



Vitamin and mineral supplements and fatigue: a prospective study

Sisi Xie^{1,4} · Pedro Marques-Vidal¹ · Vanessa Kraege^{1,2,3}

Received: 22 August 2024 / Accepted: 9 February 2025
© The Author(s) 2025

Abstract

Purpose The consumption of vitamin/mineral supplements (VMS) and vitamin/mineral and/or dietary supplements (VMDS) is popular among the general population. However, the association of VMS/VMDS with fatigue remains sparse and conclusions are mixed. We aimed to understand the association between VMS/VMDS and fatigue.

Methods Prospective study in the city of Lausanne, Switzerland, including 1361 participants (50.3% female, mean age 61.0±9.4 years). Participants were divided into VMS/VMDS users and non-users. Fatigue levels were assessed using the Fatigue Severity Scale (FSS) and the 14-item version of the Chalder Fatigue Scale (CFS). Statistical analyses included multivariable logistic regression for categorical outcomes and analysis of variance for continuous outcomes, adjusting for relevant covariates.

Results No association was found between VMS consumption and changes in FSS (mean±standard error 0.05±0.03 vs. -0.06±0.14 for non-consumers and consumers, respectively, $p=0.440$) and CFS (-0.05±0.06 vs. 0.22±0.28, $p=0.388$). Similarly, no effect of VMS consumption was found on incidence odds ratio and 95% confidence interval: 1.75 (0.82–3.74), $p=0.149$ or remission 1.36 (0.49–3.74), $p=0.550$ of clinical fatigue. Similar findings were obtained for VMDS: FSS 0.06±0.04 vs. 0±0.08, $p=0.577$; CFS -0.07±0.08 vs. 0.04±0.15, $p=0.545$ for non-consumers and consumers, respectively. OR 1.96 (1.20–3.20), $p=0.008$ and 1.14 (0.57–2.31), $p=0.712$ for incidence and remission of fatigue. Alternate or persistent VMS/VMDS consumers had a higher incidence of clinical fatigue and a higher increase in FSS compared with never consumers.

Conclusion In this population-based sample, we found no consistent association between VMS or VMDS consumption and remission of fatigue. Conversely, VMDS users tended to develop greater fatigue.

Keywords Vitamins · Minerals · Fatigue · Epidemiology · Nutrients

Introduction

Fatigue is a common symptom in primary care, usually characterized by low energy, mental exhaustion, and poor muscle endurance. It can have a negative impact on work, family, and society [1]. Fatigue encompasses complex physiological and psychological processes. Biologically, it is closely associated with disorders in energy metabolism. For instance, abnormalities in mitochondrial structure and function can result in inadequate cellular energy production, leading to fatigue [2–4]. Additionally, inflammation, immune system dysregulation, impaired hypothalamic-pituitary-adrenal axis function, and neuroendocrine disorders can negatively impact an individual's mental state and contribute to fatigue [5–7]. Psychological factors, including chronic stress, depressive symptoms, and sleep disturbances, also play significant roles in the development of

✉ Sisi Xie
Sisi.Xie@unil.ch
Pedro Marques-Vidal
Pedro-Manuel.Marques-Vidal@chuv.ch
Vanessa Kraege
vanessa.kraege@chuv.ch

¹ Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne University Hospital, Rue du Bugnon 46, 1011 Lausanne, Switzerland

² Medical Directorate, Lausanne University Hospital (CHUV), Lausanne, Switzerland

³ Innovation and Clinical Research Directorate, Lausanne University Hospital (CHUV), Lausanne, Switzerland

⁴ Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

fatigue [8–10]. In healthy people, the underlying cause for fatigue is often unknown, and treatment options are scarce; thus, attempts to alleviate or prevent fatigue through nutritional supplements have emerged as a possibility.

The consumption of vitamin/mineral supplements (VMS) and vitamin/mineral and/or dietary supplements (VMDS) is popular among the general population. In Switzerland, 16.8% of the population aged 35 to 75 uses multivitamin and mineral supplements [11]. In the United States, there is a multibillion-dollar dietary supplement industry, at least one-third of which is sold as vitamin/mineral pills and beverages [12]. Research investigating the association between VMS/VMDS and fatigue in the general population is limited and has produced inconsistent findings. Some studies suggest that supplementation with VMS/VMDS can partially alleviate fatigue [13]. However, other research indicates that VMS/VMDS have no significant effect on reducing fatigue [14–16]. Although VMS are beneficial for people with certain clinical diseases [17–20], and with nutritional deficiencies [21, 22], in the general population, most individuals can meet their needs through a healthy diet, so micronutrient supplements are unlikely to be of any benefit [23] and may on the contrary be harmful if taken in excess [12]. Still, most people believe that taking supplements regularly will help them stay healthy, prevent disease, and live longer. This belief is further increased by an aggressive marketing of VMS and VMDS producers, who promote their products as a remedy against fatigue (<https://www.naturalia.fr/esprit-bio/parlons-bio/vitamines-contre-la-fatigue>, <https://nutriandco.com/fr/pages/vitamine-contre-la-fatigue>).

Therefore, we aimed to examine the association between VMS, VMDS and fatigue over a mean follow-up of 3.8 years by using data from a population-based prospective study to clarify and solidify recommendations and ensure accurate, useful distribution of information at a population level.

Participants and methods

Participants and study design

We used data from CoLaus|PsyCoLaus (www.colauspsycolaus.ch), a population-based study initiated in 2003 with 6733 middle-aged participants from Lausanne, Switzerland to investigate the epidemiology and genetic determinants of cardiovascular risk factors [24]. Recruitment began in 2003 and ended in 2006. The first follow-up was performed between 2009 and 2012, the second between 2014 and 2017 and the third between 2018 and 2021.

Fatigue status was only collected in the second and the third follow-ups. Hence, for this study, data collected from

the second (2014–2017) and third (2018–2021) follow-ups were examined, see supplementary Table 1 for more details. In addition, when we analyzed whether participants consumed VMS or VMDS continuously, we included data from the first follow-up of the original study (2009–2012). We define “never” as no consumption at the first (2009–2012) and second (2014–2017) follow-ups of the original study, “alternate” as consumption at the first or second follow-up and “persistent” as consumption at both the first and second follow-ups.

Vitamin/Mineral/Dietary supplements consumption

Within each survey, participants were asked to report all prescribed and over-the-counter medications and supplements taken during the previous six months. Nonetheless, data on the dosages and frequency of these supplements were not obtained. Vitamin and mineral supplements were defined according to the Swiss compendium (compendium.ch/home/fr, assessed June 2017). If the supplements were not listed in the Swiss compendium, further searches on the internet were conducted. Due to wide differences in the composition of Swiss VMS [23] and to inaccurate reporting (i.e., reporting “multivitamins from producer X” that manufactures six different types of multivitamins), it was not possible to assess the amounts of vitamins and minerals consumed by participants. Dietary supplements were defined as any other supplement that could not be considered as a VMS, such as plant extracts not considered as phytotherapy by the Swiss compendium, cod liver oil, shark cartilage or amino acids.

Assessment of fatigue

Fatigue levels were assessed once within each survey using the Fatigue Severity Scale (FSS) and the 14-item version of the Chalder Fatigue Scale (CFS).

Fatigue during the previous week was assessed by the 9-item FSS [25]. This questionnaire has been validated for a general healthy population in the Swiss setting [26] and has a high test-retest reliability [27]. The questionnaire is composed of nine questions; responses are graded using a Likert scale from 1 to 7, where 1 indicates strong disagreement and 7 strong agreements. The final score is the mean value of the 9 responses, and a score ≥ 4 is considered as severe fatigue. Fatigue was also assessed using the 14-item CFS [28]. In this study, a binary coding (presence/absence) was applied to the items, as it has been shown that near-maximal scoring of the 14 items constituting the Chalder fatigue scale supports the validity of a two-point scoring rather than the four-point Likert scoring [29].

Changes in fatigue status were computed as follows: first, using dichotomous data (clinical fatigue yes/no) at follow-up 2 (FU2), we assessed the incidence of fatigue at follow-up 3 (FU3) among participants without fatigue at FU2, and remission of fatigue at FU3 among participants with fatigue at FU2, for FSS and CFS. Second, we computed the changes in FSS and CFS as the score at FU3 minus the score at FU2; a positive value denotes an improvement (decrease) in fatigue status. Third, we compared the FSS and CFS scales at FU3 between VMS (VMDS) consumers and non-consumers.

Relevant covariates

We selected potential confounding factors based on the literature on the relationship between VMS and fatigue. We selected age (years), sex (male/female), education, marital status, weekly alcohol consumption (units), smoking, hypertension (yes/no), diabetes (yes/no), body mass index (BMI) categories and quality of dietary intake, the collection of which is detailed below.

