NS
Hobday <i>et al.</i> <sup>(27)</sup>	MOS SF-36	NS
The <i>et al.</i> <sup>(23)</sup>	SIP-8 score	NS
McDermott <i>et al.</i> <sup>(22)</sup>	WHO QOL-BREF	Social wellbeing subscale only ( $P = 0.02$ )
Vermeulen <i>et al.</i> <sup>(28)</sup>	CGI	Within group analysis showed improvement in ALC and PLC but not ALC + PLC
Brouwers <i>et al.</i> <sup>(20)</sup>	CDC symptom checklist	NS
	SIP-8 score	NS
Plioplys <i>et al.</i> <sup>(29)</sup>	CFS Impairment Index	Within group analysis showed significant improvement in total function ( $P = 0.001$ ) and physical ( $P = 0.000$ ) and mental ( $P = 0.038$ ) subsets at 8 weeks
	CFS Severity Index	Significant improvement in function ( $P = 0.031$ )
<b>Physical activity level</b>		
Ostojic <i>et al.</i> <sup>(26)</sup>	Actigraphic assessment	NS
	Energy expenditure, duration and intensity	NS
The <i>et al.</i> <sup>(23)</sup>	Actigraphic assessment	NS
Brouwers <i>et al.</i> <sup>(20)</sup>	Actigraphic assessment	NS

CDC, Centers for Disease Control and Prevention; CES-D, Centre for Epidemiologic Studies Depression Scale; CGI, Clinical Global Impression of Change; CoQ10, coenzyme Q10; GSI, Global Severity Index; HADS, Hospital Anxiety and Depression Score; LHS, London Handicap Scale; MOS SF-36, Medical Outcomes Survey Short Form; NS, no significant difference; PA, physical activity; PSDI, Positive Symptom Distress Index; PSTI, Positive Symptom Total Index; SF-36, Quality of Life Scale; SIP-8, Sickness Impact Scale.

participants; (vii) illness duration; (viii) body mass index; (ix) weight; intervention duration; washout period between trials; (x) nutrition intervention(s) being investigated; (xi) name of instrument to evaluate study outcomes; and (xii) result of intervention and level statistical significance.

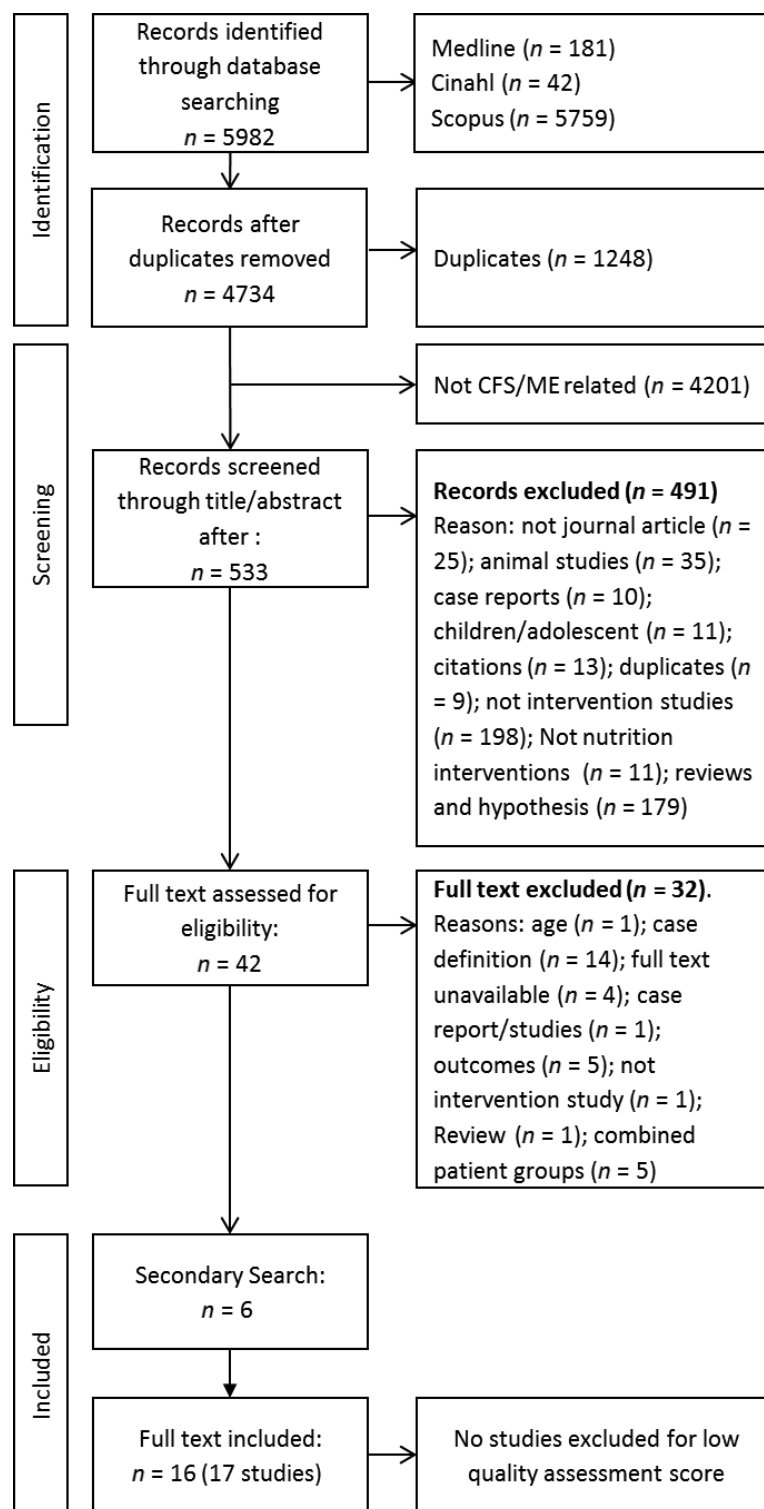
To evaluate study quality and bias, the Rosendal scale <sup>(16)</sup>, which combines the PEDro scale <sup>(17)</sup>, Jadad scoring system <sup>(18)</sup> and Delphi List <sup>(19)</sup>, was utilised (see Supporting information, Table S1). Items 15 and 16 of the Rosendal scale were excluded because outcomes associated with exercise performance (e.g.  $VO_2 \text{ max}$ ) were not

