

Serum 25-hydroxyvitamin D predicts cognitive performance in adults

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Background: Vitamin D is an endogenous hormone known to regulate calcium levels in the body and plays a role in cognitive performance. Studies have shown an association between vitamin D deficiency and cognitive impairment in older adults. Lebanon has a high 25-hydroxyvitamin D (25(OH)D) deficiency prevalence across all age groups.

Methods: In this cross-sectional study, we explored the cognitive performance and serum 25(OH)D levels using an electrochemoluminescent immunoassay in 254 older (>60 years) as well as younger (30–60 years) adults. Subjects' characteristics, including age, years of education, wearing of veil, alcohol consumption, smoking, and physical exercise, were collected. Participants were screened for depression prior to cognitive screening using the Montreal Cognitive Assessment Arabic version. Visuospatial memory was tested using the Rey Complex Figure Test and Recognition Trial, and speed of processing was assessed using the Symbol Digit Modalities test.

Results: Pearson's correlation and stepwise linear regression analyses showed that a low vitamin D level was associated with greater risk of cognitive impairment in older as well as younger adults.

Conclusion: These findings suggest that correction of vitamin D needs to be explored as an intervention to prevent cognitive impairment. Prospective longitudinal studies are needed to ascertain the effect of such interventions.

Keywords: cognitive function, aging, neuro-psychological function

Introduction

Vitamin D is an endogenous hormone that regulates calcium levels in the body and maintains bone mineral density and muscle mass and function.^{1,2} Vitamin D is metabolized by the action of the ultra violet (UV) sun rays, liver, and kidney, from its inactive cholecalciferol form into the steroid and active forms 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D. Human vitamin D levels are most commonly measured by 25(OH)D serum concentration. Vitamin D receptors are present in the brain, neurons, and glial cells, indicating additional functions. These brain receptors are present in both humans and animals, and play a role in cognitive function.^{3,4}

Older adults with higher serum vitamin D have shown better cognitive performance compared with those with lower vitamin D levels. Similarly, vitamin D deficiency in older adults with or without mild Alzheimer's disease has been correlated with decreased cognitive performance.^{5,6} In more recent studies, older adults with low vitamin D level showed more cognitive impairment than did those with sufficient levels.⁷ The majority of studies that showed association between vitamin D deficiency and cognitive impairment have been conducted on older adults, although a few studies have targeted younger adults.^{8–11} In this study, we examine the role of vitamin D on cognitive function in adults aged 30–60 and >60 years of age.

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Vitamin D deficiency or insufficiency is prevalent in most countries; it is now considered a pandemic.¹² Despite being a sunny country, Lebanon has a high prevalence of 25(OH)D deficiency in adults and older adults: 55% of older women and 25% of older men have deficient vitamin D levels.¹

In this study, we hypothesized that cognitive impairment will be associated with low vitamin D levels in older (>60 years) as well as younger adults (30–60 years).

Methods

This was a cross-sectional study of 254 adults (30 and above years) recruited from the American University of Beirut-Medical Center (AUBMC) outpatient clinics, and elderly nursing homes in the greater Beirut and outside Beirut region over a 2-year period (2010–2012). Only 22 of 97 older adults were recruited from the nursing homes – the majority were recruited from the community.

Subjects with history of neurological disorders, traumatic brain injury, psychiatric disorders, cognitive impairment, and history of alcohol and/or drug abuse/dependence were excluded from the study. Men who consumed more than 15 drinks/week and women who consumed more than eight drinks/week were considered excessive alcohol consumers¹³ and were excluded from the study. Individuals who, during the 3 months prior to screening, were on antidepressants, mood stabilizers, or medications known to affect cognitive performance were excluded as well.

Prior to testing, informed consent was secured from all the participants. Then, health, anxiety, and depression screening questionnaires were administered to further screen for eligibility, followed by cognitive tests. The same psychologist administered the tests, and then a 5 mL blood sample was collected to test for serum 25(OH)D. This study received ethics approval from the Institutional Review Board of the American University of Beirut.

