Popular scientific summary

- Supplement use is highly prevalent among myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients, with vitamins and minerals the most commonly taken supplements.
- The daily nutritional intake of ME/CFS patients is significantly different from that of the general Australian population, particularly the daily intake of fats, carbohydrates, alcohol, and caffeine.
- The relationship of nutritional intake and supplement use with health-related quality of life in ME/CFS patients remains unclear; however, there is a potential role for vitamin C.

Abstract

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, multisystem illness without a currently recognised pharmacological treatment. Dietary supplementation and modification have been posited as potential management strategies, although there is controversy surrounding their efficacy. The role of nutrition and dietary supplementation in ME/CFS has not yet been described in an Australian patient population.

Objective: This study aimed to assess the nutritional intake and supplement use of Australian ME/CFS patients and the effect on patients' health-related quality of life (HRQoL).

Design: Between February 2019 and January 2020, ME/CFS patients across Australia volunteered in this cross-sectional study in response to online advertisements. Respondents meeting the eligibility criteria (including having a diagnosis of ME/CFS according to the Canadian Consensus Criteria) were invited to complete two online self-administered questionnaires. These questionnaires investigated participants' supplement use, nutritional intake and HRQoL. The study participants' supplement use and nutritional intake were also compared to population data returned from the Australian Health Survey (2011-12).

Results: A total of 20 eligible ME/CFS patients (75% female, mean age = 45.3±10.2 years) completed the online questionnaires. Supplement use was highly prevalent among the study population (90.0%) and considerably more common compared with population data (31.9%). Total daily fat and caffeine intake were significantly higher among ME/CFS patients compared with the Australian population ($P = 0.012$ and $P = 0.036$ respectively), whereas total daily carbohydrate and alcohol consumption were significantly lower ($P < 0.001$). No consistent trends between nutrition and supplement use with patients' HRQoL could be identified.

Conclusions: The high prevalence of supplement use among the study participants foregrounds the perceived importance of supplements in ME/CFS management. Furthermore, the daily diet of ME/CFS patients appears to vary considerably from that of the general Australian population. This likely reflects dietary modification, thereby elucidating the potential role of diet in ME/CFS management.

Word count: 300 words

Keywords: Myalgic Encephalomyelitis (ME); Chronic Fatigue Syndrome (CFS); Nutrition; Nutritional Intake; Supplements; Health-Related Quality of Life (HRQoL).

Background

As a complex chronic illness, myalgic encephalomyelitis (ME) (also termed chronic fatigue syndrome (CFS)) has a considerable impact on patients' daily activities and quality of life (1–4). The pathomechanisms underlying ME/CFS currently remain unknown and controversial due to the illness' multi-system nature and heterogeneous clinical presentation (1–3, 5). A diagnosis of ME/CFS is dependent on persistent fatigue that cannot be explained by exercise or another fatiguing clinical syndrome, a significant reduction in the ability to perform one's daily activities, and post-exertional neuroimmune exhaustion (2, 3, 6, 7). Additional symptoms may include bodily pain, autonomic dysfunction, cognitive impairments and neurosensory manifestations, unrefreshing sleep, and flu-like symptoms (2, 3, 5–8). Clinical presentation ranges from mild with a considerable reduction in patients' ability to perform daily activities to very severe with patients bed-ridden and unable to complete basic daily tasks (6).

The onset of ME/CFS may be gradual or sudden and, while the illness' pathogenesis remains contentious, onset often follows a viral or bacterial infection, physical trauma, exposure to toxins, or periods of prolonged stress (9–11). Presently, 25 different case definitions exist for ME/CFS with varying stringency (12). The Fukuda Criteria, Canadian Consensus Criteria (CCC) and the International Consensus Criteria (ICC) are the most widely accepted case definitions in the ME/CFS research arena (12, 13). The availability of numerous case definitions with variable sensitivity precipitates inconsistency in ME/CFS prevalence estimates (8, 14). Generating accurate prevalence estimates is further complicated by the lack of a known illness biomarker and the absence of a laboratory test to confirm a diagnosis of ME/CFS (2–4). Hence, ME/CFS prevalence estimates range from 0.01% to 6.40% (8).

Health-related quality of life (HRQoL) is significantly compromised in ME/CFS patients when compared with healthy individuals (4, 15–17). A large Australian study conducted at the National Centre for Neuroimmunology and Emerging Diseases (NCNED), which surveyed 480 ME/CFS patients, observed significantly lower scores among ME/CFS patients across all HRQoL domains when compared to population data collected from the Australian National Health Survey (4). Falk Hvidberg et al. similarly identified significantly lower HRQoL scores among Danish ME/CFS patients compared to the general population (15). This investigation also revealed that ME/CFS was associated with the lowest HRQoL scores when compared with 20 other chronic conditions, thereby highlighting the debilitating and disabling nature of the condition (15).

As there does not currently exist a cure or commercially-available pharmacological treatment specific for ME/CFS, managing symptoms is essential to prevent further deterioration of patients' quality of life (18). Dietary modification and supplementation have been posited as potential management strategies (3, 19, 20). Dietary modification largely refers to the exclusion of trigger foods and food chemicals (18, 21). New food intolerances or sensitivities appear to be a component of ME/CFS presentation, particularly intolerances to gluten, lactose, sugar, and alcohol (18, 22, 23). Thus, suspected trigger foods should be avoided to prevent symptom exacerbation. Dietary interventions for ME/CFS management may also involve the inclusion of foods with beneficial properties, such as polyphenol-rich dark chocolate (may assist in alleviating fatigue (21)) and herbal teas (may be involved in the improvement of sleep disturbances associated with ME/CFS (18)).

Dietary supplementation has also been proposed for ME/CFS management. ME/CFS symptomatology has similarities with various vitamin and mineral deficiencies (24);

however, a systematic review published in 2017 concluded that there was insufficient evidence to implicate nutritional imbalances in the development of the condition (25). Although nutritional imbalances may not be causative of ME/CFS, supplements such as B vitamins, vitamin C, coenzyme Q (CoQ10), and amino acids (such as N-acetylcysteine and glutathione) may serve to improve the bioavailability of antioxidant compounds and, therefore, reduce inflammatory symptoms (26). However, randomised-controlled trials examining the effects of supplements on ME/CFS patients have, thus far, yielded contrasting results (19). Therefore, supplements continue to contribute to patients' economic burden in the absence of conclusive evidence to suggest their effectiveness.

Nutritional intake appears to be associated with HRQoL and symptom presentation in chronic disease populations other than ME/CFS. Dietary modification and supplementation have been posited as management strategies to improve patients' quality of life for chronic conditions such as fibromyalgia (27), rheumatoid arthritis (28), and multiple sclerosis (29). However, the role of nutrition and supplement use with HRQoL has not yet been investigated in an ME/CFS patient population. Thus, there is a paucity of literature assessing nutritional intake and supplement use within the Australian ME/CFS population. This pilot study, therefore, endeavours to examine the nutritional intake and supplement use habits among Australian ME/CFS patients to further characterise the role of these aspects in the clinical presentation of the illness, including patients' HRQoL. It is anticipated that the outcomes of this study will assist in ameliorating management strategies for ME/CFS and, consequently, patients' quality of life.

Methods

Study design and setting

This cross-sectional study collected patient-level data regarding nutritional intake, supplement use habits, and HRQoL of Australian ME/CFS patients from February 2019 to January 2020. ME/CFS patients were recruited into the study through voluntary response to online advertisements released by the NCNED. Patients who responded to the online advertisements were subsequently assessed for eligibility (Supplementary Table 1) before being invited to complete the online questionnaires. This study received approval from the Griffith University Human Research Ethics Committee (GU:2019/1005 & GU:2016/807) and the Gold Coast University Hospital Human Research Ethics Committee (HREC/2019/QGC /56469).

Online questionnaires

To determine eligibility, participants who responded to the online advertisements completed a survey through the online application, LimeSurvey (LimeSurvey, Carsten, Schmitz, Hamburg, Germany) (30). This questionnaire, which was generated by members of the NCNED research team, enquired into patients' sociodemographic information and utilised the Fukuda (31), CCC (32), and ICC (6) case definitions. A second questionnaire, also administered through LimeSurvey, collected data regarding dietary concerns, regular supplement use, and HRQoL. The online self-administered Dietary Questionnaire for Epidemiological Studies (DQES), distributed by the Cancer Council Victoria, Australia, estimated patients' daily nutritional intake by assessing food and beverage consumption over the 12 months prior to completing the questionnaire (33). Participants who had completed the online questionnaires were then anonymised with an alphanumeric code. Stringent exclusion criteria were employed to reduce the potential for confounding variables that may explain the trends observed in this study (Supplementary Table 1). Following the elimination of participants that met the study's exclusion criteria, the anonymised data were then exported to SPSS v26 (34) for statistical analysis.

Study variables

Sociodemographic characteristics

Study participants disclosed their sociodemographic information, including: (i) gender (male, female, or other); (ii) age (years); (iii) age of illness onset (years); (iv) height (cm) and weight (kg); (v) place of residence (by Australian state or territory); (vi) current employment status (unemployed, part-time, or full-time); and (vii) highest level of education obtained (primary school, high school, professional training (not university), undergraduate, or postgraduate). Participants' height and weight were used to calculate their body mass index (BMI) (kg/m^2), in which the study participants were subsequently categorised as underweight (<18.5), normal weight (18.5 to 24.9), overweight (25.0 to 29.9), or obese (≥30.0) as per the World Health Organization's BMI classification system (35).

Supplement use

Participants' regular use of supplements was recorded as either yes or no. Those currently taking supplements were subsequently required to list each supplement that they were taking and were categorised depending on the number of supplements being taken (one to three, four to six, or seven to ten). The study participants' supplement use habits were then compared with those of the general population. Population data were obtained from the Australian Health Survey: Nutrition First Results – Foods and Nutrients (AHS) (36). The AHS surveyed 12,153 Australians between 2011 and 2012. To compare the proportion of ME/CFS patients taking supplements to that of the Australian population, the supplements reported by the patients were grouped into the following categories derived from the AHS: (i) multi-vitamins or multi-minerals; (ii) single vitamins or single minerals; (iii) lipid supplements; (iv) herbal or plant-based supplements; (v) other nutritive supplements; and (vi) other non-nutritive supplements. Supplement use was then further subdivided into the number of each supplement type taken by the study participants on a three-point scale: none, one to three, or more than four.