relevant to this review. Item 15 was replaced to included 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 <sup>(16)</sup>.

## 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



**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.

dietary interventions in CFS/ME patients. The included studies were six randomised control trial (RCT) parallel designs<sup>(15,20–24)</sup>; three RCT cross-over designs where patients were their own control<sup>(6,25,26)</sup>; three comparative

studies without concurrent control (two- or three-arm parallel groups)<sup>(27–29)</sup>; one prospective cohort study (before and after)<sup>(30)</sup>; and four pilot studies<sup>(15,31–33)</sup>. All RCT (parallel and cross-over)<sup>(6,15,20–26)</sup> and two pilot

studies<sup>(31,32)</sup> reported using a double-blind design. 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%<sup>(6,15,20–24,26–28,32)</sup> (see Supporting information, Table S1).

### Participant and study characteristics

The 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<sup>(6,15,20–23,25–30,32,33)</sup>, one study used Carruthers (2003)<sup>(31)</sup> and one combined Fukuda (1994) and the Canadian Clinical Case Definition<sup>(24)</sup>. Two studies also included participants with high fatigue severity measured with subjective fatigue subscale of the Checklist Individual Strength (CIS-fatigue  $\geq 40$ )<sup>(20)</sup> and Chandler Fatigue Scale (score 10/11)<sup>(32)</sup>. 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<sup>(31)</sup>. Of the 17 studies, five studies used the Chalder Fatigue Scale<sup>(15,22,27,32)</sup>, three studies used an investigator designed symptom questionnaire<sup>(6,25,33)</sup>, two studies used the Multidimensional Fatigue Inventory<sup>(26,28)</sup>, and two studies used both the Checklist Individual Strength Fatigue Subscale and Daily Observed Fatigue<sup>(20,23)</sup>. All other studies used either the Fatigue Index Symptom Questionnaire (FIS-40)<sup>(21)</sup>, Fatigue Severity Scale<sup>(29)</sup>, Fibro Fatigue Scale<sup>(30)</sup> and Piper Fatigue Scale<sup>(24)</sup>. 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<sup>(6,15,20–26,31)</sup>. 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 ( $P < 0.05$ )<sup>(21)</sup>. Another RCT observed a significant decrease in mental fatigue after guanidinoacetic acid (GAA) supplementation compared to a placebo<sup>(26)</sup>. One RCT tested the effect of pollen and pistil extract and a placebo after 3 months of supplementation on fatigue<sup>(25)</sup>. 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<sup>(25)</sup>. 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 ( $P = 0.01$ )<sup>(32)</sup>. Other RCT either observed no significant difference between the nutrition intervention and placebo control<sup>(15,20,22–24)</sup> or did not report between group analysis<sup>(6,25)</sup>. One cohort study observed significant improvement in neurocognitive fatigue ( $P = 0.040$ ) but not in general fatigue after probiotic bacteria supplementation<sup>(33)</sup>. All other studies reported no difference either compared to a comparative intervention<sup>(27)</sup> or after the intervention<sup>(15,29,30)</sup>.