Education was categorized into high (university), middle (high school) and low (apprenticeship + mandatory). Marital status was defined as living alone (single, divorced, widowed) or with a partner. Usual alcohol consumption during the week was self-reported as number of units (glasses of wine, bottles or cans of beer, and shots of spirits) per week. Smoking was self-reported and categorized as never, former (irrespective of the time since quitting smoking) and current.

Body weight and height were measured with participants barefoot and in light indoor clothes. Body weight was measured in kilograms to the nearest 100 g using a Seca[®] scale (Hamburg, Germany). Height was measured to the nearest 5 mm using a Seca[®] (Hamburg, Germany) height gauge. BMI was calculated and categorized as normal (<25 kg/m²), overweight ≥ 25 and <30 kg/m² and obese ≥ 30 kg/m² [30].

Blood pressure (BP) was measured using an Omron[®] HEM-907 automated oscillometric sphygmomanometer after at least a 10-minute rest in a seated position, and the average of the last two measurements was used. Hypertension was defined by a systolic BP ≥ 140 mm Hg or a diastolic BP ≥ 90 mm Hg or presence of antihypertensive drug treatment [31].

Glucose was assessed by glucose dehydrogenase. Diabetes mellitus (DM) was defined as fasting plasma glucose ≥ 7.0 mmol/L and/or presence of oral hypoglycaemic or insulin treatment [32].

Dietary intake was assessed using a self-administered, semi-quantitative food frequency questionnaire (FFQ) validated on the Geneva population [33]. Briefly, this FFQ assesses the dietary intake of the previous 4 weeks and

consists of 97 different food items that account for more than 90% of the intake of calories, proteins, fat, carbohydrates, alcohol, cholesterol, vitamin D and retinol, and 85% of fibre, carotene, and iron. Dietary quality was assessed via the Alternative Healthy Eating Index (AHEI) adapted from McCullough et al. [34]. In our study, the amount of *trans* fat could not be assessed, and we considered all participants taking multivitamins as taking them for a duration ≥ 5 years. Thus, the modified AHEI score ranged between 2.5 and 77.5 instead of 2.5 and 87.5 for the original AHEI score. Higher values represented a healthier diet.

Exclusion criteria

We excluded participants with missing data for (1) follow-up 3; (2) fatigue; and (3) covariates.

Statistical analysis

Statistical analyses were conducted using Stata v.18 (Stata Corp, College Station, TX, USA). Descriptive results were expressed as number of participants (percentage) for categorical variables and as average \pm standard deviation for continuous variables. Between-group comparisons were conducted using chi-square for categorical variables and student's t-test for continuous variables. Multivariable analyses were conducted using logistic regression for categorical variables, and results were expressed as odds ratio and (95% confidence interval). Multivariable analyses were conducted using analysis of variance (ANOVA) for quantitative variables and results were expressed as adjusted mean \pm standard error. Multivariable analyses were adjusted for the covariates defined previously.

As a significant number of participants were excluded, we conducted sensitivity analyses using inverse probability weighting as defined previously [35]. First, we computed the probability of being included using a logistic model including the variables that differed significantly between included and excluded participants, then we used the inverse of this probability as weight for the multivariable logistic models described previously.

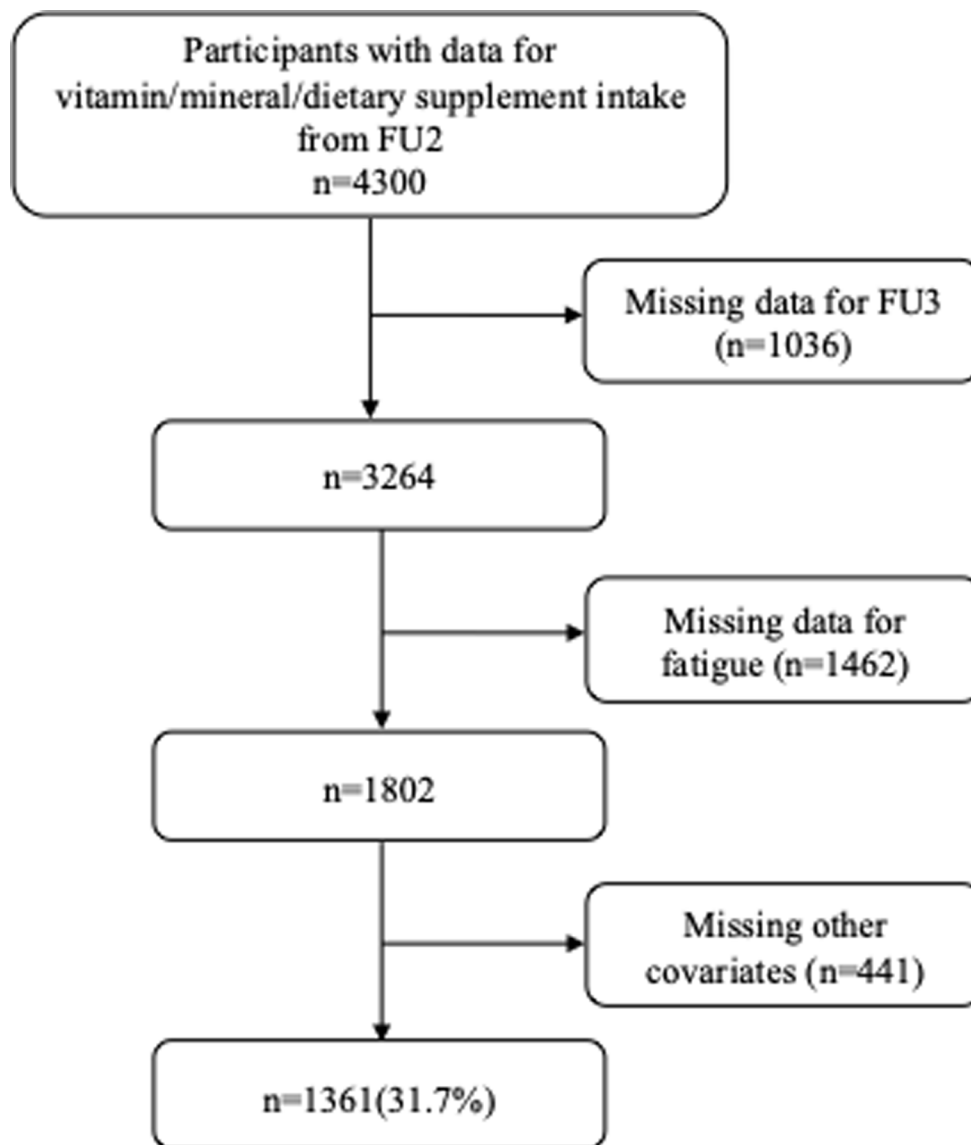
Statistical significance was considered for a two-sided test with $p < 0.05$.

Results

Selection of participants

Of the initial 4300 participants, 1361 (31.7%) were included in the analyses. The reasons for exclusion are indicated in Fig. 1 and the comparison between included and excluded

Fig. 1 Selection of participants from FU2 (2014–2017). CoLaus study, Lausanne, Switzerland



participants is provided in Supplementary Table 2. Compared with the included participants, excluded participants were older, more frequently female, living alone, abstaining from alcohol, and with lower education levels, and more frequently with hypertension, diabetes, obesity, and lower total energy intake. Excluded participants scored higher than included participants regarding FSS and CFS.

Among participants enrolled in the study at the FU2, 79 (5.8%) consumed VMS and 350 (25.7%) consumed VMDS. Table 1 summarizes the characteristics of participants according to VMS and VMDS consumption. Compared with participants who did not consume VMS, participants who consumed VMS were more frequently female, lived alone, and had higher education levels and AHEI (Table 1). Compared with participants who did not consume VMDS, participants who consumed VMDS were older, more frequently female, highly educated, lived alone,

abstaining from alcohol, and non-obese, and had a higher AHEI (Table 1).

Association between VMS and VMDS consumption and change in fatigue indicators

A summary of the association between VMS consumption and changes in fatigue indicators after a median follow-up of 3.8 (interquartile range: 3.6–3.9) years is shown in Table 2. In bivariate and multivariable analyses, there was no association between VMS consumption and changes of FSS and CFS, incidence or remission of clinical fatigue, and fatigue scores at FU3 (Table 2). Figures 2 and 3 show the differences between FU3 and FU2 in FSS and CFS, respectively.

