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Vitamin D Levels and Depressive Symptoms' Severity Among University Employees in Lebanon

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Abstract

Background: Despite the evidence that the association between serum vitamin D level and susceptibility to depression is altered by ethnicity and vitamin D receptor gene polymorphisms, high prevalence of vitamin D deficiency, and parallel substantial burden of depression among Middle Eastern/ Arab adult populations, research exploring whether low serum vitamin D level is associated with increased risk of depression among Arab adult populations is almost non-existent.

Objective: This study aims to investigate the relationship between serum vitamin D levels and severity of depressive symptoms among a sample of healthy Lebanese adults, controlling for multiple confounders.

Methods: A total of 351 employees at a private university in Lebanon were surveyed. Information about sociodemographic, lifestyle habits, medical/ family history; and depressive symptoms were collected using a background questionnaire, international physical activity questionnaire –short form, and Patient Health Questionnaire, respectively. Anthropometric measurements and fasting blood samples were collected using standard methods. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured by means of ELISA. Multiple linear regression analyses were conducted. A p-value of less than 0.05 was considered statistically significant.

Results: Sample mean age was 42.36 years. In the fully adjusted model, higher depression scores were found to be border-line significantly (p= 0.058) associated with lower serum 25-(OH)D levels and significantly associated with younger age, female sex, lower income, chronic illness diagnosis, family history of mental illness, number of stressful life events, and intake of antidepressants.

Conclusion: We did not find any significant independent association between serum 25(OH)D levels and severity of depressive symptoms in a sample of Lebanese employees of a private university.

Keywords: serum 25-hydroxyvitamin D [25(OH)D], depressive symptoms, healthy employees

1. Introduction

The relationship between vitamin D and depression in the general adult population has come under scrutiny by many investigators worldwide owing to research reports revealing high prevalence of vitamin D deficiency (Arabi, El Rassi, & El-Hajj Fuleihan, 2010; Holick & Chen, 2008), presence of vitamin D receptors in areas of the brain involved in mood regulation (Eyles, Liu, Josh, & Cui, 2014; Eyles, Smith, Kinobe, Hewison, & McGrath, 2005) and the high burden of depression/ depressive disorders in the general adult population (World health Organization, 2017). Findings from systematic reviews and meta-analyses of observational studies have not been consistent. While one meta-analysis of 9 cross-sectional studies found an increased, though non-significant, adjusted odds ratio (OR) of depression for the lowest versus the highest vitamin D categories (OR = 1.31, 95% CI 1.00-1.71, p=0.05) (Anglin et al., 2013), a second meta-analysis of 11 cross-sectional studies arrived at a pooled estimate of adjusted ORs of depression of 0.96 for a 10 ng/ml increase in 25(OH)D levels (95% CI = 0.94-0.99, p=0.003) (Ju et al., 2013). Summary estimates from three meta-analyses of the same 3 cohort studies suggested a borderline statistically significant inverse association between serum vitamin D levels and depression; whereas estimate obtained from a fourth meta-analysis of the same 3 cohort studies did not reveal an association (Anglin et al., 2013). Another meta-analysis of 5 cohort studies showed a non-significant association between serum vitamin D levels and depression; the pooled adjusted OR of depression for a 10 ng/ml increase in 25(OH)D levels was found to be 0.92 (95% CI = 0.87-0.98, p= 0.090) (Ju et al., 2013). Moreover, findings from systematic reviews and

meta-analyses of randomized controlled trials (RCTs) which tested the effect of vitamin D supplementation on depression revealed no overall significant effect of vitamin D supplementation (Li et al., 2014; Shafffer et al., 2014). Results from individual RCTs were inconsistent and were partly accounted for by methodological limitations (comparison groups, baseline serum 25(OH)D level of study groups, baseline depressive symptoms of study groups, and variations in vitamin D supplementation protocol). Investigators noted that vitamin D supplementation is likely to be effective in reducing depressive symptoms in subjects with clinically significant depressive symptoms or depressive disorder (Li et al., 2014; Shaffer et al., 2014; Spedding et al., 2014).

Several studies revealed that the association between serum vitamin D level and susceptibility to disease (cancer, diabetes type 2, autoimmune diseases, depression, etc.) is altered by ethnicity and vitamin D receptor (VDR) gene polymorphisms (VDR genetic variants) of the studied population (Abdollahzadeh, et al., 2016; Kuningas, et al., 2009; Shaikh, Baig, & Jamal, 2016; Yu, et al., 2016). Despite published reports revealing high prevalence of vitamin D deficiency (Arabi et al. 2010; Bassil, Rahme, Hoteit, & Fuleihan, 2013; Fuleihan, et al., 2015), and parallel substantial burden of depression (Charara et al., 2017; Karam, et al., 2008; Mokdad, 2017) among Middle Eastern/ Arab adult populations, including Lebanon, research exploring whether low serum vitamin D level is associated with increased risk of depression or severity of depressive symptoms among Arab adult samples is almost non-existent. This study aims to investigate the relationship between serum vitamin D levels and severity of depressive symptoms among a sample of healthy Lebanese adults.