Health-related quality of life

HRQoL was examined through the use of items derived from the 36-Item Short Form Health Survey (SF-36) (37). The items derived from the SF-36 utilised Likert scales from zero to 100 to assess study participants' HRQoL across seven domains: (i) physical functioning (PF); (ii) the role of limitations due to physical health problems (RP); (iii) bodily pain (BP); (iv) social functioning (SF); (v) general mental health (MH); (vi) the role of limitations due to emotional problems (RE); and (vii) general health perceptions (GH). The scores returned from the questionnaire are directly proportional to the study participants' HRQoL for the corresponding domain.

Nutritional intake

Following the completion of the LimeSurvey questionnaire, study participants were invited to complete the online DQES. Dietary intake was assessed through 80 items across five domains, including: (i) cereals, sweets, and snacks; (ii) dairy, meat, and fish; (iii) fruits; (iv) vegetables; and (v) alcoholic beverages. The items included within the DQES that assessed dietary intake were categorised as either ordinal or nominal. Ordinal items assessed the quantity of a particular food or beverage that was consumed per day, week or month, or per portion of the food or beverage in question. Nominal items investigated the types of a particular food group that were typically included within the participants' diet. Such nominal items were composed of both single-selection questions (where the most frequently consumed food type was queried), as well as multi-selection questions that requested all applicable options to be chosen. Participants' daily nutritional intake was subsequently calculated based on data derived from Nutrient Tables 2010 (NUTTAB) (38) and the Australian Food, Supplement, and Nutrient Database 2007 (AUSNUT) (39). The study population means were then compared with those of the Australian population for the nutritional intake variables that were common between the DQES and the AHS.

Statistical analysis

The data generated from the two online questionnaires were analysed using SPSS v26. Supplement use data are presented as the number of participants (percentage of total participants) unless stated otherwise. Data returned by the AHS are also provided where the relevant statistics were available and are presented as the percentage of AHS participants.

Nutritional intake data are presented as the population mean ± standard deviation, as well as the means generated from the AHS. Daily nutritional intake and daily intake of major and sub-major food groups variables were assessed for normality with the Shapiro-Wilk test. One-sample *t*-tests were performed for all normally-distributed nutritional intake variables. The *t*-scores and *P*-values ($\alpha < 0.05$) generated from these tests were then tabulated. For non-normally-distributed daily nutritional intake and daily intake of major and sub-major food groups variables, one-sample Kolmogorov-Smirnov tests were conducted. The *D*-statistics and *P*-values ($\alpha < 0.05$) returned from these tests are provided.

To assess the relationship of HRQoL with nutrition and supplement use, multiple linear regression analysis was performed for the seven SF-36 domains. The Akaike Information Criterion was used to compare regression models and the model with the lowest Akaike Information Criterion was employed. Therefore, variables were included in the model if $P < 0.10$. The models generated for the seven SF-36 domains were adjusted for age, gender, BMI, education, and employment. Following this, noteworthy supplements and all statistically significant daily intake variables were included in the forward stepwise procedure to generate the final model for each HRQoL domain. For all variables included in the final model, the unstandardised B (95% confidence intervals), standard error of B (SE(B)), standardised *ß*, *t*-value, and *P*-value are provided, in addition to the R^2-value, adjusted R^2-value, and *P*-value, for the model.

Results

Sociodemographic characteristics

Twenty ME/CFS patients completed the two online self-administered questionnaires. Table 1 summarises the sociodemographic data of the study population. All study participants had received a diagnosis of ME/CFS meeting the CCC criteria. The average age of the study participants was 45.3±10.2 years and the average age of onset was 30.8±11.1 years. The majority of the study population was female (75.0%), of normal weight (50.0%), and unemployed (80.0%). Most study participants had achieved an undergraduate-level of education (55.0%). In terms of location, those residing in either New South Wales or Queensland occupied the largest proportion study participants (50.0%).

Table 1 should appear here.

Supplement use

The frequency of supplement use among the study participants is outlined in Table 2. Most of the study participants were regularly taking at least one supplement (90.0%). This is a considerably larger proportion than the general population (31.9%). Of the total study population of ME/CFS patients, 70.0% took between four and ten supplements. For each supplement group and subgroup where data from the AHS was available, the proportion of individuals taking the supplement in question was higher among ME/CFS patients than the general population (with the exception of 'other supplements').

Multi-vitamins and multi-minerals were the most frequently taken supplements and were taken by 75.0% of the study population. Single vitamin and single mineral supplements were also common among ME/CFS patients (70.0%). The high prevalence of vitamin and mineral supplementation among the study participants contrasted with that of the general population, in which the study population had a higher proportion of supplement use for every single vitamin and single mineral category compared with the Australian population. Interestingly, lipid supplements were the most frequently taken supplement among the Australians included in the AHS (14.0%), where multi-vitamins and multi-minerals were taken by 10.1% and every single vitamin and single mineral was taken by less than 5%. The most frequently taken single vitamin or single mineral among the ME/CFS patients was zinc (40.0%), followed by magnesium (30.0%) and vitamin D (30.0%). Multi-vitamins or multi-minerals and single vitamins or single minerals were also the only supplement groups where the study participants took four or more of such supplements. Non-nutritive supplements were taken by 55.0% of the study population compared to only 5.3% of the Australian population. The most noteworthy non-nutritive supplements were probiotics, which were taken by 45.0% of study participants.

Table 2 should appear here.

Daily nutritional intake

There appears to be a significant difference in the daily intake of fats and carbohydrates among Australian ME/CFS patients when compared with the general population (Table 3). The daily intake of total fats was elevated among ME/CFS patients when compared with the national average ($P = 0.012$). Notable increases in the daily intakes of monounsaturated fats ($P = 0.001$), polyunsaturated fats ($P = 0.005$), linolenic acid ($P = 0.003$), and long-chain omega-3 fatty acids ($P = 0.002$) were observed among the ME/CFS study population when compared with the general population. The total daily intakes of carbohydrates, sugars, and starch were significantly lower among ME/CFS patients when compared with the Australian population ($P < 0.001$, $P = 0.017$, and $P < 0.001$ respectively). Interestingly, no significant difference in daily energy intake was observed between ME/CFS patients and the general population ($P = 0.279$).

Significant differences were also observed in the daily intake of vitamins and minerals. Compared with the general population, ME/CFS patients' daily intakes of natural folate, vitamin C, and vitamin E appeared to be significantly higher ($P = 0.001$, $P = 0.041$, and $P = 0.039$ respectively), whereas patients' daily intakes of folic acid, vitamin B6, and vitamin B12 were notably lower ($P = 0.002$, $P = 0.007$, and $P < 0.001$ respectively). In terms of minerals, the daily intakes of iron, magnesium, and potassium were significantly elevated ($P = 0.018$, $P = 0.004$, and $P = 0.006$ respectively) among ME/CFS patients compared with the Australian population, whereas the daily intakes of iodine and sodium were considerably lower ($P < 0.001$). Daily caffeine intake among ME/CFS patients was also significantly higher compared with the general population ($P = 0.036$) and daily alcohol intake was significantly lower ($P < 0.001$).

Table 3 should appear here.

Daily intake of major and sub-major food groups

Table 4 summarises the study participants' daily intake of major and sub-major food groups, in which each food category displayed statistical significance (with the exception of 'water'). Noteworthy significant increases were observed in ME/CFS patients' daily intakes of herbal tea ($P < 0.001$), gluten-free bread ($P < 0.001$), and yoghurt ($P = 0.002$). Fruit and vegetable consumption also appears to be significantly higher among ME/CFS patients when compared with the Australian population, in which all fruit and vegetable subgroups returned a significance level of $P < 0.001$ with the exception of 'bananas' ($P = 0.004$). Interestingly, the daily intakes of sausages, processed meats, and sugar were significantly lower ($P < 0.001$) among the study population. Additionally, ME/CFS patients appear to consume less alcohol on a daily basis than the general population. For all types of alcohol assessed in the study, ME/CFS patients had a significantly lower ($P < 0.001$) daily intake when compared with the Australian population.

Table 4 should appear here.

Health-related quality of life

The multivariate analysis results for each HRQoL domain are presented in Table 5 and Table 6, corresponding to the physical (PF, RP, BP, and GH) and mental (SF, MH, and RE) health domains respectively. Complete statistics (including the unstandardised B, 95% confidence intervals, and SE(B)) for each HRQoL domain can be found in Supplementary Tables 2 to 8.

Statistically significant associations were found in neither PF nor RE, with 31.8% (adjusted $R^2 = 0.318$, $P = 0.069$) and 6.8% (adjusted $R^2 = 0.068$, $P = 0.342$) of the variance explained by the variables included in the models respectively. A significant positive association was observed between daily folic acid intake and RP, with a regression coefficient of 0.094 (95% CI: 0.028 – 0.161, $P = 0.009$); however, the model was not significant (adjusted $R^2 = 0.383$, $P = 0.053$). Similarly, daily iodine intake was positively associated with SF with a regression coefficient of 0.304 (95% CI: 0.031 – 0.576, $P = 0.032$) yet the model did not display significance (adjusted $R^2 = 0.190$, $P = 0.202$).