### Interventions on secondary outcomes

Of the 17 studies, 14 studies evaluated the effect of the nutrition intervention on either quality of life ( $n = 10$ )<sup>(20,22,23,26–30,32,33)</sup>, physical activity ( $n = 3$ )<sup>(20,23,26)</sup> and/or psychological wellbeing ( $n = 8$ )<sup>(15,22,24,27,29,31,32)</sup> (Table 3). Three studies observed improvement in psychological wellbeing<sup>(29,31,32)</sup>. One RCT study observed decrease in anxiety but not depression following probiotic supplementation<sup>(31)</sup>. Two comparative studies reported significant improvement in both anxiety and depression after consumption of polyphenol rich chocolate<sup>(32)</sup> and L-carnitine<sup>(29)</sup> compared to baseline. Consumption of L-carnitine also improved five other psychometric tests<sup>(29)</sup>. Two RCT observed significant difference in quality of life for supplementation of BioBran<sup>TM</sup> MGN-3 (Daiwa Pharmaceutical, Tokyo, Japan) (social wellbeing subscale only)<sup>(22)</sup> and guanidinoacetic acid<sup>(26)</sup>. Two comparative studies reported improvement in quality of life after supplementation of acetyl-L-carnitine and propionyl-L-carnitine<sup>(28)</sup>, as well as L-carnitine<sup>(29)</sup>. No studies reported improvement in physical activity level; however, one study reported significant improvement in quadriceps isometric strength and  $VO_{2\max}$  after 3 months of supplementation of guanidinoacetic acid in patients compared with controls<sup>(26)</sup>. All other studies observed no difference of the nutrition intervention on any of the secondary outcomes<sup>(15,20,23,27,30,33)</sup>.

### 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<sup>(12)</sup>. 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<sup>(34)</sup>. 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<sup>(7,9,35)</sup> and individuals aged 35 and 45 years<sup>(7,9)</sup>. 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<sup>(9)</sup>.

The majority of studies in this review exclusively used the Fukuda (1994) case definition<sup>(2)</sup>. A common criticisms of this case definition include a combination of broad nonspecific symptoms<sup>(1,36)</sup>, thus being less likely to identify a homogeneous patient population<sup>(1,36)</sup>. 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<sup>(1)</sup>. 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<sup>(6,15,21,29)</sup>. NADH alone<sup>(6)</sup> and in combination with CoQ10<sup>(21)</sup> 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.*<sup>(6)</sup> 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<sup>(37)</sup>. Reduced levels of CoQ10 have been reported in CFS/ME patients compared to healthy controls<sup>(38)</sup>. Only one RCT has investigated supplementation of Ubiquinol-10 for 12 week in CFS/ME patients<sup>(15)</sup>. 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<sup>(39–41)</sup>. 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 assessed by the London Handicap Scale, compared to when patients consumed an iso-caloric low polyphenol chocolate in CFS/ME patients<sup>(32)</sup>. 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<sup>(42–44)</sup>. 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<sup>(45)</sup>. This review identified two pilot studies each investigating different outcomes. These studies suggest that probiotic bacteria may improve neurocognitive function<sup>(33)</sup> and anxiety<sup>(31)</sup>. Furthermore, Sullivan *et al.*<sup>(33)</sup> 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<sup>(1,46)</sup>. The therapeutic treatment with antioxidants in CFS/ME is limited<sup>(20,25,30)</sup>. The studies identified in the present review suggest that the provision of pollen extract may improve CFS/ME symptoms and patients overall wellbeing<sup>(25)</sup>. However, no therapeutic benefits were observed in CFS/ME patients after multinutritional supplementation<sup>(20,30)</sup>. The results reported by Ockerman<sup>(25)</sup> 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<sup>(27)</sup>. Therefore, future research may consider eliminating potential trigger foods in CFS/ME (e.g. 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 (Rosendal score >60%; Table S1), despite not

reporting all methods (e.g. 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 pre-trial 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. 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<sup>(47)</sup>. 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<sup>(47)</sup> in accordance with the dietary guidelines for healthy people. However, supplementations may be considered as indicated<sup>(47)</sup>; 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 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. 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<sup>(1)</sup>. 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.*<sup>(48)</sup> 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.