2. Methods

2.1 Study Design

This study used a cross-sectional research design and was conducted in a sample of employees (faculty members, administrators, and staff) of Notre Dame University (NDU), Lebanon between October and December 2016.

2.2 Recruitment and Data Collection Methods

Researchers sent an email to all NDU employees to inform them about the study purpose and solicit their participation in the study. Following the e-invitation, trained graduate research assistants (GRAs) arranged appointments with all faculty members, administrators and staff, and visited them in their offices to elaborate on the study objectives, confirm their interest in participation and clarify any existing study-related inquiries. Employees who expressed an interest in enrollment were then screened for eligibility; exclusion criteria were: pregnant and lactating women, and individuals with a pacemaker or a metal piece in the body. Those who were found to be eligible were then asked to read and sign a consent form. After completion of the consenting process, study participants were either interviewed by the GRA during the visit or contacted by the study investigators to arrange an interview appointment with a GRA, for about 30 minutes in the participant's office. At the beginning of the interview, the GRA assigned a numeric code to each participant and then filled out four questionnaires (Background Questionnaire, International Physical Activity Questionnaire - Short Form (IPAQ-SF), Food Frequency Questionnaire (FFQ) for vitamin D intake assessment and the Patient Health Questionnaire-9 (PHQ-9)) based on the participant's responses . All questionnaires were pre-tested using a random sample of thirty NDU employees. Revisions and corrections were done before initiating the study. At the end of the interview, GRAs scheduled appointments with participants for anthropometric measurements (body weight, height, and waist circumference (WC), body composition) and a fasting blood sample draw at the Nutrition Research Lab, Department of Nursing and Health Sciences. Participants were instructed to fast for at least 8 hours prior to their research lab morning appointment. The file linking the participants' names with their codes was password-protected and saved on the principal investigator (PI)'s computer.

2.3 Measures

2.3.1 Sociodemographic, Lifestyle Habits, and Medical History Data

We developed a questionnaire (Background Questionnaire) to collect data on sociodemographic variables (age, sex, educational level, income, marital status), lifestyle habits (smoking, alcohol drinking, daily sun exposure, and sunscreen use), recent medical history (diagnosis with chronic illnesses- any of cardiovascular diseases, diabetes, asthma, liver disease, kidney disease, thyroid gland disorders, neurological diseases, cancer, mental illness diagnosis; intake of medications including antidepressants), family history of mental illness, and stressful life events during the past year.

2.3.2 Physical Activity Level

We used the International Physical Activity Questionnaire - Short Form (IPAQ-SF) to measure level of physical activity among study participants. IPAQ-SF assesses total minutes of walking, moderate and vigorous intensity

activity in the last week. Participants' levels of physical activity were categorized as follows: low (MET-minutes per week < 600), moderate (600 ≤ MET-minutes per week < 3000), and high (MET-minutes per week ≥ 3000) (Booth, 2000).

2.3.3 Dietary Intake of Vitamin D

We used an adapted version of a Food Frequency Questionnaire (FFQ) prototype, developed by study investigators, for assessment of intake (consumption frequency, number of servings, and average portion size) of vitamin D- rich foods and supplements during the past month (El Hayek et al., 2014). Nutritionist Pro diet analysis software, the Middle-East Food Composition Tables (Pellett & Shadarevian, 2013), and the Canadian Nutrient File (Government of Canada, 2017) were used to generate estimates of dietary intake of vitamin D.

2.3.4 Depressive Symptoms' Severity

We used the Patient Health Questionnaire-9 (PHQ-9) to determine depressive symptoms' severity (Kroenke, Spitzer, Williams, & Löwe, 2010). PHQ-9 is a nine-item self- reported depression questionnaire which scores each of the 9 DSM IV- items as "0" (not at all) to "3"(nearly every day), giving a total severity score of 0 to 27. Higher PHQ-9 scores indicate more severe depressive symptoms**,** with threshold scores of 5, 10, 15, and 20 or higher indicating mild, moderate, moderately severe and severe depression (Pfizer, 2016), respectively.

2.3.5 Anthropometric Measurements

Body weight and height of participants were measured without shoes and wearing light clothes to the nearest 0.1 kg and 0.1 cm and using a digital scale and portable stadiometer, respectively. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). Weight status was determined as follows: underweight (BMI < 18.5), normal weight (BMI =18.5 - 24.9), overweight (BMI = 25.0 - 29.9), or obese (BMI ≥ 30.0) (WHO Expert Consultation, 2004). Waist circumference (WC) was measured just above the iliac crest at the midaxillary line with a measuring tape at the end of normal expiration to the nearest 0.1 cm. WC value > 102 cm in men and > 88 cm in women is considered an indicator of increased cardio-metabolic disease risk (CDC, 2007).