BP was directly proportional to daily total fat intake (B = 0.550 (95% CI: 0.230 – 0.870), $P = 0.003$) and indirectly proportional to daily potassium intake (B = -0.030 (95% CI: -0.051 – -0.009), $P = 0.010$), with 53.5% of the variance of BP explained by the variables in the model (adjusted $R^2 = 0.535$, $P = 0.026$). Taking vitamin C supplements was associated with increased MH scores, with a regression coefficient of 19.681 (95% CI: 8.072 – 31.291, $P = 0.003$). MH was also positively associated with daily total protein intake, with a regression coefficient of 0.313 (95% CI: 0.102 – 0.524, $P = 0.007$). The variance of MH explained by the variables in the model was 60.1% (adjusted $R^2 = 0.601$, $P = 0.008$); however, age (B = 0.740 (95% CI: 0.330 – 1.149), $P = 0.002$) and education (B = 6.159 (95% CI: 1.411 – 10.906), $P = 0.015$) were significant confounders. Similarly, a significantly positive association was observed between daily vitamin C intake and GH (adjusted $R^2 = 0.466$, $P = 0.017$), with a regression coefficient of 0.102 (95% CI: 0.021 –

0.183, $P = 0.018$); however, gender (B = -14.713 (95% CI: -27.289 – -2.137), $P = 0.025$) and education (B = -6.399 (95% CI: -12.653 – -0.144), $P = 0.046$) were significant confounders.

Table 5 and Table 6 should appear here.

Discussion

The primary objective of this study was to assess the role of supplement use and diet in ME/CFS by comparing the study population to the results of the AHS. Furthermore, as dietary modification and supplementation currently exist as potential management strategies for ME/CFS (19, 40), this study aimed to collect patient-level data for the purpose of describing dietary supplementation and nutritional intake among ME/CFS patients and their effect on patients' HRQoL. A noteworthy finding of this study is that dietary supplementation is highly prevalent among ME/CFS patients despite having little observable effect on patients' HRQoL. It also appears that the daily diet of ME/CFS is considerably different from that of the general Australian population.

The sample population of ME/CFS patients in the present study reflected the sociodemographic distribution of patients observed in previous cross-sectional studies (7, 9, 41–45). The majority of the study participants were female, of normal weight, and unemployed, which is consistent with the current literature (7, 9, 41–45). In congruence with other studies, the mean age of the study participants fell between 40 and 50 years, where the mean age of onset was similarly within the 30 to 40 years range (7, 9, 41, 44). Unusually, almost three-quarters of the study population had achieved at least an undergraduate-level education. This proportion is considerably larger than observed in other studies (4, 7, 41, 42), which may be due to selection bias as a result of the study design relying on voluntary response.

It should also be noted that all participants met the CCC case definition. This inclusion criterion was employed to create a sample population with less heterogeneity in terms of clinical presentation. As the Fukuda case definition has lower specificity than the CCC and ICC definitions, there is an increased potential for overdiagnosis and psychological comorbidity (13, 46). Thus, by ensuring all participants met at least the CCC case definition, there was a reduced potential for less severe patients (or patients with psychological comorbidity that may explain their symptoms) to confound the relationship of supplement use and nutritional intake with HRQoL.

The present study reports a novel finding that supplement use is highly prevalent among Australian ME/CFS patients when compared with the general population. However, there exists limited information in the current literature concerning supplement use among ME/CFS patients to validate these findings. While Jones et al. (45) report that the use of supplements or vitamins was significantly more prevalent among ME/CFS patients meeting the Fukuda criteria when compared with non-ME/CFS participants (P = 0.018), a study conducted by Boneva et al. found that less than half of the study participants meeting the Fukuda criteria were taking supplements (44.2%), which was lower than the prevalence of supplement use among the healthy participants (52.4%) (47). In support of the present study, Dykman et al. report in their 1998 paper that supplements were used by 100% of the study population (48). However, the study population was a small convenience sample and included both ME/CFS and fibromyalgia patients (48). Thus, it is difficult to compare the results of the current study with the available literature, as there is a lack of recently published studies, the sample sizes of the available studies are relatively small, and their results are likely influenced by confounding sociodemographic factors. The variability of supplement use among ME/CFS patients in the current literature may also be attributable to patients being provided with inadequate information regarding supplement use as a result of inconsistencies in supplement use recommendations (19).

A further novel finding from this investigation was that vitamins and minerals were not only the most frequently taken supplements among Australian ME/CFS patients, but were the only supplement categories in which multiple different types of such supplements were taken. A multi-vitamin-multi-mineral supplement appeared to significantly improve fatigue, sleep, and autonomic function in ME/CFS patients in a 2014 study (49); however, there are few similar studies to confirm these findings. A 2002 randomised controlled trial investigating the efficacy of a multi-nutrient supplement on fatigue, physical activity, and quality of life among ME/CFS patients did not return statistically significant results (19, 50). Thus, the role of multi-vitamins and multi-minerals as an effective management strategy for ME/CFS remains controversial.

Similarly, there did not exist a statistically significant improvement in fatigue among ME/CFS patients (meeting the Fukuda and CCC criteria) in a 2015 randomised controlled trial using vitamin D3 supplementation (51). However, the current literature suggests that CoQ10 supplementation may be a more promising approach to ME/CFS management (52–54). Although the efficacy of CoQ10 supplementation on fatigue remains unclear, this supplement may be useful for the management of the depressive symptoms, neurocognitive dysfunction, and sleep disturbances associated with ME/CFS (52–54). Despite this, less than one-quarter of the present study's participants took CoQ10 supplements. Interestingly, just under half of the study population were taking probiotics. Although some studies have suggested that probiotics may assist in relieving inflammatory symptoms and improving cognition and well-being (55–57), there appears to be insufficient evidence to support the use of probiotics as a therapeutic approach to ME/CFS (58, 59).

Therefore, due to disparate results in the literature, the role of supplements in the management of ME/CFS remains unclear. A systematic review published in 2017 concluded that, although significant results were reported by some studies, no supplement was consistently associated with a significant improvement in ME/CFS patients' condition (19). This is reflected in the results of the present study, in which no supplement consistently displayed a significant positive relationship with HRQoL across the seven SF-36 domains. The only dietary supplement exhibiting a statistically significant association with HRQoL was vitamin C, in which taking vitamin C supplements was associated with increased MH scores.

Vitamin C has been proposed as a supplement recommendation for ME/CFS due to commonalities in the clinical presentation of ME/CFS and vitamin C deficiency (24, 40); however, an intervention study assessing the effect of vitamin C supplementation in ME/CFS is yet to be conducted. Statistically significant increases in HRQoL following intravenous vitamin C supplementation have been observed among cancer patients (60, 61). Additionally, patients with vitamin C depletion reported significantly increased depressive symptoms when compared with patients with adequate serum vitamin C levels in a study examining patients over 65 years hospitalised for acute illness (62). Daily vitamin C intake was also positively associated with GH in the current study. Therefore, the results of the present study, in addition to observations in other immunocompromised patient populations, suggest a potential role for vitamin C supplementation in the management ME/CFS. This should be further investigated through an intervention study with a large study population and sufficient follow-up period (19).

Surprisingly, multi-vitamin and multi-mineral supplements did not appear to have a statistically significant association with any of the HRQoL domains despite the high prevalence of their use in the study population. However, this observation should be confirmed in a future investigation with a larger study population before definitively deeming these supplements ineffective in the management of ME/CFS.

Another novel finding of this investigation is that the daily diet of ME/CFS patients appears to differ considerably when compared with the Australian population. To the best of the authors' knowledge, there does not currently exist a study, national or international, that investigates the daily nutritional and food intake of ME/CFS patients (19). A study conducted by Goedendorp et al. identified that ME/CFS patients' intakes of fruits, vegetables, and fibre were not adequate to be considered healthy through the use of three eating habits questionnaires (63). These questionnaires ranked patients' intake of fat, fruits and vegetables, and fibre with scores below the specified threshold (or above in the case of the fat questionnaire) deemed 'unhealthy' (63). The significant differences in diet observed between ME/CFS patients' and the general population in the present study are likely due to dietary modification, including the consumption of specific foods to relieve ME/CFS symptoms, as well as specific food avoidance due to intolerances and tendency for certain foods to trigger ME/CFS symptoms.

Noteworthy differences between the study participants and the Australian population lay within the daily intake of carbohydrate and fat, whereby ME/CFS patients appear to have a significantly lower daily intake of carbohydrates and significantly higher daily intake of fat when compared with the general population. These trends may be attributable to common dietary modifications that are recommended for ME/CFS patients, such as ketogenic diets (low-sugar, high-fat diets), which may assist in alleviating inflammatory symptoms associated with ME/CFS (22). The study population's significantly higher daily intake of natural folate, vitamin C, and vitamin E may be attributable to the high prevalence of dietary supplementation among ME/CFS patients. However, supplement recommendations proposed for the management of ME/CFS include folic acid, vitamin C, vitamin B6, and vitamin B12 (20). Thus, the significantly lower daily intake of folic acid, vitamin B6, and vitamin B12 among the ME/CFS population appears unusual.

The significant increase in daily caffeine intake among ME/CFS patients compared to the general population is also worth noting. This is likely attributable to attempts to alleviate fatigue symptoms (18). However, as ME/CFS patients often experience heightened sensitivity to drugs and food chemicals (64), caffeine would be expected to exacerbate ME/CFS symptoms, such as anxiety and cardiovascular manifestations (65). The decreased daily intake of alcohol among ME/CFS patients compared to the Australian population was anticipated. Alcohol intolerance appears to be a component of ME/CFS presentation for many patients, likely due to its role in fatigue and cognition (9). Therefore, the significantly lower daily alcohol intake observed within the study population is likely due to avoidance for the purpose of preventing symptom exacerbation.

However, as the study population appears to have unusual daily nutritional intake given current dietary modification and supplementation recommendations, it may be that Australian ME/CFS patients are not be receiving adequate education regarding appropriate diet and supplement use in the management of their condition. This is likely due to the limited information regarding food intolerance and sensitivity, as well as trigger foods and food chemicals, in the current Australian ME/CFS clinical guidelines (66). Therefore, to improve patients' awareness of appropriate dietary and supplement use habits in the management of their condition, the Australian clinical guidelines must be updated to more comprehensively describe the role of nutrition and supplement use in ME/CFS based on recent research.

