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Serum 25-hydroxyvitamin D concentrations are associated with mental health and psychosocial stress in young adults

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Running title: 25(OH)D and mental health in young adults

Abbreviations

25(OH)D = 25-hydroxyvitamin D_3; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; PSS = Perceived Stress Scale; CMHS = Cook-Medley Hostility Scale; SES = socioeconomic status; BP = blood pressure; SD = standard deviation; ANOVA = analysis-of-variance; CNS = central nervous system; BDNF = brain-derived neurotrophic factor.

Abstract

We aimed to test the hypothesis that serum 25-hydroxyvitamin D_3 [25(OH)D] concentration is associated with mental health and life stress measures in young adults, and investigate sex and racial disparities in these associations. This study comprised 327 black and white participants. Depression, trait anxiety, perceived stress, and hostility were measured by validated instruments: Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS), and Cook-Medley Hostility Scale (CMHS). Linear regression was used to estimate correlations between serum 25(OH)D concentration and mental health measurements in total population and in subgroups stratified by sex and race. In this sample (28.2 ± 3.1 years, 48% male, 53% black), serum 25(OH)D concentration was negatively related to BDI, STAI, PSS, total CMHS score and the majority of CMHS subscale scores (p-values < 0.05). Stratified by sex, most of these associations remained significant only in women (p-values < 0.05). Stratified by race, higher 25(OH)D concentrations in the whites were significantly related to lower BDI, STAI, PSS, and CMHS-cynicism subscale (p-values < 0.05); 25(OH)D concentrations in the blacks were only inversely associated with CMHS and most CMHS subscales (p-values < 0.05), but not with BDI, STAI and PSS. We present novel findings of consistent inverse relationships between serum 25(OH)D concentration and various measures of mental health and life stress. Long-term interventional studies are warranted to investigate the roles of vitamin D supplementation in prevention and mitigation of depression, anxiety and psychological stress in young adults.

Keywords: 25-hydroxyvitamin D_3; depression, anxiety; perceived stress; hostility

1. Introduction

Mental health is an important dimension of health, affecting the overall quality of life, and mental disorders impose significant economic, social and public health burden [1]. Mental disorders not only compromise the quality of life, but also are important risk factors for physical/somatic diseases. Studies suggest that depression is associated with inflammation [2] and cardiovascular disease [3]. Higher perceived stress has been related to worse outcomes of aging [4] and immunity [5]. In addition to depression, other areas of mental health and stress can affect disease. For example, anxiety was significantly associated with coronary artery calcification [6], and hostility is related to insulin resistance and inflammation [7].

Many studies which examined plasma levels of vitamin D and association with mental health disorders have focused upon depression. The outcomes of these studies have been mixed. Inverse association between circulating vitamin D concentration and depression has been observed in adults in New Zealand [8], Australia [9], Finland [10], and the U.S. elderly [11]. Other studies found that the association was not statistically significant among elderly in Italy [12], Netherlands [13], nor adults in Denmark [14] and the U.S. [15].

The relationship between serum 25(OH)D concentration and anxiety symptoms has been assessed in a few studies, and the associations were mostly not significant [9,10,14,16]. However, those findings may be limited by the fact that in most studies, the anxiety measures were limited and typically were subscales of depression in questionnaires [9,10,14,16,17]. The association between vitamin D and perceived stress or hostility is also under-studied. Only one study found serum 25(OH)D concentration inversely associated with perceived stress. The study involved Korean female elders, and perceived stress was characterized as a dummy variable based on a single question [18].

The majority of the studies conducted to date involved the elderly, and evidence is scarce in young adults, especially in the United States. Therefore, we aimed to test the hypothesis that serum 25(OH)D concentration is associated with mental health and life stress measurements including depression, trait anxiety, perceived stress and hostility of young adults, and to investigate sex and racial disparities in these associations.

