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Effect of Low-Fat Dairy Products Fortified with Encapsulated Vitamin D3 on Anxiety, Depression and Stress in People with Cardiovascular Risk Factors

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ABSTRACT

Background: Vitamin D deficiency is a worldwide condition, which has been linked to a variety of health-related issues. Vitamin D can be beneficial to cardiovascular patients and those suffering from depression and anxiety, based on Survey of Ultraviolet Intake by Nutritional Approach (SUVINA study), ,showing the potential effects of vitamin D-fortified dairy products on anxiety, depression, and stress in subjects with cardiovascular disease (CVD) risk factors. **Methods:** It was a quadruple-blind randomized controlled trial. Individuals were randomly allocated to one of four groups: fortified low-fat milk (FM), non-fortified low-fat milk (NFM), fortified low-fat yogurt (FY), and non-fortified low-fat yogurt (NFY). FM and FY groups were fortified with 1500 IU nano-encapsulated vitamin D3. Anthropometric parameters as well as depression, anxiety, and stress scores were measured at baseline and after a ten-week trial in Mashhad, Iran. **Results:** Totally, 289 participants (143 men, 146 women) with a mean age of 41.86±7.81years were enrolled in the study. There was no statistical difference between the scores of depression, anxiety, and stress in participants with and without CVD risk factors (P>0.05). No statistical difference was found in the subgroup analysis based on milk and yogurt consumption. **Conclusions:** Fortified low-fat milk containing 1,500 IU of vitamin D has no impact on improving depression, anxiety, and stress during ten weeks. However, further studies with higher vitamin D doses for a longer duration are recommended.

Keywords: *Vitamin D; Fortification; Anxiety; Depression*

Introduction

Vitamin D is a nutrient available in some foods from both animal and plant sources; however, it is mostly synthesized from 7-dehydrocholesterol in skin during sun exposure, especially 260–

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320 nm ultraviolet wavelength (Holick *et al.*, 2011, Hossein-nezhad and Holick, 2013, Jäpelt and Jakobsen, 2013). Although the main role of vitamin D is in musculoskeletal development and bone health, the receptors for vitamin D are also widely found in the body, which include brain, heart, skin, gonads, prostate, breast, and gut (Amiri *et al.*, 2021, Marino and Misra, 2019). Recent studies have shown a possible role of vitamin D in mental health(Ganji *et al.*, 2010, Zhao *et al.*, 2010). Furthermore, other studies have found an association between serum vitamin D status and mood disorders (Cuomo *et al.*, 2019, Shah and Gurbani, 2019). Recent reports have revealed that high prevalence of anxiety, depression, and stress among patients with cardiovascular disease (CVD) can cause adverse outcomes and economic burdens for health care systems (Cohen *et al.*, 2015).

Anxiety, depression and stress are three major mood disorders in Iran with a prevalence of 42%, 44%, and 40%, respectively (Casseb *et al.*, 2019, Drozdenko *et al.*, 2014, Khayyatzadeh *et al.*, 2020, Milliken *et al.*, 2012, Peirce and Alviña, 2019, Valizadeh *et al.*, 2016). Regarding recent meta-analysis, the consumption of high-quality foods are associated with reduced depressive symptoms. Some studies have shown that functional microorganism within dairy products such as yogurt and milk may have beneficial effects on gut microbiome, and hypothesized that dairy products' consumption may change the mood indirectly. Previous studies have shown that vitamin D fortified dairy products can be good for heart and metabolic health. However, a recent review found that the results have been inconsistent (Valizadeh *et al.*, 2016). In accordance with inconsistent results of studies and beneficial impacts of reduction in depression, anxiety, and stress among patients suffering from CVD risk factors, the authors evaluated the effect of low-fat dairy products fortified with 1500IU nano-encapsulated vitamin D3 on anxiety, depression, and stress in subjects with cardiovascular risk factors.

Materials and Methods

Study population: This is a report from the Survey of Ultraviolet Intake by Nutritional Approach (SUVINA), and the study protocol was published elsewhere (Sharifan *et al.*, 2021a). The goal of SUVINA trial was production and intervention of dairy products fortified with nano-encapsulated vitamin D to determine its impact on physical and mental aspects of health. The authors designed the sample size based on anxiety (n=38) depression (n=174), and stress (n=174), then the maximum sample size was considered for depression and stress. The sample size was obtained on the basis of a 95% confidence interval, 80% power, and the standardized effect size of 0.3 as considered at least for 174 people in each group (Dean *et al.*, 2011, Munro, 2005).