A summary of the association between VMDS consumption and changes in fatigue indicators is shown in Table 3. In bivariate and multivariable analyses, there was

Table 1 Characteristics of the participants, according to VMS use, FU2 (2014–2017) of the CoLaus|PsyColaus study, Lausanne, Switzerland

	VMS non-consumers (<i>n</i> =1282)	VMS consumers (<i>n</i> =79)	<i>P</i> -value	VMDS non-consumers (<i>n</i> =1011)	VMDS consumers (<i>n</i> =350)	<i>P</i> -value
Age (years)	61.0±9.5	61.0±9.0	0.989	60.7±9.3	62.1±9.7	0.015
Women (%)	634 (49.5)	51 (64.6)	0.009	458 (45.3)	227 (64.9)	<i>P</i><0.001
Educational level (%)			0.028			0.028
Low	572 (44.6)	26 (32.9)		461 (45.6)	137 (39.2)	
Middle	402 (31.4)	24 (30.4)		317 (31.4)	109 (31.1)	
High	308 (24.0)	29 (36.7)		233 (23.0)	104 (29.7)	
Marital status, %			0.002			0.002
Living alone	406 (31.7)	38 (48.1)		306 (30.3)	138 (39.4)	
Living in a couple	876 (68.3)	41 (51.9)		705 (69.7)	212 (60.6)	
Alcohol consumption, %			0.758			0.029
None	238 (18.6)	18 (22.8)		172 (17.0)	84 (24.0)	
1–13 units/week	852 (66.5)	48 (60.8)		681 (67.4)	219 (62.6)	
14–27 units/week	162 (12.6)	11 (13.9)		135 (13.3)	38 (10.8)	
28+ units/week	30 (2.3)	2 (2.5)		23 (2.3)	9 (2.6)	
Smoking categories (%)			0.479			0.371
Never	525 (41.0)	27 (34.2)		421 (41.6)	131 (37.4)	
Former	521 (40.6)	35 (44.3)		404 (40.0)	152 (43.4)	
Current	236 (18.4)	17 (21.5)		186 (18.4)	67 (19.2)	
BMI categories (%)			0.371			0.027
Normal	574 (47.8)	32 (40.5)		433 (42.8)	173 (49.4)	
Overweight	518 (40.4)	38 (48.1)		417 (41.3)	139 (39.7)	
Obese	190 (14.8)	9 (11.4)		161 (15.9)	38 (10.9)	
Hypertension (%)	524 (40.9)	30 (38.0)	0.611	416 (41.2)	138 (39.4)	0.573
Diabetes (%)	90 (7.0)	3 (3.8)	0.271	71 (7.0)	22 (6.3)	0.638
Total energy intake (kcal/d)	1735±616	1611±491	0.081	1733±613	1713±600	0.595
AHEI	31.9±10.0	35.7±10.1	0.001	31.2±9.7	34.7±10.6	<i>P</i><0.001

Results are expressed as number of participants (column percentage) for categorical variables and as average±standard deviation for continuous variables. Between-group comparisons performed using chi-square for categorical variables and student's *t*-test for continuous variables. Abbreviations: VMS: Vitamin/mineral supplements; VMDS: Vitamin/mineral and/or dietary supplements; BMI: Body mass index; AHEI: Alternate Healthy Eating Index

Table 2 Bivariate and multivariable associations between VMS consumption and changes in fatigue, CoLaus|PsyColaus study, Lausanne, Switzerland

	Bivariate			Multivariable		
	VMS non-consumers	VMS consumers	<i>P</i> -value	VMS non-consumers	VMS consumers	<i>P</i> -value
Incident clinical fatigue ¹	1 (ref.)	1.63 (0.78–3.42)	0.193	1 (ref.)	1.75 (0.82–3.74)	0.149
Remission of clinical fatigue ²	1 (ref.)	1.17 (0.47–2.92)	0.742	1 (ref.)	1.36 (0.49–3.74)	0.550
Changes in Fatigue score ³	0.05±0.03	-0.05±0.14	0.462	0.05±0.03	-0.06±0.14	0.440
Changes in Chalder score ⁴	-0.05±0.06	0.18±0.28	0.415	-0.05±0.06	0.22±0.28	0.338
Fatigue score ⁵	2.83±1.38	2.99±1.41	0.314	2.83±0.04	2.95±0.16	0.439
Chalder score ⁵	5.54±2.47	6.13±2.79	0.069	5.54±0.07	6.02±0.31	0.139

Results are expressed as average±standard deviation for bivariate analysis and as multivariable-adjusted average±standard error or odds ratio and 95% confidence interval. Between group comparison using ANOVA or logistic regression, multivariable analysis adjusted for age, sex, BMI categories (normal, overweight, obese), education (low/medium/high), marital status (alone, in couple), smoking (never, former, current), alcohol consumption (none, 1–13, 14–27 and 28+ per week), hypertension (yes, no), diabetes (yes, no), total energy intake (continuous), AHEI (continuous). Abbreviations: VMS: Vitamin/mineral supplements; 1: among participants who did not have clinical fatigue at FU2. 2: among participants with clinical fatigue at FU2. 3: The change in Fatigue score is the Fatigue score at FU3 minus the fatigue score at FU2. 4: The change in Chalder score is the Chalder score at FU3 minus the fatigue score at FU2. 5: The value of the FU3

Fig. 2 Differences in Fatigue Severity Scale between the FU3 and the FU2

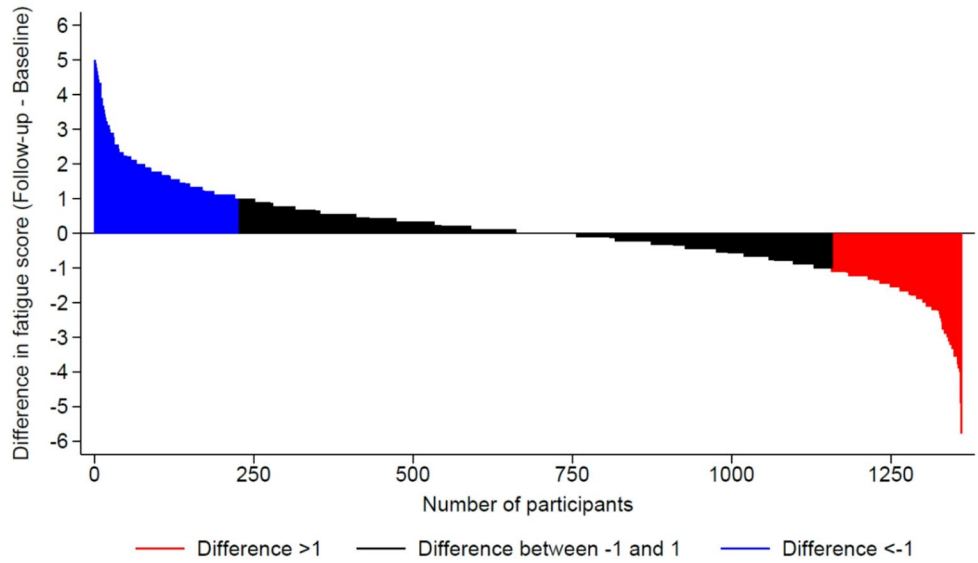


Fig. 3 Differences in Chalder Fatigue Scale between the FU3 and the FU2

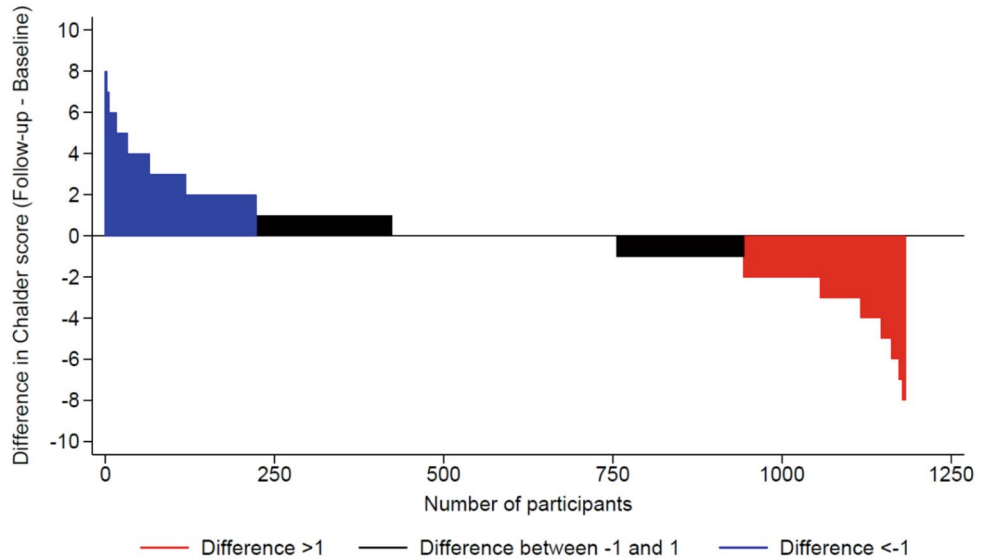


Table 3 Bivariate and multivariable associations between VMDS consumption and changes in fatigue, CoLaus|PsyColaus study, Lausanne, Switzerland