2. Materials and Methods

2.1. Participants

A total of 327 black and white participants (28.2 ± 3.1 years, 48% male, 53% black) from the southeastern region of the U.S. were included in this study. The recruitment and evaluation of participants have been described in details elsewhere [19]. General characteristics, socioeconomic status (SES) and mental health measurements were obtained by questionnaires. Serum samples were processed for serum 25(OH)D concentrations. The Institutional Review Board at the Augusta University gave approval for the study (IRB#611084-10, May 26, 2020) and informed consent of each participant was obtained.

2.2. Vitamin D measurement

Serum 25(OH)D concentrations were determined from fasting blood using an enzyme immunoassay (Immunodiagnostic Systems, Fountain Hills, AZ) according to the manufacturer's specifications. Analytical reliability of the 25(OH)D assays was monitored through participation in DEQAS (Vitamin D External Quality Assessment Scheme) and was deemed acceptable. The intra- and interassay coefficient of variations for serum 25(OH)D were 5.6 and 6.6%, respectively.

2.3. Beck Depression Inventory

Beck depression inventory (BDI) was originally developed in 1961 to identify the presence and severity of depressive symptoms [20]. It has been well validated in normal and psychiatric populations [21]. All subjects were required to complete the self-report questionnaire, which contains 21 items. These items relate to the feelings of irritability, guilt, punishment, and physical symptoms such as fatigue, weight loss and lack of interest in sex. Each item is scored on a scale value of 0 to 3. Theoretically, the total score of BDI ranges from 0 to 63, and higher scores indicate more severe depressive symptoms.

2.4. State-Trait Anxiety Inventory

Anxiety was measured using the State-Trait Anxiety Inventory (STAI) from Y-2 [22]. Anxiety can be differentiated into state anxiety and trait anxiety. In this study, we measured trait anxiety, which is considered an enduring characteristic that refers to relatively stabilizing individual differences that characterize people's anxiety or a general feeling of anxiety [22]. This inventory has 20 items. All items are rated on a 4-point scale weighted from one to four. The total score for trait anxiety is the total of each item. Higher scores indicate greater anxiety.

2.5 Perceived Stress Scale

Perception of stress was measured by the Perceived Stress Scale (PSS), which contains 10 items, and each item has five response options weighted from zero to four [23]. PSS is one of the most widely used psychological instruments for measuring nonspecific perceived stress.

2.6. Cook-Medley Hostility Scale

The Cook-Medley hostility scale (CMHS) is a 50-item true/false questionnaire derived from the Minnesota Multiphasic Personality Inventory [24]. CMHS measures tendencies toward cynicism,

hostile affect and aggressive responding. Five subscales were identified: cynicism, hostile attributions, hostile affect, aggressive responding, and social avoidance.

2.7. Hollingshead Social Status

Hollingshead Four-Factor Social Status Index was calculated on the basis of parental education level, employment status, and occupation; a higher value indicates higher SES [25]. The Hollingshead parental education level is rated on a 7-point scale that lists the highest grade completed, and the occupational prestige is rated on a 9-point scale. SES was then calculated by multiplying the occupation scale value by a weight of 5 and the education scale value by 3 and summing the products. Hollingshead Index scores range from 8 to 66.

2.8. Statistical analysis

The general characteristics of the subjects are presented as mean ± standard deviation (SD) for continuous variables and N (%) for categorical variables. Normality of each continuous variable was tested based on a combination test statistics of skewness and kurtosis. To test mean differences in continues measures by sex and race, analysis-of-variance (ANOVA) was conducted for variables with normal distribution, while the Kruskal-Wallis test was used instead for non-normally distributed variables. Chi-square tests were conducted for categorical variables. Linear regression was used to estimate associations of psychological and psychosocial stress measures with 25(OH)D concentrations while adjusting for age, race, sex in the base model, and then further adjusting for SES in a separate model. Regression models were then stratified by sex and race to examine the differences by strata in the associations between 25(OH)D concentrations and the various mental health and stress-related scores. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using Stata version 12.0 (College Station, Texas 77845 USA).