Few nutrients displayed statistically significant associations with HRQoL. As four of the seven HRQoL returned an insignificant final model and statistically significant nutrients were only associated with one HRQoL domain (with the exception of vitamin C), there does not appear to be a clear relationship between nutrition and HRQoL. However, this may be explained by the relatively small sample size and future studies should prospectively monitor a larger cohort of ME/CFS patients to investigate if a causal relationship exists between nutrition and HRQoL.

In terms of daily consumption of major and sub-major food groups, the most notable significant differences included herbal tea, yoghurt, gluten-free bread, and sugar. Patients' significantly greater consumption of herbal tea and yoghurt may be explained as herbal and probiotic approaches to alleviating ME/CFS symptoms. The increase of gluten-free bread and decrease of sugar in the study participants' diet may be attributable to the dietary intolerances observed in the study population, in which food intolerance is often a component of ME/CFS presentation (41, 64).

It should also be noted that the study population may be more conscious of their dietary intake than the general population, particularly as dietary modification and supplementation are posited as potential management strategies for ME/CFS. This may explain the higher daily intake of fruits and vegetables among study participants when compared with the Australian population.

This study is not without limitations. Daily fruit and vegetable consumption trends should be interpreted with caution, as only a limited number of fruit and vegetable products could be compared due to differences between the DQES administered to the study participants and the AHS. In addition, it is assumed that the DQES is an appropriate tool to measure this study population's daily intake of nutrients and major and sub-major food groups. However, as this study is the first to employ the DQES in an ME/CFS patient population, there does not exist another study to which the findings of the present study can be compared. Also, although this food frequency questionnaire has been validated in Australian populations (67, 68), the study participants consisted only of adult Australian residents born in Australia, Greece, or Italy. Thus, the DQES may have less suitability to ME/CFS patients from other cultural backgrounds.

While the results of the AHS are assumed to be normally-distributed based on central limit theorem (69), normality tests could not be performed on the AHS data available to confirm this. Additionally, there is potential for selection bias due to the nature of this study and the study's generalisability is compromised as a result of the small sample size. Therefore, the trends identified in this paper should be confirmed with a larger sample size of ME/CFS patients with matched healthy controls to more accurately compare the nutritional intake and supplement use of ME/CFS patients to healthy individuals. This investigation also highlights the importance of validating the existing supplement recommendations for ME/CFS management, particularly regarding vitamins and minerals. As there is insufficient evidence to justify supplements as an ME/CFS management strategy, large international randomised controlled trials should be conducted to improve current recommendations. Such research is imperative, as the elimination of ineffective supplements from management protocols may alleviate part of the economic burden that ME/CFS patients endure as a result of their condition.

Conclusion

The objective of this cross-sectional study was to assess the daily nutritional intake and use of supplements among Australian ME/CFS patients and the effect of nutrition and supplement use on patients' HRQoL. Supplement use appears to be considerably more prevalent among ME/CFS patients when compared with the Australian population. Therefore, it appears that supplement use is a common management strategy for ME/CFS. Additionally, the daily intake of fats is higher and carbohydrates is lower among ME/CFS patients when compared with the general population. This likely reflects the common dietary modifications that have been implicated in the alleviation of ME/CFS symptoms, thereby highlighting the role of diet in ME/CFS management. No clear conclusions regarding the effect of nutritional intake and supplement use on ME/CFS patients' HRQoL could be deduced from the results of this study. Vitamin C supplementation may be associated with improved HRQoL among ME/CFS patients; however, the relationship of nutrition and supplement use with HRQoL in ME/CFS remains ambiguous. It is recommended that further research be pursued in this area with a larger sample size to validate the findings of this investigation.

References

1. Sotzny F, Blanco J, Capelli E, Castro-Marrero J, Steiner S, Murovska M, et al. Myalgic encephalomyelitis/chronic fatigue syndrome – Evidence for an autoimmune disease. Autoimmun Rev. 2018;17(6):601-9. doi: 10.1016/j.autrev.2018.01.009
2. Missailidis D, Annesley SJ, Fisher PR. Pathological mechanisms underlying myalgic encephalomyelitis/chronic fatigue syndrome. Diagnostics (Basel). 2019;9(3):80. doi: 10.3390/diagnostics9030080
3. Castro-Marrero J, Sáez-Francàs N, Santillo D, Alegre J. Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: All roads lead to Rome. Br J Pharmacol. 2017;174(5):345-69. doi: 10.1111/bph.13702
4. Eaton-Fitch N, Johnston SC, Zalewski P, Staines D, Marshall-Gradisnik S. Health-related quality of life in patients with myalgic encephalomyelitis/chronic fatigue syndrome: An Australian cross-sectional study. Qual Life Res. 2020;29(6):1521-31. doi: 10.1007/s11136-019-02411-6
5. Rasa S, Nora-Krukle Z, Henning N, Eliassen E, Shikova E, Harrer T, et al. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). J Transl Med. 2018;16(1):268. doi: 10.1186/s12967-018-1644-y
6. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, et al. Myalgic encephalomyelitis: International consensus criteria. J Intern Med. 2011;270(4):327-38. doi: 10.111/j.1365-2796.2011.02428.x
7. Johnston SC, Staines DR, Marshall-Gradisnik SM. Epidemiological characteristics of chronic fatigue syndrome/myalgic encephalomyelitis in Australian patients. Clin Epidemiol. 2016;8:97-107. doi: 10.2147/CLEP.S96797
8. Johnston S, Brenu EW, Staines DR, Marshall-Gradisnik S. The adoption of chronic fatigue syndrome/myalgic encephalomyelitis case definitions to assess prevalence: A

systematic review. Ann Epidemiol. 2013;23(6):371-6. doi: 10.1016/j.annepidem.2013.04.003

9. Chu L, Valencia IJ, Garvert DW, Montoya JG. Onset patterns and course of myalgic encephalomyelitis/chronic fatigue syndrome. Front Pediatr. 2019;7:12. doi: 10.3389/fped.2019.00012

10. Morris G, Maes M, Berk M, Puri BK. Myalgic encephalomyelitis or chronic fatigue syndrome: How could the illness develop? Metab Brain Dis. 2019;34(2):385-415. doi: 10.1007/s11011-019-0388-6

11. Underhill RA. Myalgic encephalomyelitis, chronic fatigue syndrome: An infectious disease. Med Hypotheses. 2015;85(6):765-73. doi: 10.1016/j.mehy.2015.10.011

12. Lim E-J, Son C-G. Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). J Transl Med. 2020;18(1):289. doi: 10.1186/s12967-020-02455-0

13. Brurberg KG, Fønhus MS, Larun L, Flottorp S, Malterud K. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): A systematic review. BMJ Open. 2014;4(2):e003973. doi: 10.1136/bmjopen-2013-003973

14. Lim E-J, Ahn Y-C, Jang E-S, Lee S-W, Lee S-H, Son C-G. Systematic review and meta-analysis of the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). J Transl Med. 2020;18(1):100. doi: 10.1186/s12967-020-02269-0

15. Falk Hvidberg M, Brinth LS, Olesen AV, Petersen KD, Ehlers L. The health-related quality of life for patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). PLOS One. 2015;10(7):e0132421. doi: 10.1371/journal.pone.0132421

16. Nacul LC, Lacerda EM, Campion P, Pheby D, Drachler MdL, Leite JC, et al. The functional status and well being of people with myalgic encephalomyelitis/chronic

fatigue syndrome and their carers. BMC Public Health. 2011;11(1):402. doi: 10.1186/1471-2458-11-402

17. Strand EB, Mengshoel AM, Sandvik L, Helland IB, Abraham S, Nes LS. Pain is associated with reduced quality of life and functional status in patients with myalgic encephalomyelitis/chronic fatigue syndrome. Scand J Pain. 2018;19(1):61-72. doi: 10.1515/sjpain-2018-0095
18. Friedberg F, Bateman L, Bested AC, Friedman KJ, Gurwitt A, et al. ME/CFS: A primer for clinical practitioners. 2012 ed. Chicago, USA: International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012. Available from: https://www.iacfsme.org/assets/docs/PrimerFinal.pdf
19. Campagnolo N, Johnston S, Collatz A, Staines D, Marshall-Gradisnik S. Dietary and nutrition interventions for the therapeutic treatment of chronic fatigue syndrome/myalgic encephalomyelitis: A systematic review. J Hum Nutr Diet. 2017;30(3):247-59. doi: 10.1111/jhn.12435
20. Morris DH, Stare FJ. Unproven diet therapies in the treatment of the chronic fatigue syndrome. Arch Fam Med. 1993;2(2):181-6. doi: 10.1001/archfami.2.2.181
21. Sathyapalan T, Beckett S, Rigby AS, Mellor DD, Atkin SL. High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. Nutr J. 2010;9:55. doi: 10.1186/1475-2891-9-55
22. Craig C. Mitoprotective dietary approaches for myalgic encephalomyelitis/chronic fatigue syndrome: Caloric restriction, fasting, and ketogenic diets. Med Hypotheses. 2015;85(5):690-3.
23. Trabal J, Leyes P, Fernández-Solá J, Forga M, Fernández-Huerta J. Patterns of food avoidance in chronic fatigue syndrome: Is there a case for dietary recommendations? Nutr Hosp. 2012;27(2):659-62.

24. Werbach MR. Nutritional strategies for treating chronic fatigue syndrome. Altern Med Rev. 2000;5(2):93-108.

25. Joustra ML, Minovic I, Janssens KAM, Bakker SJL, Rosmalen JGM. Vitamin and mineral status in chronic fatigue syndrome and fibromyalgia syndrome: A systematic review and meta-analysis. PloS One. 2017;12(4):e0176631.

26. Logan AC, Wong C. Chronic fatigue syndrome: Oxidative stress and dietary modifications. Altern Med Rev. 2001;6(5):450-9.

27. Silva AR, Bernardo A, Costa J, Cardoso A, Santos P, de Mesquita MF, et al. Dietary interventions in fibromyalgia: A systematic review. Ann Med. 2019;51(sup1):2-14.