The case group consumed dairy products fortified with 1500 IU of nano-vitamin D once a day at breakfast for ten weeks, and the control groups received non-fortified dairy products concurrently. Before the beginning of the research, all the subjects provided written informed consent.

Participants: 306 participants were recruited from among 30-50 staff and students with central obesity, according to the International Diabetes Federation (IDF) from Mashhad University of Medical Sciences (Alberti *et al.*, 2006). The researchers used the following exclusion criteria: all the individuals with a history of weight changes (even 5 Kg) in the previous year, patients who used drugs interacting with vitamin D and calcium, alcohol consumption or positive smoking habit, patients diagnosed with a disease or started a special treatment, intolerance to dairy products, and pregnant and lactating women. Finally, 289 participants finished the trial. The results were analyzed according to completed questionnaires for depression, anxiety, and stress, and therefore, the number of remaining participants was different for variables of vitamin D, depression, anxiety, and stress.

Randomization and blinding: Qualifying participants underwent stratified permuted block randomization with the 1:1:1:1 allocation ratio according to gender and centers' condition. Then, the subjects were randomly allocated to one of the

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following groups, including: 1- "FY": fortified low-fat yogurt including 1500 IU nano-encapsulated vitamin D3/per serve (150g/d), 2- "NFY": non-fortified low-fat yogurt (150g/d), 3), "FM": fortified low-fat milk containing 1500 IU nano-encapsulated vitamin D3/per serve (200 ml/d), and 4- "NFM": non-fortified low-fat milk (200 ml/d); NFM and NFY were considered control groups. Sealed envelopes containing A or B labels were applied for allocation to any intervention group and its related control group, separately. Random allocation was accomplished by a staff member who was not involved in data collection, analysis, and reporting. All the participants, clinicians, statisticians, and the researchers responsible for randomizing subjects were blinded to the subjects of the groups (quadruple blind).

Dairy products manufacture: The production of vitamin D nano-particles has been discussed by Jafarifar *et al.* and Sharifan *et al*.(Jafarifar *et al.*, 2022, Sharifan *et al.*, 2021b) The fortification process of low-fat milk and yogurt was undertaken at Salamat pilot dairy product factory supervised by the Faculty of Food Sciences and Technology, Ferdowsi University of Mashhad, Iran. Nutritional constituents for 100 gr yogurt and milk were 56 kcal, 7 g protein, sugar-free, 3 g fat, and 0.04 g trans fatty acids. The authors performed delivery and consumption of products on manufacturing day or the day after. To ensure that products were consumed on production day or the next day, the empty labeled containers from participants were required.

Outcome measurements: Weight, body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) were obtained and blood samples were collected from all the participants after a 12-hour fasting before the beginning of the intervention. The case group received fortified yogurt with 1500 IU of nano-vitamin D once a day at breakfast for ten weeks. During the study, patient's history was required to assess the side effects of dairy products' intake. At least 1500 IU Vitamin D was applied for daily consumption due to possible toxicity for the subject based on endocrine society's clinical practice guideline (Holick *et al.*, 2011). In addition, BMI, systolic and diastolic blood pressure, fasting blood glucose, and lipid profile were evaluated before and after the ten weeks of intervention.

Dietary intake and physical activity assessment: Participants were asked not to change their diet and not to use any extra vitamin D supplements or fortified food during the trial period. Besides, to ensure that there was no significant change in their diet, the food intake in participant was recorded at the beginning, middle, and end of the trial through a 3-day food record. The food registration was coded and analyzed by converting into gram and applying Nutritionist IV software. Finally, the average of food records was considered as dietary intake. The researchers used Beck physical activity questionnaire to assess the participants' physical activity (Baecke *et al.*, 1982). This 16-parts questionnaire is categorized into three indices; work index, sports index, and free time index. The summation of these three indices detected the severity of physical activity. The questionnaire's internal reliability and Cronbach's alpha 0.79 were calculated using the method previously described by Etemad and Ismaeilnasab (Etemad and Esmailnasab, 2012).

Anthropometric indices: A wall stadiometer with an accuracy of 0.1 cm was applied to evaluate height at baseline. A digital bio-impedance analyzer (TANITA BC 418) was used to analyze weight and fat mass with light clothes and shoes. BMI was measured by the following formula: weight (kg)/height^2 (m^2). WC was computed twice with a flexible tape by the single expert staff at the midpoint between the lower edge of the *ribs and* the iliac crest at the end of a normal exhalation (Mason and Katzmarzyk, 2009). In addition, hip circumference (HC) was assessed around the broadest part of the buttocks. The formula WC (cm)/ HC (cm) was used to measure WHR.