3. Results

3.1. Participant Characteristics

Among 327 participants, the mean serum 25(OH)D concentration was 59.2 ± 26.1 nmol/L. We compared general characteristics among the four groups defined by sex and race. Age, 25(OH)D concentration, SES and CHMS among the four groups were significantly different (p-value < 0.05) (Table 1).

Table 1. General characteristics stratified by sex and race

Characteristics	White male (N=83)	Black male (N=75)	White female (N=70)	Black female (N=99)	Total (N=327)	p-values
Age (years)	27.3 ± 3.1	28.7 ± 3.2	28.4 ± 3.2	28.3 ± 2.8	28.2 ± 3.1	**0.031**
25(OH)D (nmol/L)	74.7 ± 24.7	46.5 ± 18.1	76.0 ± 26.8	43.9 ± 15.3	59.2 ± 26.1	**<0.001**
SES	41.5 ± 15.8	37.9 ± 15.3	43.2 ± 14.5	34.9 ± 13.9	39.0 ± 15.2	**0.001**
BDI	6.4 ± 7.4	6.9 ± 8.2	6.1 ± 6.3	7.0 ± 7.9	6.6 ± 7.5	0.848
STAI	24.3 ± 5.9	24.6 ± 6.0	24.0 ± 6.7	24.9 ± 6.1d	24.5 ± 6.1	0.580
PSS	15.2 ± 6.5	15.7 ± 6.3	15.8 ± 7.5	16.4 ± 6.5	15.8 ± 6.7	0.691
CMHS	21.6 ± 9.2	24.6 ± 8.2	16.0 ± 8.8	18.4 ± 9.7	20.1 ± 9.5	**<0.001**
CMHS cynicism	6.4 ± 3.1	7.8 ± 3.1	4.2 ± 2.9	5.4 ± 3.6	5.9 ± 3.4	**<0.001**
CMHS hostile affect	2.1 ± 1.3	2.2 ± 1.3	1.7 ± 1.3	1.8 ± 1.3	1.9 ± 1.3	0.088
CMHS aggressive responding	4.0 ± 2.0	4.3 ± 1.7	2.7 ± 2.0	3.2 ± 2.1	3.6 ± 2.0	**<0.001**
CMHS hostile attribution	4.5 ± 2.7	5.7 ± 2.7	3.5 ± 2.4	4.1 ± 2.5	4.4 ± 2.7	**<0.001**
CMHS social aversion	1.8 ± 1.2	2.0 ± 1.1	1.7 ± 1.0	1.7 ± 1.1	1.8 ± 1.1	0.332

25(OH)D = 25-hydroxyvitamin D_3; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; PSS = Perceived Stress Scale; CMHS = Cook-Medley Hostility Scale; SES = socioeconomic status.

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3.2. Adjusted associations between mental health measurements and serum 25(OH)D concentrations

In the base models, as shown in Table 2, higher serum 25(OH)D concentrations were significantly related to lower scores on the BDI, STAI, PSS, CMHS and three CMHS subscales (p-values < 0.05) after adjustment for age, sex and race; aggressive responding (p-value = 0.067) and social aversion (p-value = 0.094) CMHS subscales were not related to 25(OH)D. Further adjustment for SES did not alter the findings significantly, but the association between 25(OH)D and the aggressive responding subscale became modestly significant (p-value = 0.045).