2.3.6 Serum 25(OH)D Level and Other Biochemical Measurements

Upon the visit to the Research Nutrition Lab, a nurse collected a fasting blood sample from study participants. Blood fractionation by centrifugation for 15 minutes at a speed of 1,800 rpm occurred at site of blood withdrawal within 2 hours of collecting blood samples. After fractionation, serum was pipetted into separate tubes while the other components of blood were discarded. Serum samples were stored at -20°C for a maximum period of 6 weeks before analysis. Serum 25(OH)D levels were measured using enzyme linked immunosorbent assay (ELISA) kit (from Calbiotech, Inc, USA), The inter-assay coefficient of variation (CV) was 5.63%, and the intra-assay CV was 4.95%. Vitamin D status was assessed according to Institute of Medicine (IOM) and Endocrine Society (ES). IOM considers subjects with serum 25(OH)D levels ≤10 ng/ml deficient, >10-20 ng/ml insufficient and >20 ng/ml sufficient (Ross, Taylor, Yaktine, & Del Valle, 2011). However, ES considers subjects with serum 25(OH)D levels ≤20 ng/ml deficient, >20-30 ng/ml insufficient and >30 ng/ml sufficient (Holick et al., 2011).

2.4 Statistical Analyses

Assuming that the prevalence rate of moderate-severe depression among community-dwelling general adult population in Lebanon is about 10% (Karam et al., 2008), the sample size was calculated and found to be 138 individuals. Data were entered, the data file was checked for errors and errors were corrected before data analysis. Continuous variables were summarized as mean ± standard deviation/median (interquartile range), whereas categorical variables were summarized as n (%). Mean values of continuous variables for independent groups were compared using independent sample T Test/ Mann-Whitney-U-test/Analysis of variance.

Multiple linear regression analysis was used to assess the independent association between serum 25(OH)D levels and severity of depressive symptoms (PHQ-9 score). Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Normality of the variables was assessed and log transformations were performed. The correlation between each of the independent variables included in the regression models and tolerance/VIF values were examined to pick up problems with multicollinearity (Tolerance < 0.1, VIF > 10). Normality of the residuals was assessed by inspecting the normal probability plot of the regression standardized residual and the residuals scatterplot.

Model 1 was unadjusted, showing the main effect of serum 25(OH)D levels (independent variable) on severity of depressive symptoms (dependent variable); model 2 was adjusted for socio-demographic characteristics (age, sex, income, and marital status) and BMI; model 3 was additionally adjusted for lifestyle habits (smoking, alcohol

drinking and physical activity). Model 4 was our fully adjusted model in which socio-demographics, lifestyle habits, and physical and mental health- related variables (chronic illness diagnosis, other mental illness diagnosis, family history of mental illness, number of stressful life events, and intake of antidepressants) were controlled for. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 22 for Windows. P-values of less than 0.05 were regarded as statistically significant.

2.5 Ethical Approval

The study protocol was approved by the Institutional Review Board at NDU. All participants signed informed consent prior to data collection.

3. Results

3.1 Sample Characteristics

The sample consisted of 351 NDU faculty and staff members (49% men and 51% women) with a mean age of 42.36 ± 11.52 years. The majority of the study participants reported to be married (~66%), live in urban areas (61%), have a university degree or its equivalent (~79%) with a monthly income of at least $2,250 (~68%). With regard to disease risk, a substantial percentage of the surveyed participants were found to have risk factors for disease including overweight/obesity (~64%), risky waist circumference (as per description in section 2.3.5) (~ 51%), low physical activity levels (65 %), smoking (38%), vitamin D inadequacy (IOM:≤ 20 ng/ml; ES:≤ 30 ng/ml) (IOM: 32%- 38%; ES:63%-73%, without and with excluding those taking vitamin D supplement, respectively), with about 41% reporting to have had a recent diagnosis with a chronic disease. In addition, about 29% of the study participants were found to have depression symptoms, after excluding those taking antidepressants (Table 1).

Table 1. Sample characteristics: sociodemographic, anthropometric, and lifestyle factors, serum 25-(OH)D levels, and depressive symptoms' severity (n=351)

	Mean ± SD Or n (%)		**Mean ± SD Or n (%)**
Age (years)	42.36 ± 11.52	**Sunscreen use**	
Sex		No	249 (70.9)
Male	172 (49)	Yes	102 (29.1)
Female	179 (51)	**Smoking**	
Residence		No	218 (62.1)
Urban	214 (61)	Yes	133 (37.9)
Rural	137 (39)	**Alcohol drinking**	
Marital status		No	261 (74.4)
Single, separated, divorced	119 (33.9)	Yes	90 (25.6)
Married	232 (66.1)	**Physical activity level**	
Income (monthly) ($)		Low	227 (64.7)
< 1,250	31 (8.8)	Moderate	113 (32.2)
1,250- 2,250	83 (23.6)	High	11 (3.1)
2,250- 4,000	88 (25.1)	**Chronic illness diagnosis**	
4,000- 5,333	70 (19.9)	No	207 (59.1)
> 5,333	79 (22.5)	Yes	143 (40.9)
Education level		**25(OH)D level** (ng/ml) (n=348)	28.15 ± 13.93
High school	75 (21.4)	**25(OH)D status**	
Bachelor	90 (25.6)	≤ 10 ng/ml	16 (4.6)
Graduate	186 (53.0)	> 10 to ≤ 20 ng/ml	95 (27.3)
BMI		> 20 to ≤ 30 ng/ml	108 (31.0)