Laboratory measurements: Blood samples of all the participants were collected into two tubes; a

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tube including EDTA for complete blood count (CBC) test, and a gel tube for biochemical and hormonal tests after 12 hours of overnight fasting. To separate serum and aliquots of serum kept frozen at -80 °C for future analysis; samples were centrifuged at 5,000 g for 15 minutes at 4 °C. The researchers used enzymatic methods (Sperry *et al.*, 2018) to determine serum triglyceride (TG) and total cholesterol (TC) using Pars Azmun kits (Tehran, Iran), and low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) using Pishtaz Teb kits on a BT-3000 auto-analyzer (Biotechnical, Rome, Italy). Serum insulin levels were measured on the samples transported on ice to the laboratory, which were rapidly separated using the ELISA method applying Demeditec kits (Kiel, Germany). The homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were determined based on the suggested definition (Gutch *et al.*, 2015). Commercial ELISA kits (Pishgaman Sanjesh- Iran) were used to determine total serum 25(OH)D levels, and the result was read with a Microplate Reader Awareness/Stat Fax 2100 analyzer (SECA 217, Hamburg, Germany).

Metabolic syndrome diagnosis: Fasting blood glucose ≥100 mg/dl, systolic or diastolic blood pressure ≥130 or ≥85 mmHg; HDL-C <50 mg/dl for women or <40 mg/dl for men; TG≥150 mg/dl; and WC ≥80 cm for women or ≥94 cm for men, are the five features used for the diagnosis of metabolic syndrome based on the International Diabetes Federation (IDF) definition (Asadi *et al.*, 2019).

Depression/anxiety/stress Test: the 42-item depression anxiety stress scales (DASS-42) was employed according to the overlaps of depression and anxiety beside their different concepts. Each scale includes 14 items. Depression subscale evaluates dysphoric mood types such as depreciation, low self-esteem, despair, and lack of motivation. Anxiety subscale calculates arousal state, like autonomic arousal, muscular rigidity, and anxious affect. Finally, nervous tension and irritability were checked out by the items related to stress subscale. The validation of this questionnaire was performed for the Iranian population previously (Bayani, 2010).

Blood pressure measurement: Blood pressure was measured by an experienced physician in the morning at baseline and follow-up assessments were done after individuals stopped fasting. Calculation was done twice over a period of 5 minutes using a mercury sphygmomanometer (Model Riester, Germany), and the average for each systolic and diastolic blood pressures was reported.

Safety considerations: Trained staff distributed dairy products daily to improve adherence of subject, and participants consumed the product in front of the staff as far as possible and returned the numerical coded container. Moreover, to make sure of daily consumption, the products were delivered on the weekend, and the participants were asked to consume and return empty coded package on the day after the weekend. A member of the research staff team visited the participants every day to evaluate possible side effects. The physician of the team excluded the participants from the research and referred them to a specialist for more evaluations if their symptoms were related to the intervention.

Ethical considerations: This study was approved by Ethics Committee of Mashhad University of Medical Sciences (Mums), Mashhad, Iran. Informed consent was obtained from all the participants using protocols approved by Ethics Committee of the National Institute for Medical Research Development (NIMAD) with protocol ID: IR.NIMAD.REC.1396.027). The trial was registered in http://www.irct.ir with ID: IRCT20101130005280N27)

Data analysis: SPSS version 18 was used for all the statistical analyses. The Kolmogorov-Smirnov test and Q-Q plot test were applied to check the normality of data for each variable. Descriptive statistics containing mean, median, frequency, standard deviation(SD), and inter quartile range were defined for all the variables and were stated

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as mean±SD for the variables with normal distribution or median ± IQR for the ones without a normal distribution variable. The researchers applied chi-square, or Fisher exact tests for categorical parameters. ANCOVA and Bonferroni correction were applied between group analyses, and changes were explained as mean differences and standard errors (mean ± SE). Intention-to-treat was done for all the participants who completed the trial, and the P-values of <0.05 were considered significant.

Results

Baseline characteristics of this study demonstrated that total of 289 participants (143 men, 146 women) with CVD risk factors were enrolled. The mean age of the participants was 41.86±7.81 years; and the mean for stress, anxiety, and depression scores were 14.21±6.68, 7.83±4.41, and 8.16±5.75, respectively. The prevalence of dyslipidemia, hypertension, metabolic syndrome, obesity, and diabetes among the patients were 81.7%, 33.1%, 40.3%, 24.4% and 7%, respectively. The mean of serum vitamin D in participants was 14.63±5.29 (ng/ml). Demographic characteristics of these research participants are presented in **Table 1**. According to **Table 2**, there were no significant associations between CVD risk factors (dyslipidemia, hypertension, syndrome metabolic, diabetes and obesity) and the scores of depression, anxiety and stress tests at base line. According to the results of Student *t-test*, the difference between pre- and post-intervention values was not statistically significant for depression, anxiety and stress scores based on (CVD) risk factors in both groups. The results of stress, anxiety, and depression score based on CVD risk factors before and after intervention in male and female are indicated in supplementary **Tables** of **1** and **2**, respectively. The results of stress, anxiety and depression scores based on CVD risk factors before and after intervention of yogurt and milk are indicated in **Tables 3** and **4** respectively.