	Bivariate			Multivariable		
	VMDS non-consumers	VMDS consumers	P-value	VMDS non-consumers	VMDS consumers	P-value
Incident clinical fatigue ¹	1 (ref.)	1.64 (1.07–2.49)	0.022	1 (ref.)	1.96 (1.20–3.20)	0.008
Remission of clinical fatigue ²	1 (ref.)	0.85 (0.50–1.44)	0.542	1 (ref.)	1.14 (0.57–2.31)	0.712
Changes in Fatigue score ³	0.06±0.04	0.01±0.06	0.562	0.06±0.04	0±0.08	0.577
Changes in Chalder score ⁴	0±0.07	-0.16±0.13	0.269	-0.07±0.08	0.04±0.15	0.545
Fatigue score ⁵	2.77±1.35	3.01±1.48	0.005	2.78±0.05	2.99±0.09	0.053
Chalder score ⁵	5.42±2.41	6.03±2.67	P<0.001	5.44±0.09	5.98±0.17	0.008

Results are expressed as average±standard deviation or number of participants (column percentage) for bivariate analysis and as multivariable-adjusted average±standard error or odds ratio and 95% confidence interval. Between group comparison using ANOVA or logistic regression, multivariable analysis adjusted for age, sex, BMI categories (normal, overweight, obese), education(low/medium/high), marital status (alone, in couple), smoking (never, former, current), alcohol consumption (none, 1–13, 14–27 and 28+per week), hypertension (yes, no), diabetes (yes, no), total energy intake (continuous), AHEI (continuous). Abbreviations: VMDS: Vitamin/mineral and/or dietary supplements; 1: among participants who did not have clinical fatigue at FU2. 2: among participants with clinical fatigue at FU2. 3: The change in Fatigue score is the Fatigue score at FU3 minus the fatigue score at FU2. 4: The change in Chalder score is the Chalder score at FU3 minus the fatigue score at FU2. 5: The value of the FU3

Table 4 The association between VMS and VMDS consumption based on the FU1 (2009–2012) and the FU2 (2014–2017) of the original study, and evolution of fatigue between FU2 (2014–2017) and FU3 (2018–2021), CoLausPsyColaus study, Lausanne, Switzerland

	Never	Alternate	Persistent	<i>P</i> -value for trend
For VMS consumption				
Incident clinical fatigue ¹	1 (ref.)	1.27 (0.58–2.79)	3.81 (1.31–11.12)	0.014
Remission of clinical fatigue ²	1 (ref.)	1.56 (0.66–3.68)	nc	nc
Changes in Fatigue score ³	0.05±0.03	-0.12±0.12	0.57±0.27	0.053
Changes in Chalder score ⁴	-0.06±0.07	0.07±0.24	0.72±0.53	0.145
Fatigue score ⁵	2.81±0.04	3.05±0.14	3.13±0.3	0.291
Chalder score ⁵	5.53±0.07	6.02±0.27	5.71±0.59	0.759
For VMDS consumption				
Incident clinical fatigue ¹	1 (ref.)	1.36 (0.82–2.26)	2.73 (1.42–5.27)	0.003
Remission of clinical fatigue ²	1 (ref.)	1.22 (0.62–2.4)	0.7 (0.22–2.17)	0.531
Changes in Fatigue score ³	0.06±0.04	-0.03±0.07	0.14±0.12	0.544
Changes in Chalder score ⁴	-0.07±0.08	-0.02±0.14	0.14±0.24	0.427
Fatigue score ⁵	2.79±0.05	2.86±0.08	3.15±0.14	0.017
Chalder score ⁵	5.45±0.09	5.83±0.16	5.9±0.27	0.119

Nc, not computable. Results are expressed as multivariable-adjusted average±standard error or odds ratio and 95% confidence interval. Between group comparison using ANOVA or logistic regression adjusting for age, sex, BMI categories (normal, overweight, obese), education (low/medium/high), marital status (alone, in couple), smoking (never, former, current), alcohol consumption (none, 1–13, 14–27 and 28+ per week), hypertension (yes, no), diabetes (yes, no), total energy intake (continuous), alternate healthy eating index (continuous). Abbreviations: VMS: Vitamin/mineral supplements; VMDS: Vitamin/mineral and/or dietary supplements. 1: among participants who did not have clinical fatigue at FU2. 2: among participants with clinical fatigue at FU2. 3: The change in Fatigue score is the Fatigue score at FU3 minus the fatigue score at FU2. 4: The change in Chalder score is the Chalder score at FU3 minus the fatigue score at FU2. 5: The value of the FU3

no association between VMDS consumption and changes of CFS and FSS, remission of clinical fatigue (Table 3). However, participants consuming VMDS had higher incidence of clinical fatigue and CFS (Table 3).

Using inverse probability weighting to correct for exclusions led to similar findings (supplementary Table 3).

Association between VMS and VMDS (non) persistent consumption and change in fatigue indicators

The association between never, alternate, or persistent VMS and VMDS consumption and fatigue indicators at follow-up are indicated in Table 4. For VMS, multivariable analysis showed that alternate or persistent VMS consumers had a higher incidence of clinical fatigue compared with never consumers. Similar findings were obtained for VMDS, alternate or persistent consumers having a higher incidence of clinical fatigue than never consumers and FSS. Using inverse probability weighting to correct for exclusions led to similar findings (supplementary Table 4).

Discussion

In this study, we investigated the association between VMS consumption and VMDS and fatigue in community-dwelling Swiss adults. Our prospective study failed to find any evidence of a beneficial effect of VMS and VMDS consumption and changes in fatigue status.

Association between VMS and VMDS and fatigue

There are few studies on the potential association between vitamins and minerals and dietary supplements and fatigue in the general population, and the conclusions are mixed. Therefore, in Supplementary Table 5 we summarize the effects of oral vitamins and minerals and dietary supplements on fatigue, according to literature.

Vitamin and mineral supplements

Several studies have shown that individual supplements of vitamin B1 [36], vitamin B12 [37], vitamin C [17, 38], vitamin D [21, 39, 40], vitamin E [41], as well as iron [42, 43], and zinc [44] can relieve fatigue symptoms. Similarly, supplementing with a variety of vitamins and minerals can also reduce fatigue to a certain extent [13].

However, contrary to the above positive results, several studies found no effect of vitamin or mineral supplements in reducing fatigue. A randomized controlled trial showed that oral vitamin D3 did not improve fatigue in patients with chronic fatigue syndrome [14]. Data from Brouwers et al. found no statistically significant relationship between multivitamins and mineral supplementation and symptoms of chronic fatigue syndrome [15]. Also, a meta-analysis revealed that vitamin and mineral status did not lead to clinical improvement in chronic fatigue syndrome [16].

We found that, for participants devoid of fatigue at FU2, after 3.8 years of follow-up, VMS consumption had no effect on the incidence of fatigue. Moreover, for participants who presented with fatigue at FU2, after 3.8 years of follow-up, consuming VMS had no effect on remission. Hence, our results confirm the negative findings of previous studies [14–16].

However, interestingly, when we categorized VMS consumption as never, alternate, and persistent, and among participants devoid of fatigue at FU2, participants who consumed VMS alternatively or persistently had a higher prevalence of clinical fatigue at follow-up and a higher increase in FSS score than participants who never consumed VMS. One possible explanation for this finding is that some participants consume VMS to avoid fatigue in the future. Still, as no information was collected regarding the reason to consume VMS, further studies are needed to clarify this issue.

Dietary supplements

As shown in Supplementary Table 5, supplements such as dietary polysaccharides [45], coenzyme Q10 [46, 47], omega-3 polyunsaturated fatty acids [48], dietary nitrate [49, 50], soluble dietary fiber [51], astaxanthin and sesamin [52], acetyl L-carnitine [53], superoxide dismutase-melon concentrate supplementation [54], and gut probiotics [55] have been suggested to reduce fatigue burden. However, two systematic reviews found limited evidence that dietary supplements can help relieve symptoms of chronic fatigue syndrome, findings being inconsistent across studies [56, 57]. Another study showed no significant association between dietary supplement intake and fatigue severity or functional impairment [58].

In our study, among participants devoid of fatigue at FU2, those who consumed VMDS had a higher incidence of fatigue and had higher FSS and CFS scores after 3.8 years of follow-up than those who did not consume VMDS. Similar findings were obtained when we categorized VMDS consumption as never, alternate, and persistent, persistent consumers having a higher incidence of fatigue and higher FSS scores after 3.8 years of follow-up.