Underweight	3 (0.9)	> 30 ng/ml	129 (37.1)
Normal	124 (35.3)	**Depressive symptoms severity**[1] (n=335)	
Overweight	133 (37.9)	None	239 (71.3)
Obese	91 (25.9)	Mild	78 (23.3)
WC		Moderate- severe	18 (5.4)
Normal	173 (49.3)		
Risky	178 (50.7)		
Intake of vitamin D supplement past 3 mo			
No	276 (78.6)		
Yes	75 (21.4)		
Daily exposure to direct sunlight			
5 min or less	57 (16.2)		
5-15 min	81 (23.1)		
16-30 min	65 (18.5)		
31-60 min	51 (14.5)		
More than 1 hour	97 (27.6)		

[1]Excluding subjects taking antidepressant medication (n=16).

3.2 Associations of Sociodemographic, Anthropometric & Lifestyle Factors With Serum 25-Hydroxyvitamin D Levels

Lower serum 25(OH)D levels were found to be associated with lack of vitamin D supplementation (no: 25.52±12.51; yes: 37.86±14.69, p=0.000), risky waist circumference (risky: 26.40±13.67; healthy: 29.91±14.01, p=0.010) and low/moderate physical activity levels (low: 27.59±14.20; moderate: 27.92±11.89; high: 41.92±20.86, p=0.042) (Table 2). Furthermore, lower 25(OH)D levels were found to be significantly correlated with lower vitamin D intake from food (r=0.181, p=0.001) (Data not shown).

Table 2. Associations of sociodemographic, anthropometric, and lifestyle factors with serum 25-(OH)D level (n=351)

	Mean ± SD	**P value**
Age (years)		0.271
≤ 36	26.63 ± 12.92	
37-48	29.04 ± 14.27	
≥ 49	28.90 ± 14.61	
Sex		0.737
Male	28.38 ± 15.01	
Female	27.92 ± 12.84	
Income (monthly) ($)		0.328
< 1,250	30.47 ± 14.73	
1,250- 2,250	26.27 ± 14.71	
2,250- 4,000	27.24 ± 13.11	
4,000- 5,333	28.41 ± 13.74	
> 5,333	30.02 ± 13.83	

Education level		0.651
High school	26.99 ± 14.32	
Bachelor degree	28.13 ± 14.10	
Graduate	28.61 ± 13.74	
Residence		0.551
Urban	28.58 ± 14.13	
Rural	27.47 ± 13.63	
Daily exposure to direct sunlight		0.547
5 min or less	27.15 ± 14.20	
5-15 min	29.21 ± 14.76	
16-30 min	25.78 ± 11.11	
31-60 min	26.78 ± 11.26	
More than 1 hour	30.09 ± 15.74	
Sunscreen use		0.071
No	27.57 ± 14.39	
yes	29.53 ± 12.72	
Intake of vitamin D supplement past 3 mo		0.000
No	25.52 ± 12.51	
Yes	37.86 ± 14.69	
BMI excluding underweight (3 participants)		0.217
Normal	29.27 ± 14.22	
Overweight	27.93 ± 13.34	
Obese	26.23 ± 13.78	
WC		0.010
Normal	29.91 ± 14.01	
Risky	26.40 ± 13.67	
Chronic illness diagnosis		0.468
No	27.61 ± 13.33	
Yes	28.96 ± 14.82	
Smoking		0.093
No	27.35 ± 13.89	
Yes	29.45 ± 13.95	
Alcohol drinking		0.051
No	27.35 ± 13.88	
Yes	30.42 ± 13.91	
Physical activity level		0.042
Low	27.59 ± 14.20	
Moderate	27.92 ± 11.89	
High	41.92 ± 20.86	
Depressive symptoms' severity [1]		0.353
None	28.66 ± 14.06	
Mild	26.82 ± 14.18	
Moderate-severe	24.17 ± 9.52	

[1] Excluding subjects taking antidepressant medication (n=16).