Table 1. Baseline characteristics of the study population

Variables	N , Mean ± SD
Age (y)	289, 41.86 ± 7.81
Stress score	184, 14.21 ± 6.68
Anxiety score	185, 7.83 ± 4.41
Depression score	185, 8.16 ± 5.75
Vitamin D (ng/ml)	242, 14.63 ± 5.29
	N (%)
Gender	
Male	143 (49.48)
Female	146 (50.51)
Dyslipidemia	236(81.7)
Hypertension	N(33.1)
Syndrome Metabolic	N(40.3)
Obesity (Body mass index≥30 kg/m^2)	N(24.4)
Diabetes (FBG≥126 mg/dl)	N(7.0)

Table 2. Scores of depression, stress, and anxiety based on CVD risk factors at base line.

Diseases (N)		Depression		Anxiety		Stress	
		Mean ± SD	P-value[a]	Mean ± SD	P-value[a]	Mean ± SD	P-value[a]
Dyslipidemia (236)	Yes	8.14 ± 5.72	0.742	8.02 ± 4.52	0.273	14.37 ± 6.86	0.484
	No	7.79 ± 5.38		7.13 ± 3.23		13.49 ± 5.79	
Hypertension (95)	Yes	6.91 ± 4.97	0.098	7.19 ± 3.96	0.361	13.24 ± 6.08	0.356
	No	8.41 ± 5.74		7.82 ± 4.35		14.21 ± 6.52	
Metabolic syndrome (116)	Yes	8.27 ± 6.06	0.751	8.02 ± 4.54	0.59	13.98 ± 6.83	0.746
	No	8.00 ± 5.47		7.67 ± 4.27		14.31 ± 6.58	
Diabetes (20)	Yes	7.17 ± 6.35	0.537	8.17 ± 4.60	0.789	14.92 ± 6.51	0.706
	No	8.23 ± 5.72		7.81 ± 4.41		14.16 ± 6.71	
Obesity (69)	Yes	7.49 ± 5.30	0.476	7.20 ± 4.42	0.307	12.41 ± 6.80	0.067
	No	8.20 ± 5.70		7.98 ± 4.23		14.55 ± 6.38	

[a]:Student t-test.

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Table 3. Scores of stress, anxiety and depression based on CVD risk factors before and after intervention with yogurt.