For participants who presented with fatigue at FU2, after 3.8 years of follow-up, consuming VMDS had no effect on remission, and similar findings were obtained when we categorized VMDS consumption as never, alternate, and persistent. Again, a possible explanation is that participants consume VMDS in the hope of reducing the fatigue that may occur.

Potential mechanisms and explanations

The reasons why this study failed to find a beneficial effect of VMS and VMDS on fatigue may include the following: (1) Most of the general population already meets their micronutrient requirements through a balanced diet. Therefore, additional supplement intake may not bring additional benefits in terms of fatigue reduction. In some cases, excessive intake of certain vitamins and minerals may even lead to adverse reactions, which may aggravate fatigue symptoms [12]. (2) The association we observed between continuous or occasional use of supplements and increased fatigue prevalence may reflect reverse causation. That is, individuals who feel tired are more likely to use supplements in the hope of relieving symptoms, rather than supplements causing fatigue. This self-selection bias complicates the interpretation of observational data. (3) Fatigue is a multifactorial condition that is affected by a combination of biological, psychological, and social factors. VMS and VMDS may not address the complex mechanisms that cause fatigue, such as chronic inflammation, hormone imbalance, or psychological stress. Effective fatigue management may require comprehensive lifestyle adjustments, psychological interventions, and targeted medical treatments. (4) The effectiveness of supplements may vary depending on their formulation, dosage, and bioavailability. Differences in product quality and the presence of other active or inactive ingredients may affect their potential effects on fatigue, leading to inconsistent study results.

Strengths and limitations

This is a prospective study with a large population-based sample, making our findings more generalizable than studies conducted in experimental settings or within specific populations such as athletes [36, 51]. Second, we used two methods to quantify/classify fatigue, leading to similar findings.

Our study also has some limitations. First, the inaccurate reporting of VMS composition and dosages by the participants prevented us from assessing the amount of vitamins and minerals consumed by participants. Second, the study was conducted in a limited geographical location, which might not be representative of the entire country. Still, the prevalence of VMS or VMDS users was similar to other countries [59, 60]. Third, possible reverse causation (i.e., participants taking VMS/VMDS to prevent fatigue) cannot be excluded, although it is unlikely that participants consuming VMS/VMDS did so to prevent fatigue over a 5-year period.

Conclusion

In this Swiss population-based sample, no consistent association was found between the consumption of VMS and VMDS and fatigue incidence or remission. Therefore, in the general population, consumption of VMS and VMDS does not have a significant impact on fatigue.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00394-025-03615-y>.

Acknowledgements The authors would like to thank all the people who participated in the recruitment of the participants, data collection and validation, particularly Nicole Bonvin, Yolande Barreau, Mathieu Firmann, François Bastardot, Julien Vaucher, Panagiotis Antiochos, Cédric Gubelmann, Marylène Bay, Benoît Delabays and Adelin Barrier.

Authors contribution Sisi Xie: formal analysis, investigation, visualization, writing-original draft. Vanessa Kraege and Pedro Marques-Vidal: conceptualization, supervision, validation, writing-review & editing.

Funding Open access funding provided by University of Lausanne. The CoLaus|PsyCoLaus study was supported by unrestricted research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (grants 3200B0-105993, 3200B0-118308, 33CSO-122661, 33CS30-139468, 33CS30-148401, 33CS30_177535 and 3247730_204523) and the Swiss Personalized Health Network (grant 2018DRI01). The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Data availability The data of CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of the Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals requiring baseline data only, will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate.

Declarations

Ethics approval The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the CoLaus-PsyCoLaus study (project number PB_2018-00038, reference 239/09). All participants gave their signed informed consent before entering the study.

Competing interests The authors have no competing interests to declare that are relevant to the content of this article.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Nicholson K, Stewart M, Thind A (2015) Examining the symptom of fatigue in primary care: a comparative study using electronic medical records. *J Innov Health Inf* 22:235–243. <https://doi.org/10.14236/jhi.v22i1.91>
2. Tomas C, Brown AE, Newton JL, Elson JL (2019) Mitochondrial complex activity in permeabilised cells of chronic fatigue syndrome patients using two cell types. *PeerJ* 7:e6500. <https://doi.org/10.7717/peerj.6500>
3. Plioplys AV, Plioplys S (1995) Electron-microscopic investigation of muscle mitochondria in chronic fatigue syndrome. *Neuropsychobiology* 32:175–181. <https://doi.org/10.1159/000119233>
4. Tomas C, Brown A, Strassheim V et al (2017) Cellular bioenergetics is impaired in patients with chronic fatigue syndrome. *PLoS ONE* 12:e0186802. <https://doi.org/10.1371/journal.pone.0186802>
5. Hughes A, Kumari M (2018) Age modification of the relationship between C-reactive protein and fatigue: findings from understanding Society (UKHLS). *Psychol Med* 48:1341–1349. <https://doi.org/10.1017/s0033291717002872>
6. Mensah FKF, Bansal AS, Ford B, Cambridge G (2017) Chronic fatigue syndrome and the immune system: where are we now? *Neurophysiol Clin* 47:131–138. <https://doi.org/10.1016/j.neucli.2017.02.002>
7. Tsigos C, Chrousos GP (2002) Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res* 53:865–871. [https://doi.org/10.1016/s0022-3999\(02\)00429-4](https://doi.org/10.1016/s0022-3999(02)00429-4)
8. Kerr JR, Matthey DL (2008) Preexisting psychological stress predicts acute and chronic fatigue and arthritis following symptomatic parvovirus B19 infection. *Clin Infect Dis* 46:e83–e87. <https://doi.org/10.1086/533471>
9. Kampaite A, Gustafsson R, York EN et al (2024) Brain connectivity changes underlying depression and fatigue in relapsing-remitting multiple sclerosis: a systematic review. *PLoS ONE* 19:e0299634. <https://doi.org/10.1371/journal.pone.0299634>
10. Lee KA (2001) Sleep and fatigue. *Annu Rev Nurs Res* 19:249–273
11. Marques-Vidal P, Pécoud A, Hayoz D et al (2009) Prevalence and characteristics of vitamin or dietary supplement users in Lausanne, Switzerland: the CoLaus study. *Eur J Clin Nutr* 63:273–281. <https://doi.org/10.1038/sj.ejcn.1602932>
12. McCormick DB (2010) Vitamin/mineral supplements: of questionable benefit for the general population. *Nutr Rev* 68:207–213. <https://doi.org/10.1111/j.1753-4887.2010.00279.x>
13. Maric D, Brkic S, Tomic S et al (2014) Multivitamin mineral supplementation in patients with chronic fatigue syndrome. *Med Sci Monit* 20:47–53. <https://doi.org/10.12659/msm.889333>