Table 2. Adjusted associations between mental health measurements and serum 25(OH)D concentrations

Dependent variables	Base model*		Base model + SES*	
	β (SE)	*p*	β (SE)	*p*
BDI**	-0.16 (0.07)	**0.018**	-0.17 (0.07)	**0.012**
STAI***	-0.19 (0.07)	**0.005**	-0.20 (0.07)	**0.003**
PSS	-0.20 (0.07)	**0.004**	-0.21 (0.07)	**0.002**
CMHS	-0.20 (0.06)	**0.002**	-0.22 (0.06)	**0.001**
Cynicism	-0.23 (0.06)	**<0.001**	-0.24 (0.06)	**<0.001**
Hostile affect	-0.16 (0.07)	**0.022**	-0.16 (0.07)	**0.015**
Aggressive responding	-0.12 (0.07)	0.067	-0.13 (0.07)	**0.045**
Hostile attribution	-0.19 (0.07)	**0.005**	-0.19 (0.07)	**0.003**
Social aversion	-0.12 (0.07)	0.094	-0.12 (0.07)	0.071

25(OH)D = 25-hydroxyvitamin D_3; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; PSS = Perceived Stress Scale; CMHS = Cook-Medley Hostility Scale; SES = socioeconomic status.

*Serum 25(OH)D was log-transformed and adjusted for age, sex and race in the base model. Standardized β coefficients are presented.

**Square root transformed. ***Log transformed.

3.3. Sex differences in the associations between mental health measurements and serum 25(OH)D concentrations

Serum 25(OH)D concentrations were significantly related to lower scores on the BDI, STAI, PSS, CMHS and all subscales of CMHS among females (p-values < 0.05) when adjusted for age and race. However, among males, serum 25(OH)D concentrations were only significantly associated with cynicism (p-value < 0.05). Further adjustment for SES did not change those findings. (Table 3)

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Table 3. Adjusted associations between mental health and serum 25(OH)D concentrations stratified by sex

Dependent variable	Male* (N=158)				Female* (N=169)			
	Base model		Base model + SES		Base model		Base model + SES	
	β (SE)	*p*	β (SE)	*p*	β (SE)	*p*	β (SE)	*p*
BDI**	-0.07 (0.10)	0.478	-0.05 (0.09)	0.563	-0.26 (0.09)	**0.006**	-0.22 (0.09)	**0.013**
STAI***	-0.14 (0.09)	0.138	-0.13 (0.09)	0.142	-0.25 (0.10)	**0.015**	-0.21 (0.09)	**0.028**
PSS	-0.08 (0.09)	0.399	-0.08 (0.09)	0.376	-0.33 (0.10)	**0.001**	-0.29 (0.10)	**0.03**
CMHS	-0.06 (0.09)	0.483	-0.05 (0.08)	0.506	-0.38 (0.09)	**<0.001**	-0.35 (0.09)	**<0.001**
Cynicism	-0.23 (0.08)	**0.007**	-0.23 (0.08)	**0.007**	-0.24 (0.10)	**0.012**	-0.22 (0.09)	**0.018**
Hostile affect	0.00 (0.09)	0.994	0.02 (0.09)	0.868	-0.34 (0.10)	**0.001**	-0.31 (0.09)	**0.001**
Aggressive responding	0.04 (0.09)	0.648	0.05 (0.08)	0.559	-0.31 (0.10)	**0.002**	-0.29 (0.10)	**0.003**
Hostile attribution	-0.01 (0.10)	0.905	-0.00 (0.09)	0.984	-0.40 (0.09)	**<0.001**	-0.36 (0.08)	**<0.001**
Social aversion	0.09 (0.10)	0.376	0.09 (0.10)	0.343	-0.34 (0.09)	**<0.001**	-0.34 (0.09)	**<0.001**

25(OH)D = 25-hydroxyvitamin D_3; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; PSS = Perceived Stress Scale; CMHS = Cook-Medley Hostility Scale; SES = socioeconomic status.

* Serum 25(OH)D was log-transformed and adjusted for age and race in the base model. BDI was square root transformed and STAI was log transformed in the regression. Standardized β coefficients are presented. **Square root transformed. ***Log transformed.