28. Tedeschi SK, Frits M, Cui J, Zhang ZZ, Mahmoud T, Iannaccone C, et al. Diet and rheumatoid arthritis symptoms: Survey results from a rheumatoid arthritis registry. Arthritis Care Res (Hoboken). 2017;69(12):1920-5.

29. Bagur MJ, Murcia MA, Jiménez-Monreal AM, Tur JA, Bibiloni MM, Alonso GL, et al. Influence of diet in multiple sclerosis: A systematic review. Adv Nutr. 2017;8(3):463-72.

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

31. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. Ann Intern Med. 1994;121(12):953-9.

32. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimafs NG, Lerner AM, et al. Myalgic encephalomyelitis/chronic fatigue syndrome. J Chronic Fatigue Syndr. 2003;11(1):7-115.

33. Cancer Council Victoria. Dietary questionnaires [Internet]. Victoria: Commonwealth of Australia; n.d. [cited 2020 Oct 10]. Available from: https://www.cancervic.org.au/research/epidemiology/nutritional_assessment_services

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

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

36. Australian Bureau of Statistics. Australian Health Survey: Nutrition First Results – Foods and Nutrients, 2011-12 [Internet]. Canberra: Commonwealth of Australia; 2014 [cited 2020 Jul 28]. ABS Cat. No.: 4364.0.55.007. Available from: https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.007~2011-12~Main%20Features~Key%20Findings~1

37. Stevenson CE. SF-36: Interim norms for Australian data [Internet]. Canberra: Australian Institute of Health and Welfare; 1996 [cited 2020 Oct 19]. Available from: https://www.aihw.gov.au/getmedia/13a09319-2ec0-4030-aa54-ac43478573e1/SF-36%20Interim%20norms%20for%20Australian%20data.pdf.aspx?inline=true

38. Food Standards Australia & New Zealand. Australian Food Composition Database [Internet]. Commonwealth of Australia; 2019 [cited 2020 Aug 28]. Available from: https://www.foodstandards.gov.au/science/monitoringnutrients/afcd/Pages/default.aspx

39. Food Standards Australia & New Zealand. AUSNUT 2007 [Internet]. Commonwealth of Australia; 2019 [cited 2020 Aug 28]. Available from: https://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/Pages/ausnut2007.aspx

40. Bjørklund G, Dadar M, Pen JJ, Chirumbolo S, Aaseth J. Chronic fatigue syndrome (CFS): Suggestions for a nutritional treatment in the therapeutic approach. Biomed Pharmacother. 2019;109:1000-7.

41. Castro-Marrero J, Faro M, Aliste L, Sáez-Francàs N, Calvo N, Martínez-Martínez A, et al. Comorbidity in chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide population-based cohort study. Psychosomatics. 2017;58(5):533-43.

42. Castro-Marrero J, Faro M, Zaragozá MC, Aliste L, de Sevilla TF, Alegre J. Unemployment and work disability in individuals with chronic fatigue syndrome/myalgic encephalomyelitis: A community-based cross-sectional study from Spain. BMC Public Health. 2019;19(1):840.

43. Słomko J, Newton JL, Kujawski S, Tafil-Klawe M, Klawe J, Staines D, et al. Prevalence and characteristics of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in Poland: A cross-sectional study. BMJ Open. 2019;9(3):e023955.

44. Faro M, Sàez-Francás N, Castro-Marrero J, Aliste L, Fernández de Sevilla T, Alegre J. Gender differences in chronic fatigue syndrome. Reumatol Clin. 2016;12(2):72-7.

45. Jones JF, Nisenbaum R, Reeves WC. Medication use by persons with chronic fatigue syndrome: Results of a randomized telephone survey in Wichita, Kansas. Health Qual Life Out. 2003;1(1):74.

46. Jason LA, Brown A, Clyne E, Bartgis L, Evans M, Brown M. Contrasting case definitions for chronic fatigue syndrome, myalgic encephalomyelitis/chronic fatigue syndrome and myalgic encephalomyelitis. Eval Health Prof. 2011;35(3):280-304. doi: 10.1177/0163278711424281

47. Boneva RS, Lin J-MS, Maloney EM, Jones JF, Reeves WC. Use of medications by people with chronic fatigue syndrome and healthy persons: A population-based study of fatiguing illness in Georgia. Health Qual Life Out. 2009;7(1):67.
48. Dykman KD, Tone C, Ford C, Dykman RA. The effects of nutritional supplements on the symptoms of fibromyalgia and chronic fatigue syndrome. Integr Physiol Behav Sci. 1998;33(1):61-71.
49. Maric D, Brkic S, Tomic S, Novakov Mikic A, Cebovic T, Turkulov V. Multivitamin mineral supplementation in patients with chronic fatigue syndrome. Med Sci Monit. 2014;20:47-53.
50. Brouwers FM, Van Der Werf S, Bleijenberg G, Van Der Zee L, Van Der Meer JW. The effect of a polynutrient supplement on fatigue and physical activity of patients with chronic fatigue syndrome: A double-blind randomized controlled trial. QJM. 2002;95(10):677-83.
51. Witham MD, Adams F, McSwiggan S, Kennedy G, Kabir G, Belch JJ, et al. Effect of intermittent vitamin D3 on vascular function and symptoms in chronic fatigue syndrome: A randomised controlled trial. Nutr Metab Cardiovasc Dis. 2015;25(3):287-94.
52. Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. 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. 2009;30(4):470-6.
53. Castro-Marrero J, Sáez-Francàs N, Segundo MJ, Calvo N, Faro M, Aliste L, et al. Effect of coenzyme Q10 plus nicotinamide adenine dinucleotide supplementation on

maximum heart rate after exercise testing in chronic fatigue syndrome – A randomized, controlled, double-blind trial. Clin Nutr. 2016;35(4):826-34.

54. Fukuda S, Nojima J, Kajimoto O, Yamaguti K, Nakatomi Y, Kuratsune H, et al. Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome. BioFactors. 2016;42(4):431-40.
55. Roman P, Carrillo-Trabalón F, Sánchez-Labraca N, Cañadas F, Estévez AF, Cardona D. Are probiotic treatments useful on fibromyalgia syndrome or chronic fatigue syndrome patients? A systematic review. Benef Microbes. 2018;9(4):603-11.
56. Sullivan A, Nord CE, Evengård B. Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome. Nutr J. 2009;8:4.
57. Venturini L, Bacchi S, Capelli E, Lorusso L, Ricevuti G, Cusa C. Modification of immunological parameters, oxidative stress markers, mood symptoms, and well-being status in CFS patients after probiotic intake: Observations from a pilot study. Oxid Med Cell Longev. 2019;2019:1684198.
58. Du Preez S, Corbitt M, Cabanas H, Eaton N, Staines D, Marshall-Gradisnik S. A systematic review of enteric dysbiosis in chronic fatigue syndrome/myalgic encephalomyelitis. Syst Rev. 2018;7(1):241.
59. Corbitt M, Campagnolo N, Staines D, Marshall-Gradisnik S. A systematic review of probiotic interventions for gastrointestinal symptoms and irritable bowel syndrome in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Probiotics Antimicro. 2018;10(3):466-77.
60. Fritz H, Flower G, Weeks L, Cooley K, Callachan M, McGowan J, et al. Intravenous vitamin C and cancer: A systematic review. Integr Cancer Ther. 2014;13(4):280-300.

61. Yeom CH, Jung GC, Song KJ. Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. J Korean Med Sci. 2007;22(1):7-11.

62. Gariballa S. Poor vitamin C status is associated with increased depression symptoms following acute illness in older people. Int J Vitam Nutr Res. 2014;84(1-2):12-7.

63. Goedendorp MM, Knoop H, Schippers GM, Bleijenberg G. The lifestyle of patients with chronic fatigue syndrome and the effect on fatigue and functional impairments. J Hum Nutr Diet. 2009;22(3):226-31.

64. Loblay RH, Swain AR. The role of food intolerance in chronic fatigue syndrome. The clinical and scientific basis of ME/CFS. New York: The Nightingale Research Foundation. 1992. p. 521-38.

65. Rowe PC, Underhill RA, Friedman KJ, Gurwitt A, Medow MS, Schwartz MS, et al. Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: A primer. Front Pediatr. 2017;5(121).

66. Royal Australasian College of Physicians. Chronic fatigue syndrome: Clinical practice guidelines – 2002 [Internet]. Sydney, Australia: Royal Australasian College of Physicians; 2002 [cited 2020 Sep 21]. 56 p. Available from: https://www.mja.com.au/system/files/issues/cfs2_2.pdf?fbclid=IwAR3dEhfszBGL8umStplzJb31heovK-JvIx1yJhZQ2KyNJSXn5BM7LMbUaMA

67. Ireland P, Jolley D, Giles G, O’Dea K, Powles J, Rutishauser I, et al. Development of the Melbourne FFQ: A food frequency questionnaire for use in an Australian prospective study involving an ethnically diverse cohort. Asia Pacific J Clin Nutr. 1994;3:19-31.

68. Bassett JK, English DR, Fahey MT, Forbes AB, Gurrin LC, Simpson JA, et al. Validity and calibration of the FFQ used in the Melbourne collaborative cohort study. Public Health Nutr. 2016;19(13):2357-68.

69. Kwak SG, Kim JH. Central limit theorem: the cornerstone of modern statistics. Korean J Anesthesiol. 2017;70(2):144-56.