14. 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. <https://doi.org/10.1016/j.numecd.2014.10.007>
15. Van Der Brouwers FM, 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. <https://doi.org/10.1093/qjmed/95.10.677>
16. Joustra ML, Minovic I, Janssens KAM et al (2017) Vitamin and mineral status in chronic fatigue syndrome and fibromyalgia syndrome: a systematic review and meta-analysis. *PLoS ONE* 12:e0176631. <https://doi.org/10.1371/journal.pone.0176631>
17. Huck CJ, Johnston CS, Beezhold BL, Swan PD (2013) Vitamin C status and perception of effort during exercise in obese adults adhering to a calorie-reduced diet. *Nutrition* 29:42–45. <https://doi.org/10.1016/j.nut.2012.01.021>
18. 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. <https://doi.org/10.1002/biof.1293>
19. Cordero MD, Alcocer-Gómez E, de Miguel M et al (2013) Can coenzyme q10 improve clinical and molecular parameters in fibromyalgia? *Antioxid Redox Signal* 19:1356–1361. <https://doi.org/10.1089/ars.2013.5260>
20. Costantini A, Pala MI, Tundo S, Matteucci P (2013) High-dose thiamine improves the symptoms of fibromyalgia. *BMJ Case Rep* 2013:. <https://doi.org/10.1136/bcr-2013-009019>
21. Roy S, Sherman A, Monari-Sparks MJ et al (2014) Correction of low vitamin D improves fatigue: effect of correction of low vitamin D in fatigue study (EViDiF study). *N Am J Med Sci* 6:396–402. <https://doi.org/10.4103/1947-2714.139291>
22. Brass EP, Adler S, Sietsema KE et al (2001) Intravenous L-carnitine increases plasma carnitine, reduces fatigue, and may preserve exercise capacity in hemodialysis patients. *Am J Kidney Dis* 37:1018–1028. [https://doi.org/10.1016/s0272-6386\(05\)80019-8](https://doi.org/10.1016/s0272-6386(05)80019-8)
23. Droz N, Marques-Vidal P (2014) Multivitamins/multiminerals in Switzerland: not as good as it seems. *Nutr J* 13:24. <https://doi.org/10.1186/1475-2891-13-24>
24. Firmann M, Mayor V, Vidal PM et al (2008) The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 8:6. <https://doi.org/10.1186/1471-2261-8-6>
25. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 46:1121–1123. <https://doi.org/10.1001/archneur.1989.00520460115022>
26. Valko PO, Bassetti CL, Bloch KE et al (2008) Validation of the fatigue severity scale in a Swiss cohort. *Sleep* 31:1601–1607. <https://doi.org/10.1093/sleep/31.11.1601>
27. Dittner AJ, Wessely SC, Brown RG (2004) The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 56:157–170. [https://doi.org/10.1016/s0022-3999\(03\)00371-4](https://doi.org/10.1016/s0022-3999(03)00371-4)
28. Chalder T, Berelowitz G, Pawlikowska T et al (1993) Development of a fatigue scale. *J Psychosom Res* 37:147–153. [https://doi.org/10.1016/0022-3999\(93\)90081-p](https://doi.org/10.1016/0022-3999(93)90081-p)
29. Morriss RK, Wearden AJ, Mullis R (1998) Exploring the validity of the Chalder fatigue scale in chronic fatigue syndrome. *J Psychosom Res* 45:411–417. [https://doi.org/10.1016/s0022-3999\(98\)00022-1](https://doi.org/10.1016/s0022-3999(98)00022-1)
30. Jensen MD, Ryan DH, Apovian CM et al (2014) 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the obesity society. *J Am Coll Cardiol* 63:2985–3023. <https://doi.org/10.1016/j.jacc.2013.11.004>
31. McEvoy JW, McCarthy CP, Bruno RM et al (2024) 2024 ESC guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 45:3912–4018. <https://doi.org/10.1093/eurheartj/ehae178>
32. Cosentino F, Grant PJ, Aboyans V et al (2020) 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 41:255–323. <https://doi.org/10.1093/eurheartj/ehz486>
33. Beer-Borst S, Costanza MC, Pechère-Bertschi A, Morabia A (2009) Twelve-year trends and correlates of dietary salt intakes for the general adult population of Geneva, Switzerland. *Eur J Clin Nutr* 63:155–164. <https://doi.org/10.1038/sj.ejcn.1602922>
34. McCullough ML, Feskanich D, Stampfer MJ et al (2002) Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. *Am J Clin Nutr* 76:1261–1271. <https://doi.org/10.1093/ajcn/76.6.1261>
35. Narduzzi S, Golini MN, Porta D et al (2014) [Inverse probability weighting (IPW) for evaluating and correcting selection bias]. *Epidemiol Prev* 38:335–341
36. Suzuki M, Itokawa Y (1996) Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis* 11:95–106. <https://doi.org/10.1007/bf02080935>
37. van Campen CLM, Riepma K, Visser FC (2019) Open trial of vitamin B12 nasal drops in adults with myalgic Encephalomyelitis/Chronic fatigue syndrome: comparison of responders and non-responders. *Front Pharmacol* 10:1102. <https://doi.org/10.3389/fphar.2019.01102>
38. Suh SY, Bae WK, Ahn HY et al (2012) Intravenous vitamin C administration reduces fatigue in office workers: a double-blind randomized controlled trial. *Nutr J* 11:7. <https://doi.org/10.1186/1475-2891-11-7>
39. Al-Eisa ES, Alghadir AH, Gabr SA (2016) Correlation between vitamin D levels and muscle fatigue risk factors based on physical activity in healthy older adults. *Clin Interv Aging* 11:513–522. <https://doi.org/10.2147/cia.S102892>
40. Nowak A, Boesch L, Andres E et al (2016) Effect of vitamin D3 on self-perceived fatigue: a double-blind randomized placebo-controlled trial. *Med (Baltim)* 95:e5353. <https://doi.org/10.1097/md.0000000000005353>
41. Takemoto D, Yasutake Y, Tomimori N et al (2015) Sesame lignans and vitamin E supplementation improve subjective statuses and anti-oxidative capacity in healthy humans with feelings of daily fatigue. *Glob J Health Sci* 7:1–10. <https://doi.org/10.5539/gjhs.v7n6p1>
42. Patterson AJ, Brown WJ, Roberts DC (2001) Dietary and supplement treatment of iron deficiency results in improvements in general health and fatigue in Australian women of childbearing age. *J Am Coll Nutr* 20:337–342. <https://doi.org/10.1080/07315724.2001.10719054>
43. Favrat B, Balck K, Breyman C et al (2014) Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women—PREFER—a randomized, placebo-controlled study. *PLoS ONE* 9:e94217. <https://doi.org/10.1371/journal.pone.0094217>
44. Afzali A, Goli S, Moravveji A et al (2021) The effect of zinc supplementation on fatigue among elderly community dwellers: a parallel clinical trial. *Health Sci Rep* 4:e301. <https://doi.org/10.1002/hsr2.301>
45. Zhou Y, Chu Z, Luo Y et al (2023) Dietary polysaccharides exert anti-fatigue functions via the gut-muscle Axis: advances and perspectives. *Foods* 12. <https://doi.org/10.3390/foods12163083>
46. Castro-Marrero J, Segundo MJ, Lacasa M et al (2021) Effect of Dietary Coenzyme Q10 Plus NADH supplementation on fatigue

- perception and health-related quality of life in individuals with myalgic Encephalomyelitis/Chronic fatigue syndrome: a prospective, randomized, Double-Blind, placebo-controlled trial. *Nutrients* 13. <https://doi.org/10.3390/nu13082658>
47. Mizuno K, Tanaka M, Nozaki S et al (2008) Antifatigue effects of coenzyme Q10 during physical fatigue. *Nutrition* 24:293–299. <https://doi.org/10.1016/j.nut.2007.12.007>
 48. Maes M, Mihaylova I, Leunis JC (2005) In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. *Neuro Endocrinol Lett* 26:745–751
 49. Husmann F, Bruhn S, Mittlmeier T et al (2019) Dietary nitrate supplementation improves Exercise Tolerance by reducing muscle fatigue and perceptual responses. *Front Physiol* 10:404. <https://doi.org/10.3389/fphys.2019.00404>
 50. Zoughaib WS, Hoffman RL, Yates BA et al (2023) The influence of acute dietary nitrate supplementation on skeletal muscle fatigue and recovery in older women. *Physiol Rep* 11:e15694. <https://doi.org/10.14814/phy2.15694>
 51. Hadžić E, Starcevic A, Rupčić T et al (2023) Effects of Soluble Dietary Fibre on Exercise performance and perception of fatigue in young basketball players. *Food Technol Biotechnol* 61:389–401. <https://doi.org/10.17113/ftb.61.03.23.8124>
 52. Imai A, Oda Y, Ito N et al (2018) Effects of Dietary supplementation of astaxanthin and sesamin on daily fatigue: a Randomized, Double-Blind, Placebo-Controlled, two-way crossover study. <https://doi.org/10.3390/nu10030281>. *Nutrients* 10:
 53. Malaguarnera M, Gargante MP, Cristaldi E et al (2008) Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. *Arch Gerontol Geriatr* 46:181–190. <https://doi.org/10.1016/j.archger.2007.03.012>
 54. Carillon J, Notin C, Schmitt K et al (2014) Dietary supplementation with a superoxide dismutase-melon concentrate reduces stress, physical and mental fatigue in healthy people: a randomised, double-blind, placebo-controlled trial. *Nutrients* 6:2348–2359. <https://doi.org/10.3390/nu6062348>
 55. 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. <https://doi.org/10.1186/1475-2891-8-4>
 56. Jones K, Probst Y (2017) Role of dietary modification in alleviating chronic fatigue syndrome symptoms: a systematic review. *Aust N Z J Public Health* 41:338–344. <https://doi.org/10.1111/1753-6405.12670>
 57. Campagnolo N, Johnston S, Collatz A et al (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. <https://doi.org/10.1111/jhn.12435>
 58. Goedendorp MM, Knoop H, Schippers GM, Bleijenberg G (2009) The lifestyle of patients with chronic fatigue syndrome and the effect on fatigue and functional impairments. *J Hum Nutr Diet* 22:226–231. <https://doi.org/10.1111/j.1365-277X.2008.00933.x>
 59. Kim H, Park SG (2023) Effect of a single multi-vitamin and Mineral supplement on Nutritional Intake in Korean Elderly: Korean National Health and Nutrition Examination Survey 2018–2020. *Nutrients* 15: <https://doi.org/10.3390/nu15071561>
 60. Blumberg JB, Frei BB, Fulgoni VL et al (2017) Impact of frequency of Multi-Vitamin/Multi-Mineral supplement intake on nutritional adequacy and nutrient deficiencies in U.S. adults. *Nutrients* 9. <https://doi.org/10.3390/nu9080849>

Supplementary information

Supplementary Table 1: Data used in the study, CoLaus|PsyColaus study, Lausanne, Switzerland.