3.4. Race differences in the associations between mental health measurements and serum 25(OH)D concentrations

Among white participants, serum 25(OH)D concentrations were significantly related to lower scores on the BDI, STAI, PSS, and cynicism of CMHS (p-values < 0.05) after adjustment for age and sex. Among black participants, serum 25(OH)D concentrations were associated with most CMHS subscales [cynicism, hostile affect, aggressive responding and hostile attribution (p-values < 0.05)], but were not related to depression, anxiety or perceived stress. Further adjustment for SES did not change most findings, but the estimate for the association between 25(OH)D and hostile affect among blacks was attenuated and no longer statistically significant. (Table 4)

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Table 4. Adjusted associations between mental health and serum 25(OH)D concentrations stratified by race

Dependent variable	Whites* (N=153)				Blacks* (N=174)			
	Base model		Base model + SES		Base model		Base model + SES	
	β (SE)	*p*	β (SE)	*p*	β (SE)	*p*	β (SE)	*p*
BDI**	-0.29 (0.10)	**0.003**	-0.32 (0.08)	**<0.001**	-0.05 (0.10)	0.615	0.03 (0.09)	0.723
STAI***	-0.22 (0.10)	**0.037**	-0.24 (0.09)	**0.010**	-0.17 (0.09)	0.069	-0.11 (0.09)	0.205
PSS	-0.26 (0.11)	**0.017**	-0.28 (0.10)	**0.005**	-0.15 (0.09)	0.090	-0.10 (0.09)	0.279
CMHS	-0.12 (0.10)	0.206	-0.14 (0.09)	0.104	-0.27 (0.09)	**0.002**	-0.22 (0.08)	**0.009**
Cynicism	-0.20 (0.09)	**0.025**	-0.22 (0.08)	**0.010**	-0.26 (0.09)	**0.005**	-0.22 (0.09)	**0.015**
Hostile affect	-0.12 (0.10)	0.251	-0.13 (0.10)	0.189	-0.19 (0.09)	**0.041**	-0.14 (0.09)	0.124
Aggressive responding	-0.00 (0.10)	0.963	-0.02 (0.10)	0.827	-0.21 (0.09)	**0.016**	-0.18 (0.09)	**0.041**
Hostile attribution	-0.06 (0.10)	0.551	-0.08 (0.09)	0.364	-0.29 (0.09)	**0.001**	-0.24 (0.09)	**0.006**
Social aversion	-0.19 (0.10)	0.070	-0.20 (0.10)	**0.045**	-0.06 (0.09)	0.485	-0.06 (0.09)	0.503

25(OH)D = 25-hydroxyvitamin D_3; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; PSS = Perceived Stress Scale; CMHS = Cook-Medley Hostility Scale; SES = socioeconomic status.

* Serum 25(OH)D was log-transformed and adjusted for age and sex in the base model. BDI was square root transformed and STAI was log transformed in the regression. Standardized β coefficients are presented. **Square root transformed. ***Log transformed.

4. Discussion

In this study, we found that among U.S. young adults serum 25(OH)D concentrations were significantly related with lower scores on the BDI, STAI, PSS, CMHS and most CMHS subscales (except social aversion) after accounting for age, sex, race and SES.

The associations between 25(OH)D concentration and mental health scales were generally consistent across different mental health domains. Therefore, it is possible that those mental health domains may partially share common pathways linking them to vitamin D levels. Vitamin D receptors (VDR) and the vitamin D activating enzyme 1α-hydroxylase are present in the human brain [26], and VDR knockout mice have exhibited depressive behaviors [27]. Evidence also shows that 25(OH)D can cross the blood-brain barrier, and 25(OH)D receptors exist in the central nervous system (CNS) [28]. Vitamin D may also relate to mental health through regulation of levels of brain-derived neurotrophic factor (BDNF), which is a protein encoded by the *BDNF* gene. BDNF deficiency has been associated with age-dependent impairment in spatial learning [29], neurodegeneration [30], cognitive dysfunction [31], as well as with depression [32-34]. Vitamin D supplementation may increase BDNF concentration in the hippocampus [35] - a critical brain region for emotion regulation; neural stem cells treated with vitamin D have shown increased expression of BDNF [36].