The Brief Risk Factor Surveillance System (BRFSS)¹⁴ is a screening questionnaire that inquires about the participant's current health status, medical history, physical activity (weekly frequency, type, and duration of activity), smoking habits (current and previous smoking habits), age, years of education, and alcohol consumption (weekly and monthly). Age, smoking, and excessive alcohol consumption have been associated with impaired cognitive performance.¹⁵ However, increased years of education and physical activity have been positively correlated with cognitive performance.^{16,17}

The Hopkins Symptoms Checklist-25 (HSCL-25)-Arabic was administered to screen for anxiety and depression that may affect cognitive performance negatively.¹⁸ This is a

25-item tool that has been translated into Arabic and is widely used due to its brevity, reliability, and validity.^{19–22}

The Montreal Cognitive Assessment (MoCA) is designed to screen for cognitive impairment in adults. It requires approximately 10 minutes to administer. The MoCA-Arabic version has demonstrated 92.3% sensitivity and 85.7% specificity for detecting mild cognitive impairment in older adults in Egypt.²³ In our sample, the test showed high internal consistency ($\alpha=0.83$) and excellent test–retest reliability ($\alpha=0.92$) in a subsample of healthy adults ($n=100$).

The Rey Complex Figure Test and Recognition Trial (RCFT) measures visual spatial memory and is extensively used in neuropsychological testing^{24,25} on adults. The 45-minute administration requires the participant to copy a complex shape (time to copy is measured) and immediately redraw it after 3 minutes (immediate recall [IR]), and 30 minutes from copying (delayed recall [DR]). Lastly, the participant is required to recognize parts of the initial figure from 20 shapes (recognition). The brief instructions were translated to Arabic, reviewed by the first two authors, and piloted on ten participants. This test does not require translation. An RCFT subsample ($n=50$) was rescored by the first two authors, and a 0.90 interrater reliability was found.

The Symbol Digit Modalities Test (SDMT) is a speed of processing test. It requires 10 minutes from administration to scoring.²⁶ The SDMT requires minimal instructions, which were delivered in Arabic after being translated and reviewed by the first two authors.

Serum 25(OH)D was measured in the Endocrinology Department core laboratory at AUBMC, using a protein-binding assay (DiaSorin RIA; DiaSorin, Saluggia, Italy), with intra- and interassay variation coefficients less than 13% at a serum concentration of 47 ng/mL.²⁷ The study laboratory is a participant in the international Vitamin D External Quality Assessment Scheme (DEQAS). This assay measures both 25-OHD2 and 25-OHD3. The intra-assay coefficient of variance is $5\%\pm 9\%$, based on 124 specimens run as separate samples in the assay, with a mean 25-OHD level of 19 ± 5 ng/mL. Blood for the studies was stored as serum at -20°C in the Endocrinology Department core laboratory, and samples from each subject were assayed in duplicate.

The predictor variables – 25(OH)D, sex, age, years of education, physical activity, sun exposure, use of vitamin supplements, smoking, and alcohol consumption – were analyzed using descriptive measures. Independent sample *t*-tests and Pearson's *r* correlations were performed between the predictor and outcome variables, MoCA, RCFT, and SDMT. A stepwise linear regression analysis was conducted

to examine the relationship between predictor variables and the outcome variables.

Results

A total of 380 subjects were screened for eligibility; of these, 90 subjects were excluded before being enrolled for not meeting eligibility criteria or not showing up for an appointment. Of the 290 enrolled subjects, 19 were excluded after further screening because they did not meet eligibility criteria or had motor or sensory impairment. In addition, ten participants were found to have more than a moderate level of anxiety and depression (greater than 3.2 and 3.3 respectively) and were referred to the AUBMC Psychiatry Department for management, while seven refused to continue because they found the tests to be too time-consuming and chose to withdraw from the study.