Colaus original study		Fatigue Data	Vitamin/Mineral/Diet Supplement Data
Baseline	2003-2006		
Follow-up 1	2009-2012		X
Follow-up 2	2014-2017	X	X
Follow-up 3	2018-2021	X	X

Supplementary Table 2: Characteristics of included and excluded participants, FU2 (2014-2017), CoLaus|PsyColaus study, Lausanne, Switzerland.

	Included (n=1361)	Excluded (n=2939)	P-value
Age (years)	61.0 ± 9.4	63.5 ± 10.7	<0.001
Women (%)	685 (50.3)	1674 (57.0)	<0.001
Educational level (%)			<0.001
Low	598 (43.9)	1612 (54.9)	
Middle	426 (31.3)	715 (24.4)	
High	337 (24.8)	609 (20.7)	
Marital status, %			0.003
Living alone	444 (32.6)	821 (37.5)	
Living in a couple	917 (67.4)	1366 (62.5)	
Alcohol consumption, %			<0.001
None	256 (18.8)	750 (30.6)	
1-13/week	900 (66.1)	1382 (56.3)	
14-27/week	173 (12.7)	258 (10.5)	
28+/week	32 (2.4)	63 (2.6)	
Smoking categories (%)			0.460
Never	552 (40.6)	1121 (42.4)	
Former	556 (40.8)	1030 (38.9)	
Current	253 (18.6)	495 (18.7)	
BMI categories (%)			<0.001
Normal	606 (44.5)	1109 (40.4)	
Overweight	556 (40.9)	1075 (39.1)	
Obese	199 (14.6)	564 (20.5)	
Hypertension (%)	554 (40.7)	1413 (49.6)	<0.001
Diabetes (%)	93 (6.8)	343 (12.3)	<0.001
Total energy intake (kcal/d)	1728 ± 610	1630 ± 681	<0.001
Fatigue_score	2.8 ± 1.4	3.0 ± 1.5	0.002
Chalder_score	5.6 ± 2.5	6.0 ± 2.6	<0.001
Clinical fatigue (%)	265 (19.5)	397 (24.1)	0.002
AHEI	32.1 ± 10.0	32.2 ± 10.0	0.877

Results are expressed as number of participants (column percentage) for categorical variables and as average ± standard deviation for continuous variables. Between-group comparisons performed using chi-square for categorical variables and student's t-test for continuous variables. Abbreviations: BMI: Body mass index; AHEI: Alternate Healthy Eating Index.

Supplementary Table 3: multivariable associations between VMS and VMDS consumption and changes in fatigue, CoLausPsyColaus study, Lausanne, Switzerland, using inverse probability weighting.

	Non-consumers	Consumers	P-value
For VMS consumption			
Incident clinical fatigue ¹	1 (ref.)	1.63 (0.70 - 3.76)	0.255
Remission of clinical fatigue ²	1 (ref.)	1.37 (0.49 - 3.86)	0.551
For VMDS consumption			
Incident clinical fatigue ¹	1 (ref.)	1.90 (1.14 - 3.16)	0.014
Remission of clinical fatigue ²	1 (ref.)	1.18 (0.58 - 2.40)	0.654

Results are expressed as multivariable-adjusted odds ratio and 95% confidence interval. Between group comparison using logistic regression adjusted for age, sex, BMI categories (normal, overweight, obese), education (low/medium/high), marital status (alone, in couple), smoking (never, former, current), alcohol consumption (none, 1-13, 14-27 and 28+ per week), hypertension (yes, no), diabetes (yes, no), total energy intake (continuous), AHEI (continuous). Abbreviations: VMS: Vitamin/mineral supplements; 1: among participants who did not have clinical fatigue at FU2. 2: among participants with clinical fatigue at FU2.

Supplementary Table 4: The association between VMS and VMDS consumption based on the first (2009-2012) and the second (2014-2017) follow-ups, and evolution of fatigue, CoLausPsyColaus study, Lausanne, Switzerland, using inverse probability weighting.

	Never	Alternate	Persistent	<i>P</i> -value for trend
For VMS consumption				
Incident clinical fatigue ¹	1 (ref.)	1.51 (0.63 - 3.59)	3.33 (0.93 - 11.8)	0.064
Remission of clinical fatigue ²	1 (ref.)	1.39 (0.54 - 3.56)	nc	nc
For VMDS consumption				
Incident clinical fatigue ¹	1 (ref.)	1.68 (0.97 - 2.92)	2.49 (1.21 - 5.15)	0.014
Remission of clinical fatigue ²	1 (ref.)	1.16 (0.55 - 2.46)	0.47 (0.11 - 2.04)	0.314

Nc, not computable. Results are expressed as multivariable-adjusted odds ratio and 95% confidence interval. Between group comparison logistic regression adjusting for age, sex, BMI categories (normal, overweight, obese), education (low/medium/high), marital status (alone, in couple), smoking (never, former, current), alcohol consumption (none, 1-13, 14-27 and 28+ per week), hypertension (yes, no), diabetes (yes, no), total energy intake (continuous), alternate healthy eating index (continuous). Abbreviations: VMS: Vitamin/mineral supplements; VMDS: Vitamin/mineral and/or dietary supplements. 1: among participants who did not have clinical fatigue at FU2. 2: among participants with clinical fatigue at FU2.

Supplementary Table 5: Studies about vitamin/mineral and/or dietary supplements and fatigue.

Reference	Study Design	Group	Treatment	No. of Participants	Main Findings
Suzuki et al., 1996[1]	Non-randomized study	Male athletes	Vitamin B1	16	Subjective fatigue is significantly reduced after exercise
Van Campen et al., 2019[2]	Clinical research	Chronic fatigue syndrome patients	Vitamin B12	51	After treatment, participants' fatigue scale improved
Suh et al., 2012[3]	Double-blind randomized controlled trial	healthy volunteers	Vitamin C	141	High dose intravenous vitamin C proved to be effective against fatigue in this study
Huck et al., 2013[4]	Placebo-controlled pilot trial	Obese adults	Vitamin C	20	The general fatigue score was significantly decreased in the vitamin C group compared to the control group (p = 0.001)
Al-Eisa et al., 2016[5]	Cross-sectional study	Healthy older subjects	Vitamin D	85	Vitamin D may prevent muscle fatigue
Roy et al., 2014[6]	Prospective non-randomized therapeutic study	Adult patients with fatigue	Vitamin D	174	Correction of Low Vitamin D Improves Fatigue (P < 0.001)
Nowak et al., 2016[7]	Double-blind placebo-controlled clinical trial	Healthy persons with vitamin D deficiency	Vitamin D	120	Vitamin D treatment significantly improved fatigue in otherwise healthy persons with vitamin D deficiency.
Witham et al., 2015[8]	Parallel-group, double-blind, randomized placebo-controlled trial	Patients with chronic fatigue syndrome	Vitamin D	50	High-dose oral vitamin D3 did not improve fatigue in chronic fatigue syndrome.
Takemoto et al., 2015[9]	Placebo-controlled, double-blind, parallel-group study	Healthy adults	Sesame Lignans and Vitamin E	309	The fatigue status of the experimental group was significantly improved (p<0.01)
Patterson et al., 2001[10]	Randomized controlled trial	Iron deficient women	Iron	44	Treatment of iron deficiency with either supplementation or a high iron diet results in decreased fatigue