3.3 Association of serum 25-hydroxyvitamin D levels With Depression Score (PHQ-9 Score)

Multiple linear regression models were used to assess the ability of serum 25(OH)D levels to predict severity of depression symptoms, after controlling for the influence of confounding variables. In the unadjusted model (Model 1), higher depression scores (PHQ-9 scores) were found to be borderline significantly associated with lower serum 25(OH)D levels (p=0.054), whereby PHQ-9 score increases by about 0.003 units for a 1 ng/ml decrease in serum vitamin D levels, and with serum vitamin D levels explaining about 1 % of the variance in PHQ-9 scores. This borderline association vanished upon entry of variables that represent personal characteristics (age, sex, BMI, income and marital status) into the model (Model 2); entry of these variables increased the variance in PHQ-9 scores explained by the independent variables (serum vitamin D levels, age, sex, BMI, income and marital status) to about 10%. Entry of the independent variables that pertain to lifestyle habits (smoking, alcohol drinking and physical activity) into the model (Model 3) only increased the total variance explained by the independent variables (serum vitamin D levels, age, sex, BMI, income, marital status, smoking, alcohol drinking and physical activity) by about 1%. After additional entry of variables that represent physical/mental health into the model (Model 4), the total variance explained by the independent variables (serum vitamin D levels, age, sex, BMI, income, marital status, smoking, alcohol drinking, physical activity, chronic illness diagnosis, other mental illness diagnosis, family history of mental illness, number of stressful life events, and intake of antidepressants) increased to about 19%. In the final model (Model 4), higher depression scores were found to be borderline significantly associated with lower serum vitamin D levels (β =-0.110, p=0.058) and significantly associated with younger age, female sex, lower income, chronic illness diagnosis, family history of mental illness, number of stressful life events, and intake of antidepressants, with age recording the highest beta value (β =-0.201, p=0.004) followed by income (β =-0.171, p=0.004), sex (β =0.165, p=0.009), intake of antidepressants (β = 0.157, p=0.013), chronic illness diagnosis (β = 0.140, p=0.027), number of stressful life events (β = 0.130, p=0.024), and family history of mental illness (β = 0.127, p=0.027). Specifically, after controlling for all other variables in the model, severity of depression symptoms score (PHQ-9 score) increases by 0.003 unit for a 1 ng/ml decrease in serum 25-OHD levels, by 0.006 unit for a 1 year decrease in age, and by 0.042 unit for a 1 dollar decrease in income. In addition, females, individuals who have a chronic illness, family history of mental illness, have an additional stressful life event and take antidepressants were found to have a 0.105, 0.090, 0.162, 0.053 and 0.238- unit higher PHQ-9 score (Table 3).

Table 3. Association between serum 25(OH)D level and depressive symptoms' severity score, as assessed by multiple linear regression*

	Unstandardized β	**S.E.**	**Standardized β**	**p-value**	**95% CI for unstandardized β**		**R square**
					Lower Boundary	Upper Boundary	
Model 1							0.013
Serum 25(OH)D level	-0.003	0.001	-0.115	0.054	-0.005	0.000	
Model 2							0.102
Serum 25(OH)D level	-0.002	0.001	-0.091	0.123	-0.005	0.001	
Age	-0.004	0.002	-0.130	0.048	-0.007	0.000	
Sex	0.120	0.039	0.189	0.003	0.042	0.197	
BMI	0.000	0.004	0.008	0.905	-0.008	0.009	
Income	-0.039	0.015	-0.156	0.008	-0.067	-0.010	
Marital status	0.011	0.042	0.016	0.795	-0.071	0.093	
Model 3							0.108
Serum 25(OH)D level	-0.002	0.001	-0.101	0.092	-0.005	0.000	
Age	-0.004	0.002	-0.131	0.048	-0.007	0.000	
Sex	0.133	0.041	0.209	0.001	0.052	0.213	
BMI	0.001	0.004	0.018	0.783	-0.007	0.009	
Income	-0.040	0.015	-0.163	0.007	-0.070	-0.011	
Marital status	0.012	0.042	0.018	0.776	-0.071	0.095	

Smoking	0.007	0.040	0.011	0.863	-0.072	0.086	
Alcohol drinking	0.025	0.044	0.034	0.577	-0.062	0.111	
Physical activity	0.043	0.034	0.074	0.212	-0.025	0.110	
Model 4							0.19
Serum 25(OH)D level	-0.003	0.001	-0.110	0.058	-0.005	0.000	
Age	-0.006	0.002	-0.201	0.004	-0.009	-0.002	
Sex	0.105	0.040	0.165	0.009	0.026	0.184	
BMI	-0.001	0.004	-0.023	0.716	-0.010	0.007	
Income	-0.042	0.015	-0.171	0.004	-0.071	-0.014	
Marital status	0.015	0.041	0.023	0.708	-0.065	0.096	
Smoking	-0.002	0.039	-0.003	0.964	-0.078	0.074	
Alcohol drinking	0.027	0.043	0.037	0.529	-0.057	0.111	
Physical activity	0.042	0.033	0.073	0.202	-0.023	0.107	
Chronic illness diagnosis	0.090	0.041	0.140	0.027	0.010	0.171	
Other mental illness diagnosis	-0.090	0.114	-0.049	0.431	-0.314	0.135	
Family history of mental illness	0.162	0.073	0.127	0.027	0.019	0.306	
Number of stressful life events	0.053	0.023	0.130	0.024	0.007	0.099	
Intake of antidepressants	0.238	0.096	0.157	0.013	0.050	0.427	

* Dependent Variable: Depressive symptoms' severity score (log total PHQ-9 score).