Inflammation is correlated with mental health. Proinflammatory cytokines can induce depressive symptoms by affecting neurotransmitter metabolism, impairing neuronal health, and altering brain activity in mood-relevant brain regions [37]. Vitamin D may have a positive influence on human mental health through its regulatory effects on systemic inflammation. A review article based on five large cross-sectional studies found significant inverse associations between 25(OH)D and inflammation markers in persons with low 25(OH)D concentrations and

in adults with high inflammation levels [38]. Another review noted that vitamin D supplementation can robustly reduce TNF-α and IL-6, but not other cytokines, yet TNF-α and IL-6 were the two cytokines most robustly associated with depression in a meta-analysis [39]. Similarly, stress and hostility have also been positively correlated with TNF-α and IL-6 [40,41].

Oxidative stress has been linked to both depression and anxiety. Oxidative stress is increased in depressive subjects [42,43] and has been shown to increase anxiety in animal behavioral models [44]. Indeed, it has been proposed that products of oxidative stress have potential to serve as parameters for measuring and predicting of depression status as well as for determining the effectiveness of administrated antidepressants [45]. Vitamin D supplementation is also related to reduced oxidative stress markers in several human studies [46]. Vitamin D treatment is able to reduce the apoptosis-related gene expression, prevent the loss of mitochondrial potential and the consequent cytochrome C release and caspase activation [47].

In the current study, inverse associations between serum 25(OH)D concentration and psychological and psychosocial measures were significant only among females when sex-stratified analyses were conducted. Several other studies observed similar findings [12]. For example, Toffanello ED *et al.* found that serum 25(OH)D concentration correlated inversely with the Geriatric Depression Scale only among women [12]. Mieun Gwon *et al*. found that serum 25(OH)D concentration was significantly associated with less perceived stress among Korean female older adults, while this association was not significant among male participants [18].

In addition to sex differences, we also observed differences by race in the associations between mental health and serum 25(OH)D concentrations. Lower levels of 25(OH)D were associated with increased depression, anxiety and stress among white participants, but were more associated with hostility measures among blacks. These differences suggest possible differences

by race in burden or distribution of different mental health or symptom variables. Nevertheless, measurement-related factors (e.g., differential item functioning, or item bias, on scales by race) cannot be excluded. Historically, reporting of depression may have been stigmatized among blacks [48,49]; thus, seen in this context, experiences of hostility or hostile attribution might be considered more sensitive indicators of problems in the mental health domain. However, while older literature [49] has suggested this possibility, more recent work has shown that, in fact, higher burden of depressive symptoms may be present among black compared to white adults – especially among older adults [50]. Therefore, it is clear overall that further research is required to address racial differences and disparities in mood outcomes, and predictors therein.

To the best of our knowledge, this study is the first to analyze the association between serum 25(OH)D concentration and measures of hostility. First, the study included a range of psychological and psychosocial measures that were specific for their respective domains; this is in contrast, for example, with prior studies that may have relied on capturing anxiety using subscales of depression in questionnaires [9,10,14,16], or measuring perceived stress with one question [18]. Second, this study focused on young adults, which is the age group at highest risk for new onset of mental disorders. Thus, identifying modifiable predictors of adverse psychological and psychosocial status has direct relevance to public health. Limitations of this study should also be noted. First, this observational study cannot establish a causal relationship between serum 25(OH)D concentration and mental health. Second, we cannot exclude possible confounding by unmeasured factors (e.g., smoking, physical activity) that may be related to vitamin D and/or mood status. It is hoped that results from long-term randomized trials with experimental control of vitamin D levels using supplementation can shed more light on causal associations of 25(OH)D with mental health.

5. Conclusion

We observed consistent relationships between lower serum 25(OH)D concentrations and various measures of psychosocial stress and poorer mental health in a large sample of community-based young adults. Future work might address whether vitamin D supplementation and optimization of 25(OH)D levels could be potential modalities for prevention and/or amelioration of psychological distress in young persons.

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Declarations of interest

None

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