Tables

Table 1. Frequency of sociodemographic characteristics

	N (%)
Gender	
Female	15 (75.0%)
Male	5 (25.0%)
Other	0 (0.0%)
Age (years, mean ± SD)	45.3 ± 10.2
Age of onset (years, mean ± SD)	30.8 ± 11.1
BMI (kg/m^2)	
Underweight (<18.5)	0 (0.0%)
Normal weight (18.5 – 24.9)	10 (50.0%)
Overweight (25.0 – 29.9)	9 (45.0%)
Obese (≥30.0)	1 (5.0%)
Location	
New South Wales	5 (25.0%)
Victoria	3 (15.0%)
Queensland	5 (25.0%)
South Australia	0 (0.0%)
Western Australia	4 (20.0%)
Northern Territory	0 (0.0%)
Australian Capital Territory	1 (5.0%)
Tasmania	2 (10.0%)
Employment	
Unemployed	16 (80.0%)
Part-time	3 (15.0%)
Full-time	1 (5.0%)
Education	
Primary school	0 (0.0%)
High school	2 (10.0%)
Professional training	2 (10.0%)
Undergraduate	11 (55.0%)
Postgraduate	5 (25.0%)

Abbreviations: *N* Number; *SD* Standard Deviation; *BMI* Body Mass Index

Table 2. Frequency of supplement use

	ME/CFS (N = 20) N (%)	AHS (N ≈ 12,153)* %
Supplement use		
Yes	18 (90.0%)	31.9%
One to three	4 (20.0%)	
Four to six	8 (40.0%)	
Seven to ten	6 (30.0%)	
No	2 (10.0%)	68.1%
Multi-vitamins or multi-minerals		
Yes	15 (75.0%)	10.1%
One to three	13 (65.0%)	
Four or more	2 (10.0%)	
No	3 (15.0%)	
Single vitamins or single minerals		
Yes	14 (70.0%)	
One to three	12 (60.0%)	
Four or more	2 (10.0%)	
No	4 (20.0%)	
Calcium		
Yes	2 (10.0%)	4.1%
No	16 (80.0%)	
Magnesium		
Yes	6 (30.0%)	1.0%
No	12 (60.0%)	
Zinc		
Yes	8 (40.0%)	0.4%
No	10 (50.0%)	
Vitamin C		
Yes	2 (10.0%)	3.9%
No	16 (80.0%)	
Vitamin D		
Yes	6 (30.0%)	4.3%
No	12 (60.0%)	
Lipid supplements		
Yes	7 (35.0%)	14.0%
One to three	7 (35.0%)	
Four or more	0 (0.0%)	
No	11 (55.0%)	
Fish oil		
Yes	6 (30.0%)	11.5%
No	12 (60.0%)	
Evening primrose oil		
Yes	1 (5.0%)	0.5%
No	17 (85.0%)	

Table 2 (continued).

Herbal or plant-based supplements		
Yes	6 (30.0%)	4.2%
One to three	6 (30.0%)	
Four or more	0 (0.0%)	
No	12 (60.0%)	
Other nutritive supplements		
Yes	3 (15.0%)	1.3%
One to three	3 (15.0%)	
Four or more	0 (0.0%)	
No	15 (75.0%)	
Fibre supplements		
Yes	1 (5.0%)	0.7%
No	17 (85.0%)	
Protein or amino acid supplements		
Yes	2 (10.0%)	0.6%
No	16 (80.0%)	
Other non-nutritive supplements		
Yes	11 (55.0%)	5.3%
One to three	11 (55.0%)	
Four or more	0 (0.0%)	
No	7 (35.0%)	
Probiotics		
Yes	9 (45.0%)	1.0%
No	9 (45.0%)	
CoQ10		
Yes	5 (25.0%)	0.8%
No	13 (65.0%)	
Other supplements		
Yes	0 (0.0%)	0.4%
No	18 (90.0%)	

Abbreviations: *N* Number; *ME/CFS* Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; *AHS* Australian Health Survey; *N* Number; *CoQ10* Coenzyme Q10

**N* is equal to the total number of participants aged over 2 years; however, percentages are of the total number of participants aged over 19 years.

Table 3. Daily nutritional intake

	ME/CFS (N = 20) Mean ± SD	**AHS (N ≈ 12,153)[†] Mean ± SD**	***t***	***P***
Energy (kJ/day)	8,092.76 ± 2,324.61	8,671.70 ± 5,735.84	-1.11	0.279
Macronutrients				
Protein (g/day)	83.70 ± 21.14	91.00 ± 70.22	-1.55	0.139
Total fat (g/day)	94.19 ± 32.86	73.80 ± 65.09	**2.78***	0.012
Saturated fats (g/day)	26.47 ± 9.58	27.70 ± 27.48	-0.57	0.574
Monounsaturated fats (g/day)	43.48 ± 17.90	28.40 ± 28.18	**3.77****	0.001
Polyunsaturated fats (g/day)	17.33 ± 8.26	11.40 ± 12.57	**3.21****	0.005
Linoleic acid (g/day)	15.31 ± 7.63	9.40 ± 10.36	**3.46****	0.003
Alpha-linolenic acid (g/day)[‡]	1.46 ± 1.15	1.40 ± 1.85	1.16	0.135
Long-chain omega 3 fatty acids[‡] (mg/day)	298.87 ± 171.74	281.40 ± 1,240.87	**1.86****	0.002
Total carbohydrate (g/day)	165.44 ± 68.76	225.90 ± 174.32	**-3.93*****	<0.001
Sugars (g/day)[‡]	84.42 ± 42.62	102.90 ± 113.44	**1.55***	0.017
Starch (g/day)	77.65 ± 45.70	118.30 ± 117.37	**-3.98*****	<0.001
Dietary fibre (g/day)	25.78 ± 11.17	22.90 ± 22.72	1.15	0.264
Alcohol (g/day)[‡]	1.84 ± 4.59	14.40 ± 46.04	**2.38*****	<0.001
Vitamins				
Vitamin A retinol equivalents (µg/day)	1,026.77 ± 410.29	851.80 ± 2,535.38	1.91	0.072
Natural folate (µg/day)[‡]	365.29 ± 99.84	287.80 ± 285.55	**1.91****	0.001
Folic acid (µg/day)[‡]	86.12 ± 100.64	192.60 ± 297.25	**1.85****	0.002
Total folates (µg/day)[‡]	451.50 ± 163.16	480.80 ± 424.03	1.26	0.085
Vitamin B3 (mg/day)	21.16 ± 6.83	23.90 ± 18.44	-1.80	0.089
Vitamin B6 (mg/day)[‡]	1.18 ± 0.52	1.50 ± 2.15	**1.54***	0.018
Vitamin B12 (mg/day)	3.07 ± 1.63	4.50 ± 6.95	**-3.94*****	<0.001
Vitamin C (mg/day)	133.46 ± 63.55	102.30 ± 146.61	**2.19***	0.041
Vitamin E (mg/day)	13.45 ± 5.96	10.50 ± 11.58	**2.21***	0.039

Table 3 (continued).

Minerals				
Calcium (mg/day)	802.70 ± 273.94	804.60 ± 798.30	-0.03	0.976
Iodine (µg/day)	126.01 ± 48.23	172.30 ± 151.96	**-4.29*****	<0.001
Iron (mg/day)[‡]	12.25 ± 4.24	11.10 ± 9.79	**1.54***	0.018
Magnesium (mg/day)	449.34 ± 153.62	338.70 ± 261.37	**3.22****	0.004
Phosphorus (mg/day)	1,382.95 ± 318.71	1,466.90 ± 970.27	-1.18	0.253
Potassium (mg/day)	3,588.29 ± 985.25	2,912.50 ± 2,247.53	**3.07****	0.006
Sodium (mg/day)	1,908.93 ± 573.56	2,430.50 ± 1,875.58	**-4.07*****	<0.001
Zinc (mg/day)	10.09 ± 3.38	11.00 ± 9.70	-1.21	0.242
Caffeine (mg/day)[‡]	367.65 ± 312.95	159.60 ± 246.32	**1.42***	0.036
Cholesterol (mg/day)	295.31 ± 144.61	300.50 ± 364.40	-0.16	0.874

Abbreviations: *N* Number; *ME/CFS* Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; *AHS* Australian Health Survey

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

† *N* is equal to the total number of participants aged over 2 years; however, percentages are of the total number of participants aged over 19 years.

‡ Non-normally-distributed variable; therefore, *D*-statistic is provided instead of *t*-score.

Table 4. Daily intake (g/day) of major and sub-major food groups

	ME/CFS (N = 20) Mean ± SD	AHS (N ≈ 12,153)[†] Mean ± SD	*D*	*P*
Non-alcoholic beverages				
Water	1,410.00 ± 715.23	1,071.70 ± 1,535.88	1.26	0.082
Herbal tea	314.71 ± 367.10	13.40 ± 106.36	2.05***	<0.001
Cereals and cereal products				
Gluten-free bread	15.32 ± 40.04	0.40 ± 6.57	2.13***	<0.001
Pasta and noodles	30.64 ± 26.94	17.90 ± 140.10	2.01***	<0.001
Breakfast cereals	18.47 ± 29.23	20.50 ± 61.02	1.65**	0.009
Porridge	9.62 ± 19.34	18.80 ± 109.84	1.93**	0.001
Sweet biscuits	3.49 ± 8.22	8.20 ± 31.64	1.92**	0.001
Fats and oils				
Butter	1.53 ± 2.10	1.70 ± 9.18	1.91**	0.001
Fruits and fruit products				
Berries	12.35 ± 14.95	4.50 ± 36.71	2.02***	<0.001
Oranges	22.27 ± 32.97	11.50 ± 87.48	2.00***	<0.001
Bananas	28.72 ± 36.29	18.80 ± 72.54	1.78**	0.004
Pineapples	2.79 ± 4.79	1.20 ± 23.15	2.14***	<0.001
Meat, poultry, and animal products				
Eggs	32.84 ± 29.20	7.70 ± 34.80	1.85**	0.002
Chicken	36.25 ± 28.56	24.30 ± 107.15	1.84**	0.002
Sausages	6.10 ± 11.59	10.20 ± 68.59	1.97***	<0.001
Processed meat	3.54 ± 4.31	11.20 ± 49.39	2.11***	<0.001
Bacon	3.74 ± 5.69	2.80 ± 20.37	1.99***	<0.001
Milk and dairy products				
Yoghurt	38.86 ± 39.32	23.80 ± 107.57	1.85**	0.002
Cream and sour cream	2.35 ± 4.00	1.60 ± 19.23	2.09***	<0.001
Flavoured milk	0.00 ± 0.00	27.50 ± 190.99	2.49***	<0.001

Table 4 (continued).