4. Discussion

To repeat, our study aimed to explore whether serum 25(OH)D levels are related to depressive symptoms among a sample of apparently healthy adults from Lebanon adjusting for multiple confounders. We targeted a group of employees of a private university in Lebanon aged 20 to 65 years during late fall season (November-December). Mean serum 25(OH)D levels of the study participants was found to be 28.15±13.93 ng/ml, and close to 32% had vitamin D deficiency as per ES criteria 25(OH)D levels ≤ 20 ng/ml. Just 5.4% of the total sample reported moderate to severe symptoms of depression, as determined by PHQ-9 scores. Findings from multiple linear regression analyses revealed no statistically significant association between serum 25(OH)D levels and severity of depressive symptoms in our sample, before and after adjustment for sociodemographic, and lifestyle factors, BMI, presence of current chronic medical conditions and other mental illness, family history of mental illness, and current stressful events.

Our sample mean serum 25(OH)D level (28.15±13.93 ng/ml) was higher and prevalence rate of vitamin D deficiency (≤ 20 ng/ml) (32%) were lower than those reported in two studies involving samples of healthy Lebanese adults (Gannagé-Yared et al., 2014; Malaeb, Hallit, & Salameh, 2017); this could be attributed to differences in characteristics among study samples. Mean serum 25(OH)D level was found to be 15.61 ± 7.91 ng/ml and prevalence rate of vitamin D deficiency (< 20 ng/ml) was reported at 71.4% among a sample of 392 healthy private hospital employees (nurses, medical assistants, technicians, secretaries, medical engineers, administrative employees, etc., excluding doctors and medical students) aged 20-63 years (mean age= 41.02 ±11.3 years) (81% women); none of them had been taking vitamin D supplement. Similar to our findings, there was no significant associations between serum 25(OH)D levels and age, sex, BMI, and sunscreen use; however, contrary to our study, serum 25(OH)D levels showed significant associations with educational level, and weekly hours of sun exposure (Gannagé-Yared et al., 2014). The two other studies looked at serum 25(OH)D levels and their determinants in samples of university students. In the first one (more recent) which surveyed a sample of 160 pharmacy private university students aged 21-24 years (mean age=23.24 years), mean serum 25(OH)D level was found to be 16.80 ± 5.85 ng/ml and prevalence of vitamin D deficiency (≤ 20 ng/ml) was revealed at 42.5%

(Malaeb et al., 2017). In the second study, which was conducted among 381 private university students aged 18-30 years (mean age= 23.9 ±3.9 years) (53% men), mean serum 25(OH)D level was reported to be 31 ± 12.4 ng/ml and prevalence of vitamin D deficiency (≤ 20 ng/ml) was found to be 18.6%; the study also showed, opposite to our study findings, that serum 25(OH)D level had a significant inverse correlation with BMI (Gannagé-Yared, Chedid, & Halaby, 2010).