Variables				Before	After	P-value[a]	Changes	P-value[b]
Dyslipidemia	Yes	Depression score	Intervention	7.25 ± 8.75	9.09 ± 9.09	0.41	1.84 ± 12.71	0.27
			Control	7.90 ± 8.67	7.79 ± 8.16	0.46	-0.104 ± 12.8	
		Anxiety score	Intervention	8.03 ± 6.28	7.69 ± 6.45	0.38	-0.34 ± 9.31	0.2
			Control	8.27 ± 6.29	6.96 ± 6.90	0.34	-1.31 ± 9.03	
		Stress score	Intervention	14.63 ± 10.41	14.59 ± 9.81	0.79	-0.031 ± 14.37	0.5
			Control	14.83 ± 9.38	14.56 ± 9.22	0.45	-0.27 ± 12.62	
	No	Depression score	Intervention	12.50 ± 9.19	5.63 ± 6.36	0.03	-6.87 ± 9.13	0.42
			Control	8.50 ± 12.16	3.17 ± 3,78	0.23	-5.33 ± 13.41	
		Anxiety score	Intervention	11.25 ± 6.34	4.63 ± 4.71	0.03	-6.62 ± 7.58	0.97
			Control	8.50 ± 4.09	4.68 ± 2.86	0.33	-3.83 ± 4.24	
		Stress score	Intervention	22.25 ± 10.14	10.0 ± 8.25	0.02	-12.25 ± 14.48	0.99
			Control	15.83 ± 11.63	6.17 ± 5.73	0.05	-9.66 ± 15.32	
Hypertension	Yes	Depression score	Intervention	9.29 ± 9.70	8.24 ± 8.12	0.68	1.70 ± 12.93	0.57
			Control	10.30 ± 6.70	7.20 ± 6.67	0.17	-1.40 ± 11.09	
		Anxiety	Intervention	8.62 ± 6.94	6.29 ± 6.68	0.26	0.20 ± 9.55	0.94
			Control	9.52 ± 3.90	6.82 ± 4.97	0.07	-0.10 ± 6.69	
		Stress score	Intervention	17.24 ± 11.65	13.24 ± 11.4	0.20	1.30 ± 16.31	0.67
			Control	17.36 ± 7.03	12.94 ± 7.00	0.06	-1.40 ± 10.67	
	No	Depression score	Intervention	9.19 ± 8.77	8.72 ± 8.59	0.81	-0.47 ± 12.3	0.27
			Control	12.00 ± 10.13	8.14 ± 7.43	0.10	-3.86 ± 13.73	
		Anxiety score	Intervention	8.11 ± 6.34	7.92 ± 5.98	0.90	0.19 ± 9.48	0.48
			Control	10.00 ± 6.41	8.22 ± 7.22	0.27	1.78 ± 9.58	
		Stress score	Intervention	15.60 ± 10.13	14.06 ± 9.07	0.54	1.54 ± 15.06	0.51
			Control	18.33 ± 9.70	14.53 ± 9.08	0.10	3.81 ± 13.60	
Metabolic syndrome	Yes	Depression score	Intervention	9.60 ± 10.06	10.76 ± 9.26	0.68	1.16 ± 14.03	0.25
			Control	11.26 ± 8.81	7.63 ± 7.23	0.24	-3.63 ± 13.1	
		Anxiety score	Intervention	8.40 ± 6.56	10.40 ± 7.06	0.34	-2.00 ± 10.36	0.35
			Control	8.37 ± 6.64	7.58 ± 6.19	0.71	0.79 ± 9.26	
		Stress score	Intervention	15.33 ± 10.68	15.75 ± 11.17	0.90	-0.42 ± 16.51	0.88
			Control	15.74 ± 9.08	15.53 ± 8.02	0.93	0.21 ± 10.33	
	No	Depression score	Intervention	8.87 ± 7.91	7.39 ± 7.75	0.51	-1.48 ± 10.7	0.9
			Control	11.10 ± 9.65	9.19 ± 8.3	0.43	-1.90 ± 13.4	
		Anxiety score	Intervention	8.09 ± 6.18	5.87 ± 4.32	0.17	2.21 ± 7.58	0.99
			Control	10.65 ± 5.64	8.45 ± 7.05	0.16	2.19 ± 8.48	
		Stress score	Intervention	17.22 ± 10.41	13.3 ± 7.95	0.16	3.91 ± 13.1	0.93
			Control	18.55 ± 9.89	14.97 ± 9.64	0.17	3.58 ± 14.42	
Diabetes	Yes	Depression score	Intervention	7.00 ± 6.25	8.00 ± 5.20	0.86	1.00 ± 9.17	0.14
			Control	6.33 ±1.50	4.00 ±1.10	0.28	--2.66 ±11.72	
		Anxiety score	Intervention	11.67 ± 4.51	7.33 ± 3.79	0.41	-4.33 ± 5.69	0.11
			Control	6.30 ±1.60	2.10 ±0.99	0.06	-4.33 ± 7.08	
		Stress score	Intervention	18.33 ± 14.22	13.33 ± 8.15	0.60	-5.25 ± 19.7	0.73
			Control	8.67 ±4.16	7.68 ±1.56	0.72	-1.00 ±14.38	
	No	Depression score	Intervention	9.40 ± 9.19	9.36 ± 8.82	0.98	-0.04 ± 12.76	0.44
			Control	10.80 ± 8.97	8.71 ± 7.91	0.26	-2.08 ± 12.87	
		Anxiety score	Intervention	8.29 ± 6.45	8.49 ± 6.35	0.88	-0.20 ± 9.48	0.44
			Control	9.43 ± 5.60	8.18 ± 6.74	0.29	1.24 ± 8.29	
		Stress score	Intervention	14.91 ± 10.39	16.25 ± 9.78	0.55	1.34 ± 14.79	0.82
			Control	17.20 ± 9.50	15.18 ± 9.07	0.28	2.02 ± 12.99	
Obesity	Yes	Depression score	Intervention	8.03 ± 7.40	9.33 ± 8.74	0.54	1.30 ± 16.58	0.75
			Control	7.35 ± 7.54	7.95 ± 9.21	0.59	0.59 ± 12.15	
		Anxiety score	Intervention	8.13 ± 10.13	7.5 ± 6.27	0.17	-0.63 ± 10.21	0.37
			Control	8.22 ± 6.63	7.49 ± 5.21	0.36	-0.73 ± 5.49	
		Stress score	Intervention	16.13 ± 15.65	15.30 ± 6.62	0.73	-0.83 ± 16.47	0.3