Favrat et al., 2014[11]	Randomized, placebo-controlled, single-blinded study	Iron deficient women	Iron	290	A single infusion of ferric carboxymaltose improved fatigue, in iron-deficient women with normal or borderline hemoglobin
Afzali et al., 2021[12]	A parallel clinical trial	Healthy older subjects	Zinc	150	Zinc supplementation significantly reduced fatigue (mean difference: -10.41 vs. 1.37, P<0.001)
Maric et al., 2014[13]	Prospective study	Women of reproductive age	Multivitamin mineral supplementation	38	Fatigue significantly improved (p=0.0009)
Brouwers et al., 2002[14]	Double-blind randomized controlled trial	Patients with chronic fatigue syndrome	Dietary supplements	53	No significant differences were found between the placebo and the treated group
Joustra et al., 2017[15]	A systematic review and meta-analysis	Chronic fatigue syndrome and fibromyalgia syndrome	Vitamins and minerals	5 RCTs and 40 observational studies	Little evidence was found to support the hypothesis that vitamin and mineral deficiencies play a role
Castro-Marrero et al., 2021[16]	Prospective, randomized, double-blind, placebo-controlled trial	Patients with chronic fatigue syndrome	Coenzyme Q10 and NADH	207	A significant reduction in cognitive fatigue perception (p<0.001) from baseline were observed within the experimental group
Mizuno et al., 2008[17]	Double-blinded, placebo-controlled, three crossover design	Healthy volunteers	Coenzyme Q10	17	Significant alleviation of subjective fatigue sensation measured on a visual analogue scale in the 300mg coenzyme Q10-administered group after
Maes et al., 2005[18]	Cross-sectional study	Patients with chronic fatigue syndrome (CFS) and healthy participants	Omega3	34	Total omega3/omega6 ratios were significantly lower in CFS patients than in normal controls.
Husmann et al., 2019[19]	Time-matched trial	Active males	Dietary Nitrate (beetroot juice)	12	Dietary Nitrate Supplementation reducing muscle Fatigue

Zoughaib al.,2023[39]	et	Double-blind, controlled, design	placebo-crossover	Older women	Dietary Nitrate (beetroot juice)	18	No effect on either the fatigability or recoverability of muscle in this population
Hadžić et al., 2023[21]		Double-blind, controlled trial	placebo-	Healthy male basketball players	Soluble dietary fibre	18	Fibre supplementation could have a significant effect on reducing the rating of perceived exertion
Imai et al., 2018[22]		Double blind controlled crossover study	placebo two-way	Healthy volunteers	Astaxanthin and sesamin	24	Astaxanthin and sesamin supplementation was associated with significantly improved recovery from mental fatigue
Carillon et al., 2014[23]		Randomized, double-blind, placebo-controlled trial		Healthy volunteers	Superoxide dismutase (SOD)-melon concentrate supplementation	61	SOD-melon concentrate significantly decreased physical and mental fatigue
Malaguarnera al.,2008[24]	et	Single randomized, double blind, comparative clinical trial	center,	Elderly patients with fatigue	Acetyl L-carnitine (ALC)	96	Administering ALC may reduce both physical and mental fatigue in elderly and improves both the cognitive status and physical functions.
Sullivan et al., 2009[25]		Open pilot study		Patients with chronic fatigue syndrome	Probiotic	15	6 out of 15 patients reported that they had improved according to the assessment described

References

1. Suzuki M, Itokawa Y (1996) Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis* 11:95–106. <https://doi.org/10.1007/bf02080935>
2. van Campen CLM, Riepma K, Visser FC (2019) Open Trial of Vitamin B12 Nasal Drops in Adults With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Comparison of Responders and Non-Responders. *Front Pharmacol* 10:1102. <https://doi.org/10.3389/fphar.2019.01102>
3. Suh SY, Bae WK, Ahn HY, et al (2012) Intravenous vitamin C administration reduces fatigue in office workers: a double-blind randomized controlled trial. *Nutr J* 11:7. <https://doi.org/10.1186/1475-2891-11-7>
4. Huck CJ, Johnston CS, Beezhold BL, Swan PD (2013) Vitamin C status and perception of effort during exercise in obese adults adhering to a calorie-reduced diet. *Nutrition* 29:42–45. <https://doi.org/10.1016/j.nut.2012.01.021>
5. Al-Eisa ES, Alghadir AH, Gabr SA (2016) Correlation between vitamin D levels and muscle fatigue risk factors based on physical activity in healthy older adults. *Clin Interv Aging* 11:513–522. <https://doi.org/10.2147/cia.S102892>
6. Roy S, Sherman A, Monari-Sparks MJ, et al (2014) Correction of Low Vitamin D Improves Fatigue: Effect of Correction of Low Vitamin D in Fatigue Study (EViDiF Study). *N Am J Med Sci* 6:396–402. <https://doi.org/10.4103/1947-2714.139291>
7. Nowak A, Boesch L, Andres E, et al (2016) Effect of vitamin D3 on self-perceived fatigue: A double-blind randomized placebo-controlled trial. *Medicine (Baltimore)* 95:e5353. <https://doi.org/10.1097/md.0000000000005353>
8. 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. <https://doi.org/10.1016/j.numecd.2014.10.007>
9. Takemoto D, Yasutake Y, Tomimori N, et al (2015) Sesame Lignans and Vitamin E Supplementation Improve Subjective Statuses and Anti-Oxidative Capacity in Healthy Humans With Feelings of Daily Fatigue. *Glob J Health Sci* 7:1–10. <https://doi.org/10.5539/gjhs.v7n6p1>
10. Patterson AJ, Brown WJ, Roberts DC (2001) Dietary and supplement treatment of iron deficiency results in improvements in general health and fatigue in Australian women of childbearing age. *J Am Coll Nutr* 20:337–342. <https://doi.org/10.1080/07315724.2001.10719054>
11. Favrat B, Balck K, Breymann C, et al (2014) Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women--PREFER a randomized, placebo-controlled study. *PLoS One* 9:e94217. <https://doi.org/10.1371/journal.pone.0094217>
12. Afzali A, Goli S, Moravveji A, et al (2021) The effect of zinc supplementation on fatigue among elderly community dwellers: A parallel clinical trial. *Health Sci Rep* 4:e301. <https://doi.org/10.1002/hsr2.301>
13. Maric D, Brkic S, Tomic S, et al (2014) Multivitamin mineral supplementation in patients with chronic fatigue syndrome. *Med Sci Monit* 20:47–53. <https://doi.org/10.12659/msm.889333>
14. 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. <https://doi.org/10.1093/qjmed/95.10.677>
15. Joustra ML, Minovic I, Janssens KAM, et al (2017) Vitamin and mineral status in chronic fatigue syndrome and fibromyalgia syndrome: A systematic review and meta-analysis. *PLoS One* 12:e0176631. <https://doi.org/10.1371/journal.pone.0176631>
16. Castro-Marrero J, Segundo MJ, Lacasa M, et al (2021) Effect of Dietary Coenzyme Q10 Plus NADH Supplementation on Fatigue Perception and Health-Related Quality of Life in Individuals with Myalgic

- Encephalomyelitis/Chronic Fatigue Syndrome: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* 13:. <https://doi.org/10.3390/nu13082658>
17. Mizuno K, Tanaka M, Nozaki S, et al (2008) Antifatigue effects of coenzyme Q10 during physical fatigue. *Nutrition* 24:293–299. <https://doi.org/10.1016/j.nut.2007.12.007>
 18. Maes M, Mihaylova I, Leunis JC (2005) In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. *Neuro Endocrinol Lett* 26:745–751
 19. Husmann F, Bruhn S, Mittlmeier T, et al (2019) Dietary Nitrate Supplementation Improves Exercise Tolerance by Reducing Muscle Fatigue and Perceptual Responses. *Front Physiol* 10:404. <https://doi.org/10.3389/fphys.2019.00404>
 20. Zoughaib WS, Hoffman RL, Yates BA, et al (2023) The influence of acute dietary nitrate supplementation on skeletal muscle fatigue and recovery in older women. *Physiol Rep* 11:e15694. <https://doi.org/10.14814/phy2.15694>
 21. Hadžić E, Starcevic A, Rupčić T, et al (2023) Effects of Soluble Dietary Fibre on Exercise Performance and Perception of Fatigue in Young Basketball Players. *Food Technol Biotechnol* 61:389–401. <https://doi.org/10.17113/ftb.61.03.23.8124>
 22. Imai A, Oda Y, Ito N, et al (2018) Effects of Dietary Supplementation of Astaxanthin and Sesamin on Daily Fatigue: A Randomized, Double-Blind, Placebo-Controlled, Two-Way Crossover Study. *Nutrients* 10:. <https://doi.org/10.3390/nu10030281>
 23. Carillon J, Notin C, Schmitt K, et al (2014) Dietary supplementation with a superoxide dismutase-melon concentrate reduces stress, physical and mental fatigue in healthy people: a randomised, double-blind, placebo-controlled trial. *Nutrients* 6:2348–2359. <https://doi.org/10.3390/nu6062348>
 24. Malaguarnera M, Gargante MP, Cristaldi E, et al (2008) Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. *Arch Gerontol Geriatr* 46:181–190. <https://doi.org/10.1016/j.archger.2007.03.012>
 25. 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. <https://doi.org/10.1186/1475-2891-8-4>

Population



n=1731

Female (51.2%)

Age (61.1)

A prospective study

Measurements

Fatigue Severity Scale
(FSS)



Chalder Fatigue Scale
(CFS)

Results

Vitamin
mineral
dietary
supplements

NO consistent
association

Fatigue



Vitamin/mineral
and/or dietary
supplements

Fatigue