The lack of association between serum 25(OH)D levels and depressive symptoms in our study is comparable to that reported by several other studies from the US, Germany, Finland, Denmark, South Korea, and Japan. In a population-based sample of 3,916 American adults aged ≥20 years, the adjusted odds of having moderate to severe depression (assessed using PHQ-9 score ≥ 10) did not differ significantly between the highest and the lowest quartiles of serum 25(OH)D levels. In this sample, the age-adjusted prevalence of moderate-severe depression was found to be 5.3% (Zhao, Ford, Li, & Balluz, 2010). In another study which was conducted among a population-based sample of 6,331 German adults aged 18-79 years (mean age=46.8 years), findings from both linear/ logistic regression analyses revealed no significant association between serum 25OHD levels and PHQ-9 score/ depression status (PHQ-9 score ≥10) during wintertime after adjustment for confounders. In this sample, the mean 25(OH)D was 18.51 ng/ml, mean PHQ-9 score was 4.1, and prevalence of depression (PHQ-9 score ≥10) was 7.5% (Rabenberg et al., 2016). Although the adjusted odds of presence of current clinically relevant depressive symptoms (BDI score ≥10) among individuals with serum 25 (OH)D concentrations in the highest quartile was lower compared to those with serum 25 (OH)D concentrations in the lowest quartile; yet it was statistically non-significant (OR= 0.83, 95% CI: 0.69-1.01, p =0.08) in a representative sample of 5,371 adult Finnish men and women aged 30-79 years (mean age=50.4 years) (Jääskeläinen et al., 2015). Findings from multiple linear/ logistic regression analyses of data from a Danish population-based adult sample aged 18-64 years (n=5,308) showed no significant association between serum 25(OH)D levels and self-reported depressive symptoms score/ depression score >90th percentile for each sex, assessed using the Symptom Check List (SCL)-90-R, (β-coefficient and 95% CI per 10 nmol/l serum 25(OH)D were 0.00 (-0.00 to 0.01) for depressive symptoms score) after adjustment for confounders (Husemoen et al., 2016). In a sample of 52,228 South Korean healthy employees aged 20-70 years (mean age=38.4 years, 86% men), serum 25OHD levels had no significant association with presence of depressive symptoms (defined by CES-D ≥21) after adjustment for confounders. However, when using 25OHD as a categorical variable, the association with presence of depressive symptoms was evident only with the vitamin D deficient group (<10 ng/ml) (reference group: vitamin D sufficient ≥20 ng/ml) (adjusted OR=1.158, 95% CI=1.003–1.336, p=0.046). In this sample, 70.3% had serum 25(OH)D level < 20 ng/ml and 4.8% were found to be depressed (Shin, Jung, Kim, Kim, & Lim, 2016). Findings from multivariate logistic regression analysis of data from a nationally representative sample of 15,695 South Korean adults aged ≥20 years revealed no significant association between vitamin D status and self-reported current physician diagnosis of depression after controlling for confounders (Park, Yang, Won Park, & Chung, 2016). In a sample of 368 public employees aged 21-67 years (mean age= 43.0 years; 42% women) from Japan, the multivariate adjusted OR of having depressive symptoms (assessed using the Center for Epidemiologic Studies Depression Scale (CES-D); CES-D scores ≥16) tended to decrease from the lowest (reference category) through the highest quartiles of serum 25(OH)D concentrations, yet it was statistically non-significant (Nanri et al., 2009).

On the other hand, our findings were in disagreement with others reported from the US, UK, Norway, Jordan, South Korea and Japan. Findings from logistic regression analysis of data of 12,594 American adults aged 20-90 years (mean age= 51.7 years, 68% men), showed that the adjusted OR for having depression (assessed using the Center for Epidemiologic Studies Depression Scale (CES-D); CES-D scores ≥10) for each 10 ng/ml increase in serum 25(OH)D levels was 0.92 (95% CI: 0.87-0.97, p=0.02). In this sample, mean serum 25(OH)D level was found to be 30.9 ± 12.4 ng/ml and 50.7% had serum 25(OH)D level <30 ng/ml (Hoang et al., 2011). In another study which surveyed a sample of 7,970 American adults aged 15-39 years (mean age=27.5 years, 46% men), the adjusted OR (95%CI) for having depression (assessed using the Diagnostic Interview Schedule (DIS)) among vitamin D deficient (< 20 ng/ml), compared to vitamin D sufficient (> 30 ng/ml) was 1.85 (0.90-3.81, p= 0.021). However, the adjusted OR for having depression among vitamin D insufficient (20-30 ng/ml) compared to vitamin D sufficient was not statistically significant (Ganji, Milone, Cody, McCarty, & Wang, 2010). Findings from a study which looked at data of 7,401 British cohort aged 45 years revealed significant dose-dependent inverse association between serum 25(OH)D level and depression (assessed using Clinical Interview Schedule Revised (CIS-R)). The adjusted odds of having depression among participants with serum 25(OH)D level between 75-99.9 were found to be significantly lower than that of those with serum 25(OH)D levels < 25 nmol/l (OR=0.59; 95%CI: 0.41-0.86; p=0.001) (Maddock, Berry, Geoffroy, Power, & Hyppönen, 2013). The adjusted odds ratio for depression (Hopkins Symptoms Check List 10 (SCL-10) scores ≥1.85) in the highest serum 25(OH)D quartile was found to be

significantly lower compared with the lowest serum 25(OH)D quartile) in a population-based sample of 10,086 adults aged 30-87 years from Northern Norway (Kjærgaard, Joakimsen, & Jorde, 2011). In a national population based sample of 4,002 adults aged ≥ 25 years from Jordan, the adjusted OR for having depression (assessed using depression subscale of the Depression Anxiety Stress Scales (DASS21); DASS-D score ≥14) among those with serum 25OHD level <30 ng/ml compared to those with serum 25OHD level ≥30 ng/ml was 1.38 (p=0.00). In this sample 31.8% reported having moderate to extremely severe depression (Jaddou et al., 2012). The adjusted odds of depression (assessed using a self-reported single question) among the vitamin D sufficient group (≥ 20 ng/ml) compared to the insufficient group (< 20 ng/ml) was significantly lower (OR= 0.72, 95% CI: 0.53–0.97; p= 0.032) in a nationally representative sample of 3,570 adults from South Korea aged ≥ 20 years (mean age= 43.3 years, 47% men) (Chung, Cho, Choi, & Shin, 2014). In a sample of 1,786 Japanese healthy employees aged 19-69 years (91% men), the adjusted ORs (95%CI) for presence of depressive symptoms (assessed using the Center for Epidemiologic Studies Depression Scale (CES-D)) for the highest (≥ 30 ng/ml) category of 25(OH)D versus the lowest (< 20 ng/ml) was 0.66 (0.41, 1.06) (p=0.01). The association between serum 25(OH)D concentration and depressive symptoms appeared to be inverse linear in fully adjusted models (Mizoue et al., 2015).