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No	Depression score	Control	14.59 ± 9.99	14.78 ± 11.01	0.93	0.18 ± 11.17	0.32
		Intervention	8.03 ± 8.03	9.33 ± 8.52	0.83	1.30 ± 11.7	
	Anxiety score	Control	7.35 ± 9.73	7.95 ± 7.69	0.25	0.59 ± 13.63	0.27
		Intervention	8.13 ± 5.47	7.50 ± 5.89	0.57	-0.63 ± 8.87	
	Stress score	Control	8.22 ± 6.11	7.49 ± 7.01	0.32	-8.59 ± 9.30	0.59
		Intervention	16.13 ± 9.30	15.3 ± 9.49	0.90	0.83 ± 14.57	

[a]: Paired t-test, [b]: Student t-test.

Table 4. Scores of stress, anxiety and depression based on CVD risk factors before and after intervention with milk.

Variables				Before	After	P-value[a]	Changes	P-value[b]
Dyslipidemia	Yes	Depression score	Intervention	7.40 ± 5.98	7.80 ± 7.52	0.95	0.40 ± 10.34	0.70
			Control	9.82 ± 8.39	8.96 ± 6.61	0.51	-0.85 ± 9.61	
		Anxiety score	Intervention	7.94 ± 6.48	8.14 ± 5.32	0.37	0.20 ± 9.58	0.77
			Control	9.46 ± 6.96	8.57 ± 5.23	0.48	-0.89 ± 7.57	
		Stress score	Intervention	13.29 ± 8.81	13.56 ± 8.82	0.67	0.26 ± 12.64	0.70
			Control	15.36 ± 9.87	13.86 ± 8.09	0.90	-1.50 ± 12.88	
	No	Depression score	Intervention	7.56 ± 6.01	5.67 ± 4.54	0.92	-1.88 ± 7.91	0.93
			Control	10.08 ± 6.53	7.50 ± 5.55	0.97	-2.58 ± 9.77	
		Anxiety score	Intervention	7.00 ± 6.69	6.00 ± 3.51	0.65	-1.00± 8.85	0.83
			Control	8.75 ± 6.25	5.92 ± 4.29	0.33	-2.83 ± 8.87	
		Stress score	Intervention	14.56 ± 8.64	9.11 ± 6.53	0.14	-5.44 ± 9.83	0.90
			Control	16.17 ± 10.19	10.75 ± 5.94	0.18	-5.41 ± 11.95	
Hypertension	Yes	Depression score	Intervention	4.60 ± 5.21	6.80 ± 7.35	0.54	2.2 ± 9.11	0.27
			Control	6.56 ± 4.93	9.19 ± 6.69	0.14	2.62 ± 5.92	
		Anxiety score	Intervention	6.80 ± 6.78	6.60 ± 5.37	0.94	-0.20 ± 10.48	0.71
			Control	8.06 ± 6.08	8.31 ± 5.58	0.90	0.25 ± 7.66	
		Stress score	Intervention	13.00 ± 8.15	14.2 ± 9.55	0.83	1.2 ± 12.32	0.75
			Control	13.75 ± 8.31	12.88 ± 8.3	0.71	-0.87 ± 12.18	
	No	Depression score	Intervention	7.25 ± 6.66	7.00 ± 7.17	0.77	-0.25 ± 10.69	0.48
			Control	11.95 ± 10.09	7.32 ± 5.99	0.26	-4.63 ± 12.14	
		Anxiety score	Intervention	7.71 ± 6.67	5.52 ± 4.95	0.28	-0.89 ± 9.22	0.44
			Control	9.27 ± 7.01	7.00 ± 3.68	0.27	-2.27 ± 7.13	
		Stress score	Intervention	9.71 ± 9.20	12.52 ± 8.03	0.32	2.81 ± 12.77	0.52
			Control	16.95 ± 12.23	12.55 ± 6.53	0.10	-4.40 ± 13.46	
Metabolic syndrome	Yes	Depression score	Intervention	8.90 ± 5.58	9.65 ± 8.61	0.72	0.75 ± 11.09	0.89
			Control	12.40 ± 8.42	7.73 ± 6.94	0.16	-4.67 ± 8.59	
		Anxiety score	Intervention	7.95 ± 6.31	9.45 ± 5.64	0.47	1.50± 9.58	0.75
			Control	11.87 ± 7.56	8.27 ± 4.92	0.23	-3.60 ± 7.70	
		Stress score	Intervention	13.89 ± 7.03	14.95 ± 9.46	0.76	1.05 ± 12.30	0.96
			Control	17.2 ± 9.50	13.47 ± 8.76	0.21	-3.73 ± 12.71	
	No	Depression score	Intervention	6.85 ± 6.14	6.52 ± 6.21	0.77	-0.33 ± 9.26	0.61
			Control	8.40 ± 7.41	9.00 ± 5.75	0.66	0.6 ± 10.55	
		Anxiety score	Intervention	7.52 ± 4.72	7.07 ± 6.61	0.33	-0.44 ± 9.38	0.65
			Control	7.68 ± 5.90	7.48 ± 5.04	0.66	-0.20 ± 8.19	
		Stress score	Intervention	13.52 ± 9.29	11.48 ± 8.03	0.16	-2.37 ± 12.10	0.89
			Control	14.64 ± 10.49	12.60 ± 6.40	0.14	2.04 ± 12.94	
Diabetes	Yes	Depression score	Intervention	11.75 ± 2.65	5.25 ± 5.51	0.47	3.33 ± 6.66	0.25
			Control	12.33 ± 2.52	9.95 ± 0.58	0.20	-2.67 ± 2.52	
		Anxiety score	Intervention	10.50 ± 6.93	6.25 ± 7.81	0.75	-3.00 ± 14.73	0.44
			Control	6.33 ± 1.53	2.10 ± 1.00	0.06	4.23 ± 2.08	
		Stress score	Intervention	24.25 ± 3.61	9.75 ± 9.82	0.09	7.67 ± 11.24	0.42
			Control	8.67 ± 4.16	7.67 ± 0.58	0.72	1.00 ± 4.36	
	No	Depression score	Intervention	7.44 ± 6.03	8.26 ± 7.19	0.87	0.74 ± 10.06	0.57
			Control	9.41 ± 8.04	8.67 ± 6.25	0.48	-0.74 ± 9.84	