The Alison Hunter Memorial Foundation, Change for ME, Mason Foundation, the Stafford Medical Research Foundation, the Edward P Evans Foundation, Queensland Smart State and Advance Queensland provided continued support and funding.

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.

### References

- Carruthers BM, van de Sande MI, De Meirleir KL *et al.* (2011) Myalgic encephalomyelitis: international consensus criteria. *J Intern Med* **270**, 327–338.
- Fukuda K, Straus SE, Hickie I *et al.* (1994) The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* **121**, 953–959.
- Sharpe M, Archard L, Banatvala J *et al.* (1991) A report – chronic fatigue syndrome: guidelines for research. *J R Soc Med* **84**, 118.
- Johnston S, Brenu EW, Staines D *et al.* (2013) The prevalence of chronic fatigue syndrome/myalgic encephalomyelitis: a meta-analysis. *Clin Epidemiol* **5**, 105–110.
- Jason LA, Benton MC, Valentine L *et al.* (2008) The economic impact of ME/CFS: individual and societal costs. *Dyn Med* **7**, 1.
- Forsyth LM, Preuss HG, MacDowell AL *et al.* (1999) Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* **82**, 185–191.
- Jason LA, Richman JA, Rademaker AW *et al.* (1999) A community-based study of chronic fatigue syndrome. *Arch Intern Med* **159**, 2129–2137.
- Aaron LA, Burke MM & Buchwald D (2000) Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med* **160**, 221–227.
- Johnston SC, Staines DR & Marshall-Gradisnik SM (2016) Epidemiological characteristics of chronic fatigue syndrome/myalgic encephalomyelitis in Australian patients. *Clin Epidemiol* **8**, 97.
- Scully P, McKernan DP, Keohane J *et al.* (2010) Plasma cytokine profiles in females with irritable bowel syndrome and extra-intestinal co-morbidity. *Am J Gastroenterol* **105**, 2235–2243.
- Whitehead WE, Palsson O & Jones KR (2002) Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* **122**, 1140–1156.
- Nisenbaum R, Jones JF, Unger ER *et al.* (2003) A population-based study of the clinical course of chronic fatigue syndrome. *Health Qual Life Outcomes* **1**, 1.