The lack of significant association between serum 25(OH)D levels and severity of depressive symptoms in our study can be accounted for by several possible explanations. 1) We had low prevalence rates of vitamin D deficiency (≤10 ng/ml: 4.6%; ≤20 ng/ml: 31.9%) and moderate-severe depression (PHQ-9 ≥10: 5.4%) in our sample. Though it is possible that the actual prevalence of depression in our sample is 5.4%, it could also be that members of the target population with moderate-severe depression did not participate in the study. Should the study findings (5.4% of the sample had moderate-severe depression) be accurate, then low prevalence rate of depression in our sample is quite likely one important factor accounting for lack of association between serum 25(OH)D levels and depressive symptoms. 2) The association between vitamin D status and depression is more likely to be evident when vitamin D deficient or insufficient (vs. sufficient) (Parker, Brotchie, & Graham, 2017), and serum vitamin D levels may not have a strong relationship with depressive symptoms when the levels are optimal or suboptimal (Shin et al., 2016). 3) The concept of a threshold for an effect of serum 25(OH)D level on depression may underlie the lack of association in our study. When examining association between serum 25(OH)D level at age 45 years and depression at age 50 years, analyses revealed non-linear significant association, after adjustment for confounders. Participants with serum 25(OH)D levels between 50 and 85 nmol/l at baseline (45 years) had significantly lower risk of subsequent depression at 50 years compared to those with lower or higher serum 25(OH)D concentrations (Maddock et al., 2013). 4) The effect of vitamin D supplementation on depressive symptoms was small and statistically insignificant in trials of non-clinically depressed participants (Shaffer et al., 2014). 5) Differences in methodological approaches such as differences in characteristics of study population, season of blood collection, assays used for measurement of serum 25(OH)D levels, reference categories of vitamin D concentration, instruments used for assessment of depression (self-reported symptom scale versus diagnostic interviews), conceptualization of depression (depressive symptoms continuum or "caseness" of depression), regression techniques/ types, and covariates adjusted for in regression analyses, were pointed out by many investigators as possible explanations for inconsistent results (Anglin et al., 2013; Ju et al., 2013; Parker et al., 2017). 6) The heterogeneity of depression may justify why low serum 25(OH)D levels may be relevant only in specific subgroups of depressed patients (Milaneschi et al., 2014).

4.1 Study Strengths and Limitations

Our study is the first in the Arab region to explore the relationship between serum 25(OH)D levels and depressive symptoms in healthy employees aged 18-65 years, and the second one to examine this association among healthy adults (the first one is that conducted by Jaddou et al., 2012). Compared to the study done by Jaddou et al. (2012) targeting a population-based sample of 4,002 Jordanian adults aged ≥ 25 years, we took into account adjustment for important covariates known to influence depression such as income, family history of depression, and stressful life events. We adopted validated measures of serum 25(OH)D levels and depressive symptoms.

Alternatively, our study bears several limitations. Despite a relatively good sample size, the low and narrow range of PHQ-9 scores may have reduced the ability to detect an association between 25(OH)D and depressive symptoms. Alternatively, the low prevalence rate of moderate-severe depression (5.4%) in the sample did not allow us to stratify the data. It is quite likely that cases with moderate-severe depressive symptoms were under-represented in our sample compared to background population (Karam, et al., 2008). Though the assay that we used to measure serum 25(OH)D is deemed suitable, it is possible that different 25(OH)D values could have been obtained should we had used another assay given the inter-assay differences in measurement of 25(OH)D (Fuleihan et al., 2015). Data on depressive symptoms and multiple other variables were self-reported; hence it is probable that some data may not be accurate. Though we adjusted for a wide sum of potential confounders, we

cannot exclude others such as diet quality. Collin et al. (2017) reported that a slightly low 25(OH)D level may not have a negative impact on depressive symptoms if the overall dietary quality is high. Our study targeted employees at a private university; hence, our results cannot be generalized to the general adult population in Lebanon.

In conclusion, we did not find any significant independent association between serum 25(OH)D levels and severity of depressive symptoms in a sample of Lebanese employees of a private academic institution. There remains a need for studies to further explore this association in a representative large sample of Lebanese adults, and figure out clinical significance of this association, if any. Prospective studies would provide indications as to whether low vitamin D level is a predecessor or a consequence of depression.

Authors' Disclosure

The authors declare that they have no conflict of interest.

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