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		Anxiety score	Intervention	12.67 ± 6.47	13.21 ± 4.73	0.19	0.81 ± 8.88	0.67
			Control	8.79 ± 6.93	7.85 ± 4.97	0.35	-0.94 ± 8.13	
		Stress score	Intervention	12.67 ± 8.78	13.21 ± 8.43	0.48	0.54 ± 12.3	0.26
			Control	15.21 ± 10.21	12.87 ± 7.89	0.36	-2.33 ± 13.35	
Obesity	Yes	Depression score	Intervention	6.00 ± 4.72	9.00 ± 9.79	0.62	3.00 ± 12.53	0.65
			Control	5.38 ± 7.69	8.88 ± 5.43	0.84	3.57 ± 10.49	
		Anxiety score	Intervention	7.29 ± 5.48	7.80 ± 6.51	0.97	0.57 ± 10.49	0.59
			Control	6.63 ± 5.92	7.00 ± 4.19	0.15	0.37 ± 7.30	
		Stress score	Intervention	11.14 ± 7.49	11.43 ± 8.61	0.96	0.28 ± 12.87	0.43
			Control	11.75 ± 10.6	11.13 ± 5.10	0.85	-0.62 ± 11.63	
	No	Depression score	Intervention	7.60 ± 6.56	6.54 ± 5.74	0.52	-1.05 ± 8.83	0.39
			Control	11.03 ± 8.02	8.44 ± 6.76	0.24	-2.59 ± 9.13	
		Anxiety score	Intervention	7.63 ± 7.01	7.34 ± 4.30	0.85	-0.28 ± 9.11	0.64
			Control	9.91 ± 7.20	7.97 ± 5.26	0.24	-1.93 ± 8.33	
		Stress score	Intervention	13.5 ± 9.38	12.35 ± 8.69	0.63	-1.14 ± 12.35	0.53
			Control	16.56 ± 9.76	13.38 ± 8.73	0.15	-3.18 ± 13.60	

[a]: Paired t-test, [b]: Student t-test.

Discussion

According to the results, dairy product consumption fortified with vitamin D showed no effect regarding the groups suffering from CVD risk factor. The same results were found in healthy subjects according to the scores of depression, anxiety, and stress.