Vegetable products				
Carrots	14.44 ± 12.95	8.80 ± 51.42	**1.96***	<0.001
Pumpkin	12.01 ± 12.04	4.00 ± 33.95	**2.03***	<0.001
Squash and zucchini	9.35 ± 10.57	1.20 ± 16.27	**2.11***	<0.001
Mushrooms	5.94 ± 8.76	1.40 ± 16.51	**2.09***	<0.001
Sweet corn	7.22 ± 7.80	4.60 ± 36.51	**2.01***	<0.001
Snack foods				
Corn chips	4.77 ± 11.54	0.70 ± 13.74	**2.15***	<0.001
Sugar products				
Sugar	1.00 ± 3.08	5.10 ± 17.43	**2.30***	<0.001
Jam and related spreads	5.78 ± 16.81	2.20 ± 15.76	**1.99***	<0.001
Chocolate	8.75 ± 14.07	6.90 ± 31.95	**1.85**	0.002
Other confectionary	3.42 ± 12.18	2.80 ± 18.83	**1.97***	<0.001
Alcoholic beverages				
Light beer	0.28 ± 0.89	28.00 ± 308.67	**2.38***	<0.001
Heavy beer	5.35 ± 17.08	88.70 ± 576.92	**2.28***	<0.001
Red wine	7.26 ± 17.60	25.80 ± 167.81	**1.97***	<0.001
White wine	14.55 ± 50.64	26.20 ± 155.97	**2.00***	<0.001

Abbreviations: *N* Number; *ME/CFS* Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; *AHS* Australian Health Survey

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

† *N* is equal to the total number of participants aged over 2 years; however, percentages are of the total number of participants aged over 19 years.

Table 5. Multivariate analysis of physical HRQoL domains

	PF			RP			BP			GH		
	β	*t*	*P*	*β*	*t*	*P*	*β*	*t*	*P*	*β*	*t*	*P*
Sociodemographic data												
Age (years)	0.082	0.382	0.708	0.288	1.313	0.212	0.084	0.400	0.695	0.181	0.954	0.356
Gender	-0.099	-0.480	0.639	-0.396	-1.933	0.075	-0.131	-0.613	0.550	-0.460	**-2.509***	0.025
BMI (kg/m^2)	-0.663	**-3.324****	0.005	-0.089	-0.410	0.689	0.001	0.003	0.998	0.179	1.015	0.327
Employment	-0.069	-0.344	0.736	-0.108	-0.552	0.590	-0.441	-2.002	0.067	0.110	0.600	0.558
Education	0.028	0.136	0.894	0.624	**2.267***	0.041	0.152	0.729	0.479	-0.396	**-2.194***	0.046
Dietary supplementation												
Total number of supplements used												
Multi-vitamins or multi-minerals							-0.316	-1.937	0.079			
Single vitamins or single minerals												
Calcium												
Magnesium												
Zinc												
Vitamin C												
Vitamin D												
Probiotics												
CoQ10												
Daily nutritional intake												
Total protein (g/day)												
Total fat (g/day)							0.703	**3.786****	0.003			
Total carbohydrate (g/day)												
Natural folate (µg/day)												
Folic acid (µg/day)				0.826	**3.066****	0.009						
Vitamin B6 (mg/day)	-0.368	-1.924	0.075				0.593	1.843	0.092			

Table 5 (continued).

Vitamin B12 (mg/day)												
Vitamin C (mg/day)										0.454	**2.688***	0.018
Vitamin E (mg/day)												
Iodine (µg/day)				0.469	1.919	0.077						
Iron (mg/day)												
Magnesium (mg/day)												
Potassium (mg/day)							-1.149	**-3.083***	0.010			
Sodium (mg/day)												
Caffeine (mg/day)												
R^2			0.523			0.599			0.744			0.626
Adjusted R^2			0.318			0.383			0.535			0.466
***P*-value**			0.069			0.053			**0.026***			**0.017***

Abbreviations: *PF* Physical Functioning; *RP* Role of limitations due to physical health problems; *BP* Bodily Pain; *GH* General health perceptions; *CoQ10* Coenzyme Q10

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

Table 6. Multivariate analysis of mental HRQoL domains

	SF			MH			RE		
	β	*t*	*P*	*β*	*t*	*P*	*β*	*t*	*P*
Sociodemographic data									
Age (years)	0.273	1.160	0.267	0.788	**3.934****	0.002	0.073	0.292	0.775
Gender	-0.209	-0.885	0.392	-0.199	-1.237	0.240	0.012	0.048	0.962
BMI (kg/m^2)	-0.213	-0.958	0.356	-0.072	-0.448	0.662	0.384	1.590	0.134
Employment	0.024	0.105	0.918	-0.186	-1.035	0.321	0.005	0.022	0.983
Education	0.506	1.887	0.082	0.515	**2.826***	0.015	0.268	1.115	0.284
Dietary supplementation									
Total number of supplements used									
Multi-vitamins or multi-minerals									
Single vitamins or single minerals									
Calcium									
Magnesium							0.454	1.974	0.068
Zinc									
Vitamin C	0.408	1.894	0.081	0.572	**3.694****	0.003			
Vitamin D									
Probiotics									
CoQ10									
Daily nutritional intake									
Total protein (g/day)				0.651	**3.228****	0.007			
Total fat (g/day)									
Total carbohydrate (g/day)									
Natural folate (µg/day)									
Folic acid (µg/day)									
Vitamin B6 (mg/day)									

Table 6 (continued).

Vitamin B12 (mg/day)									
Vitamin C (mg/day)									
Vitamin E (mg/day)									
Iodine (µg/day)	0.674	**2.407***	0.032						
Iron (mg/day)									
Magnesium (mg/day)									
Potassium (mg/day)									
Sodium (mg/day)									
Caffeine (mg/day)				-0.396	-2.081	0.060			
***R*²**			0.473			0.760			0.348
Adjusted *R*²			0.190			0.601			0.068
***P*-value**			0.202			**0.008****			0.342

Abbreviations: *SF* Social Functioning; *MH* General mental health; *RE* Role of limitations due to emotional problem; *CoQ10* Coenzyme Q10
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Supplementary material

Supplementary Table 1. Inclusion and exclusion criteria

Inclusion/eligibility criteria	To be considered for inclusion in the study, participants must: 1. Have received a diagnosis of ME/CFS according to the Canadian Consensus Criteria from a healthcare professional. 2. Be aged between 18 and 65 years. 3. Be a resident of Australia.
Exclusion criteria	Participants meeting the following criteria must be excluded from the study: 1. Have a BMI under 18.5. 2. Are a current smoker. 3. Have received a diagnosis of Coeliac disease, ulcerative colitis, Crohn’s disease, or another pre-existing chronic illness other than ME/CFS.

Supplementary Table 2. Multivariate analysis of PF

	PF				
	B (95% CI)	SE(B)	*ß*	*t*	*P*
Sociodemographic data					
Age (years)	0.161 (-0.743 – 1.065)	0.421	0.082	0.382	0.708
Gender	-4.897 (-26.782 – 16.988)	10.204	-0.099	-0.480	0.639
BMI (kg/m^2)	**-3.519 (-5.789 – -1.248)**	1.059	-0.663	**-3.324****	0.005
Employment	-2.574 (-18.628 – 13.480)	7.485	-0.069	-0.344	0.736
Education	0.692 (-10.232 – 11.616)	5.093	0.028	0.136	0.894
Dietary supplementation					
Total number of supplements used					
Multi-vitamins or multi-minerals					
Single vitamins or single minerals					
Calcium					
Magnesium					
Zinc					
Vitamin C					
Vitamin D					
Probiotics					
CoQ10					
Daily nutritional intake					
Total protein (g/day)					
Total fat (g/day)					
Total carbohydrate (g/day)					
Natural folate (µg/day)					
Folic acid (µg/day)					
Vitamin B6 (mg/day)	-15.141 (-32.024 – 1.741)	7.872	-0.368	-1.924	0.075
Vitamin B12 (mg/day)					
Vitamin C (mg/day)					
Vitamin E (mg/day)					
Iodine (µg/day)					

Supplementary Table 2 (continued).

Iron (mg/day)	
Magnesium (mg/day)	
Potassium (mg/day)	
Sodium (mg/day)	
Caffeine (mg/day)	
R^2	0.523
Adjusted *R^2*	0.318
***P*-value**	0.069

Abbreviations: *PF* Physical Functioning; *CI* Confidence Interval; *SE* Standard Error; *BMI* Body Mass Index; *CoQ10* Coenzyme Q10

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

Supplementary Table 3. Multivariate analysis of RP

	RP				
	B (95% CI)	SE(B)	*ß*	*t*	*P*
Sociodemographic data					
Age (years)	0.329 (-0.212 – 0.870)	0.250	0.288	1.313	0.212
Gender	-11.427 (-24.202 – 1.347)	5.913	-0.396	-1.933	0.075
BMI (kg/m^2)	-0.276 (-1.730 – 1.178)	0.673	-0.089	-0.410	0.689
Employment	-2.346 (-11.524 – 6.833)	4.249	-0.108	-0.552	0.590
Education	**9.091 (0.426 – 17.755)**	4.011	0.624	**2.267***	0.041
Dietary supplementation					
Total number of supplements used					
Multi-vitamins or multi-minerals					
Single vitamins or single minerals					
Calcium					
Magnesium					
Zinc					
Vitamin C					
Vitamin D					
Probiotics					
CoQ10					
Daily nutritional intake					
Total protein (g/day)					
Total fat (g/day)					
Total carbohydrate (g/day)					
Natural folate (µg/day)					
Folic acid (µg/day)	**0.094 (0.028 – 0.161)**	0.031	0.826	**3.066****	0.009
Vitamin B6 (mg/day)					
Vitamin B12 (mg/day)					
Vitamin C (mg/day)					
Vitamin E (mg/day)					
Iodine (µg/day)	0.120 (-0.015 – 0.255)	0.062	0.469	1.919	0.077

Supplementary Table 3 (continued).