Of the 254, 61.8% were adults aged 30–60 years old (with mean \pm standard deviation of 44.31 ± 8.72 years) and 38.2% were older than 60 years old (71.26 ± 0.77 years). Their mean HSCL-25 anxiety and depression scores were 1.49 ± 0.40 and 1.80 ± 0.52 respectively. The majority were female (68.9%), among whom 83.1% did not wear a veil. The majority (67%) had received 12 or more years of education (Figure 1). Approximately 26% were smoking at the time of the study, and 40% were ever smokers, while 26.7% drank a moderate amount of alcohol. The majority (76.4%) had low 25(OH)D <30 ng/mL (25.50 ± 12.67 ng/dL). The mean 25(OH)D level in veiled women ($n=41$) was lower than that in the rest ($n=134$) of the sample (16.02 ± 7.73 ng/dL vs 27.11 ± 14.15 ng/dL) ($P < 0.0001$). The difference in 25(OH)D level between males and females was not statistically significant (21.25 ± 9.59 ng/dL vs 24.51 ± 13.75 ng/dL, respectively) ($P = 0.057$) (Table 1).

A total of 75 older adults came from their homes to the AUBMC or Ain Wa Zein Hospital for testing and returned to their homes. Only 22 were residents of a nursing home. The research team, including the geriatrician coauthor on this study, screened the 22 nursing home residents carefully. The characteristics of the 22 older adults were compared with

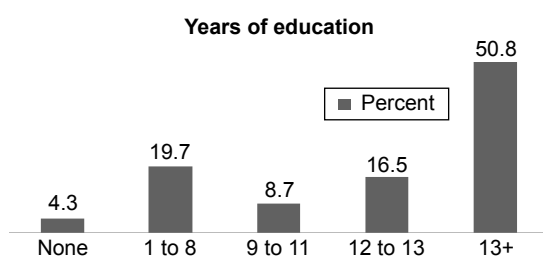


Figure 1 Sample characteristics: years of education.

Table 1 Sample characteristics

	Frequency (N=254)	Percent
Age, years		
<60	157	61.8
60+	97	38.2
25(OH)D ng/mL		
<30	194	76.4
≥ 30	60	23.6
Sex		
Male	79	31.1
Female	175	68.9
Veiled		
No	211	83.1
Yes	43	16.9
MoCA total		
<26	132	51.6
≥ 26	122	48.4
RCFT immediate recall		
≤ 5 th percentile	87	34.3
> 5 th percentile	160	63.0
RCFT delayed recall		
≤ 5 th percentile	102	40.2
> 5 th percentile	144	56.7
RCFT recognition		
≤ 5 th percentile	91	35.8
> 5 th percentile	154	60.6
SDMT (n=133)		
Normal	54	40.6
Low	21	15.8
Moderately low	20	15.0
Very low	38	28.6
Ever smokers	102	40.0
Current smokers: cigarettes	65	25.5
Quantity		
Less 1 pack/day	52	20.4
1–2 packs/day	11	4.3
2+ packs/day	2	1.0
Current smokers: water pipe	61	24.01
Frequency		
Everyday	10	3.9
2–3 times per week	6	2.4
Once a week	11	4.3
Once a month	9	3.5
Occasionally	25	9.8
Physical exercise	130	51
Frequency		
Once a day	59	23.1
Every 2 days	9	3.5
2–3 times per week	40	15.7
Once per week	13	5.1
Once per month	9	3.5
Duration		
10 min	18	7.1
20–30 min	27	10.6
Almost 1 hr	50	19.6
More than 1 hr	35	13.7
Alcohol	68	26.7
Frequency (drinks/month)		
1	15	5.9
2	29	11.4
3 to 60	27	9.4

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MoCA, Montreal Cognitive Assessment; RCFT, Rey Complex Figure and Recognition Trial Test; SDMT, Symbol Digit Modalities Test; min, minutes; hr, hour.

Table 2 Bivariate correlation matrix: cognitive tests scores

	MoCA	RCFT copy	RCFT immediate recall	RCFT delayed recall	SDMT
Pearson's correlations					
Age	-0.607**	-0.510**	-0.523**	-0.540**	-0.678**
MoCA		0.726**	0.603**	0.583**	0.731**
RCFT copy trial			0.652**	0.632**	0.658**
RCFT immediate recall				0.922**	0.654**
RCFT delayed recall					0.685**

Notes: **Correlation is significant at the 0.01 level (two-tailed). MoCA and RCFT: n=246. SDMT: n=133.