It is reported that depression affects around 300 million people around the world and leads to suicide in 800 thousand depressed people. Suicide is the second leading cause of death in the age group of 15-29 years. This epidemiology should be addressed with respect to the fact that 76% to 85% of the people in low- and middle-income countries receive no treatment for their disorder (James *et al.*, 2018). Anxiety also is estimated to affect 3.6% of the people around the world. Just like depression, anxiety has affected around 300 million people in different parts of the world. This condition affects the normal life of the patients (World Health Organization, 2017). Besides environmental and social factors, deficiency in many micronutrients play a role in developing these two disorders (Kimball *et al.*, 2018, Rucklidge *et al.*, 2016).

It is reported that vitamin D is a modulator of many inflammatory processes, and has positive effects on brain like increasing some neurotransmitters like dopamine, noradrenalin, and adrenalin; it also increases the expression of tyrosine hydroxylase gene. Furthermore, this vitamin affects cholinergic system by activating choline acetyltransferase (Ersoy and Ersoy). There is evidence that 25(OH)D may be converted into 1,25(OH)2D within the human brain parenchyma. In fact, vitamin D modulates cell proliferation, neurotransmitters production, biosynthesis of monoamine, calcium and redox homeostasis, mitochondrial function, and cell apoptosis in the brain. Besides, anti-inflammatory effects of vitamin D, antioxidant features have been reported that make this vitamin more beneficial for central nervous system and effective against developing depression and anxiety, as inflammation and oxidative stress have a role in developing these disorders (Casseb *et al.*, 2019, Patki *et al.*, 2013). However, the mechanism of the action of vitamin D on brain is not fully understood (Ersoy and Ersoy).

Although vitamin D deficiency is clearly reported to be associated with depression through systematic review studies (Amini *et al.*, 2019, Anglin *et al.*, 2013), the role of vitamin D supplementation is debated. A systematic review study in 2015 proposed that vitamin D supplementation has no role on improving depressive symptoms (Gowda *et al.*, 2015). However, more recent meta-analysis in 2020 reported that vitamin D can enhance negative feelings (Cheng *et al.*, 2020). Another recent systematic review and meta-analysis also reported that vitamin D favorably impacts major depressive

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cases, with a moderate effect size. However, controversies has remained, and more studies are needed (Vellekkatt and Menon, 2019). There is also another controversy in relation to the role of vitamin D supplementation in improving anxiety. Some believe that this micronutrient ameliorates symptoms of anxiety and increases circulation of serotonin level (Bicikova *et al.*, 2015, Darroudi *et al.*, 2019). However, some studies have reported no association between vitamin D and anxiety (Kjærgaard *et al.*, 2012, Slow *et al.*, 2014, Wepner *et al.*, 2014). Furthermore, some of the studies were conducted on different populations like obese cases (Jorde *et al.*, 2008), pregnant women (Bertone-Johnson *et al.*, 2012), adolescents (Högberg *et al.*, 2012), and old people (Alavi *et al.*, 2019). This study was conducted to further help the completion of previous studies. No significant difference was found regarding depression, anxiety, and stress scores before and after vitamin D supplementation, both in those with cardiovascular risk factors and those without these risk factors. Differences regarding the results of various studies were due to using different doses, treatment duration, and fortification methods. Most of the studies with reports on the improvement of the symptoms regarding depression, used a dose of 4000 IU/day for a duration of at least 8 weeks (Gowda *et al.*, 2015).

We used a dose of 1500 IU/day for a ten-week period, and this was not effective in reducing the symptom scores. In fact, depression, anxiety, and other mental changes are chronic mental changes and should be treated chronically. Therefore, this study was limited in case of duration and dose of vitamin D fortification. Moreover, the subgroup analysis in this study lacked enough statistical power for clinical judgment. However, this research was among the few studies which assessed the role of food staples fortified with vitamin D on CVD risk factors.

Conclusions

No impact of dairy products consumption fortified by nano-encapsulated vitamin D was found in improving depression, anxiety, and stress. However, only a daily dose of 1500 IU/day was used for ten weeks, and the result of vitamin D supplementation seems to be dose dependent. Further studies are needed to explain the role of vitamin D fortified dairy products in altering mood status, particularly individuals with CVD risk factors.

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Availability of data and materials

The data which support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interests

The authors declared no conflict of interests.

Authors' contributions

Sharifan P, Ghazizadeh H, and Darroudi S did the literature research, designed the research, drafted the article, and revised the paper. Esmaily H, Ferns F, Tanbacoochi D, Ghodsi A, Saffar Soflaei S, Fazl Mashhadi MR, Mohammadi Bajgiran M, Ebrahimi dabagh A, Moazedi S and Mohamadi MA were involved in data analysis, conception and interpretation of results. Ghayour-Mobarhan M, Esmaily H conducted the final revision. All the authors read and approved the final manuscript.

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