Iron (mg/day)	
Magnesium (mg/day)	
Potassium (mg/day)	
Sodium (mg/day)	
Caffeine (mg/day)	
R^2	0.599
Adjusted R^2	0.383
***P*-value**	0.053

Abbreviations: *RP* Role of limitations due to physical health problems; *CI* Confidence Interval; *SE* Standard Error; *BMI* Body Mass Index; *CoQ10* Coenzyme Q10

$^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

Supplementary Table 4. Multivariate analysis of BP

	BP				
	B (95% CI)	SE(B)	*ß*	*t*	*P*
Sociodemographic data					
Age (years)	0.186 (-0.819 – 1.192)	0.465	0.084	0.400	0.695
Gender	-7.311(-33.064 – 18.441)	11.920	-0.131	-0.613	0.550
BMI (kg/m^2)	0.023 (-17.507 – 17.553)	8.114	0.001	0.003	0.998
Employment	-18.609 (-38.689 – 1.471)	9.295	-0.441	-2.002	0.067
Education	4.298 (-8.432 – 17.028)	5.892	0.152	0.729	0.479
Dietary supplementation					
Total number of supplements used					
Multi-vitamins or multi-minerals	-14.308 (-30.563 – 1.947)	7.385	-0.316	-1.937	0.079
Single vitamins or single minerals					
Calcium					
Magnesium					
Zinc					
Vitamin C					
Vitamin D					
Probiotics					
CoQ10					
Daily nutritional intake					
Total protein (g/day)					
Total fat (g/day)	**0.550 (0.230 – 0.870)**	0.145	0.703	**3.786****	0.003
Total carbohydrate (g/day)					
Natural folate (µg/day)					
Folic acid (µg/day)					
Vitamin B6 (mg/day)	27.595 (-5.353 – 60.543)	14.970	0.593	1.843	0.092
Vitamin B12 (mg/day)					
Vitamin C (mg/day)					
Vitamin E (mg/day)					
Iodine (µg/day)					

Supplementary Table 4 (continued).

Iron (mg/day)					
Magnesium (mg/day)					
Potassium (mg/day)	**-0.030 (-0.051 – -0.009)**	0.010	-1.149	**-3.083***	0.010
Sodium (mg/day)					
Caffeine (mg/day)					
R^2					0.744
Adjusted R^2					0.535
***P*-value**					**0.026***

Abbreviations: *BP* Bodily Pain; *CI* Confidence Interval; *SE* Standard Error; *BMI* Body Mass Index; *CoQ10* Coenzyme Q10

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

Supplementary Table 5. Multivariate analysis of SF

	SF				
	B (95% CI)	SE(B)	*ß*	*t*	*P*
Sociodemographic data					
Age (years)	0.551 (-0.475 – 1.578)	0.475	0.273	1.160	0.267
Gender	-10.664 (-36.702 – 15.374)	12.053	-0.209	-0.885	0.392
BMI (kg/m^2)	-1.168 (-3.802 – 1.467)	1.219	-0.213	-0.958	0.356
Employment	0.908 (-17.801 – 19.617)	8.660	0.024	0.105	0.918
Education	13.020 (-1.886 – 27.927)	6.900	0.506	1.887	0.082
Dietary supplementation					
Total number of supplements used					
Multi-vitamins or multi-minerals					
Single vitamins or single minerals					
Calcium					
Magnesium					
Zinc					
Vitamin C	30.166 (-4.242 – 64.573)	15.927	0.408	1.894	0.081
Vitamin D					
Probiotics					
CoQ10					
Daily nutritional intake					
Total protein (g/day)					
Total fat (g/day)					
Total carbohydrate (g/day)					
Natural folate (µg/day)					
Folic acid (µg/day)					
Vitamin B6 (mg/day)					
Vitamin B12 (mg/day)					
Vitamin C (mg/day)					
Vitamin E (mg/day)					
Iodine (µg/day)	**0.304 (0.031 – 0.576)**	0.126	0.674	**2.407***	0.032

Supplementary Table 5 (continued).

Iron (mg/day)	
Magnesium (mg/day)	
Potassium (mg/day)	
Sodium (mg/day)	
Caffeine (mg/day)	
$\boldsymbol{R^2}$	0.473
Adjusted $\boldsymbol{R^2}$	0.190
***P*-value**	0.202

Abbreviations: *SF* Social Functioning; *CI* Confidence Interval; *SE* Standard Error; *BMI* Body Mass Index; *CoQ10* Coenzyme Q10

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

Supplementary Table 6. Multivariate analysis of MH

	MH				
	B (95% CI)	SE(B)	*ß*	*t*	*P*
Sociodemographic data					
Age (years)	**0.740 (0.330 – 1.149)**	0.188	0.788	**3.934****	0.002
Gender	-4.711 (-13.008 – 3.586)	3.808	-0.199	-1.237	0.240
BMI (kg/m^2)	-0.184 (-1.082 – 0.713)	0.412	-0.072	-0.448	0.662
Employment	-3.324 (-10.322 – 3.673)	3.212	-0.186	-1.035	0.321
Education	**6.159 (1.411 – 10.906)**	2.179	0.515	**2.826***	0.015
Dietary supplementation					
Total number of supplements used					
Multi-vitamins or multi-minerals					
Single vitamins or single minerals					
Calcium					
Magnesium					
Zinc					
Vitamin C	**19.681 (8.072 – 31.291)**	5.328	0.572	**3.694****	0.003
Vitamin D					
Probiotics					
CoQ10					
Daily nutritional intake					
Total protein (g/day)	**0.313 (0.102 – 0.524)**	0.097	0.651	**3.228****	0.007
Total fat (g/day)					
Total carbohydrate (g/day)					
Natural folate (µg/day)					
Folic acid (µg/day)					
Vitamin B6 (mg/day)					
Vitamin B12 (mg/day)					
Vitamin C (mg/day)					
Vitamin E (mg/day)					
Iodine (µg/day)					

Supplementary Table 6 (continued).

Iron (mg/day)					
Magnesium (mg/day)					
Potassium (mg/day)					
Sodium (mg/day)					
Caffeine (mg/day)	-0.013 (-0.026 – 0.001)	0.006	-0.396	-2.081	0.060
***R*²**					0.760
Adjusted *R*²					0.601
***P*-value**					**0.008****

Abbreviations: *MH* General mental health; *CI* Confidence Interval; *SE* Standard Error; *BMI* Body Mass Index; *CoQ10* Coenzyme Q10
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Supplementary Table 7. Multivariate analysis of RE

	RE				
	B (95% CI)	SE(B)	*ß*	*t*	*P*
Sociodemographic data					
Age (years)	0.212 (-1.347 – 1.772)	0.727	0.073	0.292	0.775
Gender	0.878 (-38.063 – 39.820)	18.156	0.012	0.048	0.962
BMI (kg/m^2)	3.042 (-1.062 – 7.145)	1.913	0.384	1.590	0.134
Employment	0.282 (-27.797 – 28.361)	13.092	0.005	0.022	0.983
Education	9.946 (-2.613 – 62.940)	8.917	0.268	1.115	0.284
Dietary supplementation					
Total number of supplements used					
Multi-vitamins or multi-minerals					
Single vitamins or single minerals					
Calcium					
Magnesium	30.164 (-2.613 – 62.940)	15.282	0.454	1.974	0.068
Zinc					
Vitamin C					
Vitamin D					
Probiotics					
CoQ10					
Daily nutritional intake					
Total protein (g/day)					
Total fat (g/day)					
Total carbohydrate (g/day)					
Natural folate (µg/day)					
Folic acid (µg/day)					
Vitamin B6 (mg/day)					
Vitamin B12 (mg/day)					
Vitamin C (mg/day)					
Vitamin E (mg/day)					
Iodine (µg/day)					

Supplementary Table 7 (continued).

Iron (mg/day)	
Magnesium (mg/day)	
Potassium (mg/day)	
Sodium (mg/day)	
Caffeine (mg/day)	
R^2	0.348
Adjusted R^2	0.068
***P*-value**	0.342

Abbreviations: *RE* Role of limitations due to emotional problems; *CI* Confidence Interval; *SE* Standard Error; *BMI* Body Mass Index; *CoQ10* Coenzyme Q10

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

Supplementary Table 8. Multivariate analysis of GH

	GH				
	B (95% CI)	SE(B)	*ß*	*t*	*P*
Sociodemographic data					
Age (years)	0.230 (-0.287 – 0.747)	0.241	0.181	0.954	0.356
Gender	**-14.713 (-27.289 – -2.137)**	5.863	-0.460	**-2.509***	0.025
BMI (kg/m^2)	0.616 (-0.685 – 1.917)	0.607	0.179	1.015	0.327
Employment	2.653 (-6.824 – 12.130)	4.419	0.110	0.600	0.558
Education	**-6.399 (-12.653 – -0.144)**	2.916	-0.396	**-2.194***	0.046
Dietary supplementation					
Total number of supplements used					
Multi-vitamins or multi-minerals					
Single vitamins or single minerals					
Calcium					
Magnesium					
Zinc					
Vitamin C					
Vitamin D					
Probiotics					
CoQ10					
Daily nutritional intake					
Total protein (g/day)					
Total fat (g/day)					
Total carbohydrate (g/day)					
Natural folate (µg/day)					
Folic acid (µg/day)					
Vitamin B6 (mg/day)					
Vitamin B12 (mg/day)					
Vitamin C (mg/day)	**0.102 (0.021 – 0.183)**	0.038	0.454	**2.688***	0.018
Vitamin E (mg/day)					
Iodine (µg/day)					

Supplementary Table 8 (continued).

Iron (mg/day)	
Magnesium (mg/day)	
Potassium (mg/day)	
Sodium (mg/day)	
Caffeine (mg/day)	
$\boldsymbol{R^2}$	0.626
Adjusted $\boldsymbol{R^2}$	0.466
***P*-value**	**0.017***

Abbreviations: *GH* General health perceptions; *CI* Confidence Interval; *SE* Standard Error; *BMI* Body Mass Index; *CoQ10* Coenzyme Q10

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