13. Grant JE, Velde MS & Buchwald D (1996) Analysis of dietary intake and selected nutrient concentrations in patients with chronic fatigue syndrome. *J Am Diet Assoc* **96**, 383–386.
14. Jain AK, Carruthers BM, van de Sande MI *et al.* (2003) Fibromyalgia syndrome: Canadian clinical working case definition, diagnostic and treatment protocols – a consensus document. *J Musculoskelet Pain* **11**, 3–107.
15. Fukuda S, Nojima J, Kajimoto O *et al.* (2016) Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome. *BioFactors* **42**, 431–440.
16. van Rosendal SP, Osborne MA, Fassett RG *et al.* (2010) Guidelines for glycerol use in hyperhydration and rehydration associated with exercise. *Sports Med* **40**, 113–139.
17. Maher CG, Moseley AM, Sherrington C *et al.* (2008) A description of the trials, reviews, and practice guidelines indexed in the PEDro database. *Phys Ther* **88**, 1068–1077.
18. Jadad AR, Moore RA, Carroll D *et al.* (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* **17**, 1–12.
19. Verhagen AP, de Vet HC, de Bie RA *et al.* (1998) The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* **51**, 1235–1241.
20. Brouwers FM, Van Der Werf S, Bleijenberg G *et al.* (2002) The effect of a polynutrient supplement on fatigue and physical activity of patients with chronic fatigue syndrome: a double-blind randomized controlled trial. *QJM* **95**, 677–683.
21. Castro-Marrero J, Cordero MD, Segundo MJ *et al.* (2015) Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome? *Antioxid Redox Signal* **22**, 679–685.
22. McDermott C, Richards SC, Thomas PW *et al.* (2006) A placebo-controlled, double-blind, randomized controlled trial of a natural killer cell stimulant (BioBran MGN-3) in chronic fatigue syndrome. *QJM* **99**, 461–468.
23. The GKH, Bleijenberg G & van der Meer JWM (2007) The effect of acetyline in chronic fatigue syndrome: a randomized controlled trial. *PLoS Clin Trials* **2**, e19.
24. Witham MD, Adams F, McSwiggan S *et al.* (2015) Effect of intermittent vitamin D3 on vascular function and symptoms in chronic fatigue syndrome – a randomised controlled trial. *Nutr Metab Cardiovasc Dis* **25**, 287–294.
25. Ockerman P (2000) Antioxidant treatment of chronic fatigue syndrome. *Clinical Practice of Alternative Medicine* **1**, 88–91.
26. Ostojic SM, Stojanovic M, Drid P *et al.* (2016) Supplementation with guanidinoacetic acid in women with chronic fatigue syndrome. *Nutrients* **8**, 1–9.
27. Hobday RA, Thomas S, O'Donovan A *et al.* (2008) Dietary intervention in chronic fatigue syndrome. *J Hum Nutr Diet* **21**, 141–149.
28. Vermeulen RCW & Scholte HR (2004) Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. *Psychosom Med* **66**, 276–282.
29. Plioplys AV & Plioplys S (1997) Amantadine and L-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology* **35**, 16–23.
30. Maric D, Brkic S, Mikic AN *et al.* (2014) Multivitamin mineral supplementation in patients with chronic fatigue syndrome. *Med Sci Monit* **20**, 47–53.
31. Rao AV, Bsted AC, Beaulne TM *et al.* (2009) A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog* **1**, 1.
32. Sathyapalan T, Beckett S, Rigby AS *et al.* (2010) High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. *Nutr J* **9**, 55.
33. Sullivan A, Nord CE & Evengård B (2009) Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome. *Nutr J* **8**, 4.
34. Johnston S, Brenu EW, Staines DR *et al.* (2013) The adoption of chronic fatigue syndrome/myalgic encephalomyelitis case definitions to assess prevalence: a systematic review. *Ann Epidemiol* **23**, 371–376.
35. Lloyd AR, Hickie I, Boughton CR *et al.* (1990) Prevalence of chronic fatigue syndrome in an Australian population. *Med J Aust* **153**, 522–528.
36. Jason LA, Sunnquist M, Brown A *et al.* (2015) Defining essential features of myalgic encephalomyelitis and chronic fatigue syndrome. *J Hum Behav Soc Environ* **25**, 657–674.
37. Garrido-Maraver J, Cordero MD, Oropesa-Ávila M *et al.* (2014) Coenzyme q10 therapy. *Mol Syndromol* **5**, 187–197.
38. Maes M, Mihaylova I, Kubera M *et al.* (2009) Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. *Neuro Endocrinol Lett* **30**, 470–476.
39. Galleano M, Oteiza PI & Fraga CG (2009) Cocoa, chocolate and cardiovascular disease. *J Cardiovasc Pharmacol* **54**, 483.
40. Tokede O, Gaziano J & Djoussé L (2011) Effects of cocoa products/dark chocolate on serum lipids: a meta-analysis. *Eur J Clin Nutr* **65**, 879–886.
41. Desch S, Schmidt J, Kobler D *et al.* (2010) Effect of cocoa products on blood pressure: systematic review and meta-analysis. *Am J Hypertens* **23**, 97–103.
42. Lakhani SE & Kirchgessner A (2010) Gut inflammation in chronic fatigue syndrome. *Nutr Metab* **7**, 1.
43. Frémont M, Coomans D, Massart S *et al.* (2013) High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. *Anaerobe* **22**, 50–56.
44. Giloteaux L, Goodrich JK, Walters WA *et al.* (2016) Reduced diversity and altered composition of the gut

- microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. *Microbiome* **4**, 1.
45. Logan AC, Rao AV & Irani D (2003) Chronic fatigue syndrome: lactic acid bacteria may be of therapeutic value. *Med Hypotheses* **60**, 915–923.
46. Logan AC & Wong C (2001) Chronic fatigue syndrome: oxidative stress and dietary modifications. *Altern Med Rev* **6**, 450–460.
47. Carruthers B, Van de Sande M, De Meirleir K *et al.* (2012) Myalgic encephalomyelitis – adult & paediatric: international consensus primer for medical practitioners.
48. Nelson M, Margetts BM & Black AE (1993) Checklist for the methods section of dietary investigations *Metabolism* **42**, 258–259.

### 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.