Abbreviations: MoCA, Montreal Cognitive Assessment; RCFT, Rey Complex Figure and Recognition Trial Test; SDMT, Symbol Digit Modalities Test.

those of the rest of the population, and there was no statistical difference in terms of sex, vitamin D level, or cognitive performance. The 25(OH)D of older adults in nursing homes did not differ from that in the community subjects (20.26 ± 6.83 ng/dL vs 23.46 ± 11.00 ng/dL, respectively) ($P=0.516$).

After removing outliers, 51.6% of the sample scored lower than the cutoff score of 26 for cognitive impairment on the MoCA, after adjusting for years of education. It was noted in the factor analysis that the verbal fluency test had extremely low scores. Therefore, we hypothesized that lower education contributed to lower verbal fluency ($X^2=23.854$, $df=1$, $P<0.0001$). After adjusting for verbal fluency scores, 40.3% scored lower than the cutoff score.

On the different RCFT subsections, 35% to 40% of the sample scored lower than the fifth percentile. Only 133 completed the SDMT; of those, 43.6% scored moderately low or very low after adjusting for age and years of education. There was no difference in cognitive performance between males and females on any of the tests. However, in the older adults subgroup, males performed better than females on the MoCA (23.06 ± 4.22 vs 18.89 ± 5.83 , respectively) ($P=0.01$) and the RCFT-IR (11.23 ± 4.22 vs 8.53 ± 5.46 , respectively) ($P=0.029$). Of those who scored low on the MoCA, 22% were males and 59.7% females.

As a whole, the mean years of education did not differ based on sex; however, it was significantly higher in elderly males than in females ($P=0.002$). Older adults scored lower than did young adults on the MoCA (20.23 ± 5.7 vs 26.04 ± 3.23 , respectively) ($P<0.0001$), on the RCFT-IR (9.43 ± 5.56 vs 15.47 ± 6.31 , respectively) ($P<0.0001$), on

the RCFT-DR (9.01 ± 5.62 vs 15.47 ± 6.54 , respectively) ($P<0.0001$), and on the SDMT (29.92 ± 13.37 vs 49.68 ± 13.99 , respectively) ($P<0.0001$). The cognitive performance of the older adults in nursing homes was not different than those in the community.

To ensure that the participants' performance was consistent, Pearson's bivariate correlation was performed. The results showed that the different measures correlated sufficiently high to indicate that they did not measure the same cognitive domains, but they were not repetitive (Table 2).

The bivariate correlations between age, years of education, physical activity, and alcohol, known confounding variables of cognitive performance,^{16,17,28} and the cognitive tests scores were examined. The Pearson's r correlation was statistically significant and negative between age and the different cognitive tests scores ($r=-0.435$, $P<0.01$). Years of education correlated with better performance on all cognitive tests; MoCA, RCFT (IR, DR, and copy), and SDMT ($r>0.5$, $P<0.01$), and physical activity was associated with better cognitive performance on the MoCA, and RCFT-IR and -DR.

Overall, 25(OH)D level correlated positively with the RCFT-IR and -DR ($r=0.179$ and $r=0.183$, respectively; $P<0.01$). But in the older adults sample, 25(OH)D level showed a positive and statistically significant correlation with the SDMT as well as the RCFT-IR and -DR ($r=0.337$, $r=0.240$, and $r=0.260$, respectively; $P<0.01$) (Table 3). As expected, age, years of education, and alcohol were positive predictors of the MoCA, RCFT, and SDMT. Interestingly, 25(OH)D predicted

Table 3 Bivariate correlation: 25-hydroxyvitamin D and cognitive tests scores

25(OH)D levels		Age	MoCA	RCFT copy	RCFT immediate recall	RCFT delayed recall	RCFT recognition	SDMT
Total sample								
25(OH)D	Pearson correlation	-0.065	0.115	0.167**	0.179**	0.183**	0.049	0.082
Older adults (>60 years) sample								
25(OH)D	Pearson correlation	-0.115	0.150	0.297**	0.240*	0.260*	0.036	0.337**

Notes: *Correlation is significant at the 0.05 level (two-tailed). **Correlation is significant at the 0.01 level (two-tailed).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MoCA, Montreal Cognitive Assessment; RCFT, Rey Complex Figure and Recognition Trial Test; SDMT, Symbol Digit Modalities Test.

Table 4 Predictors of cognitive performance

	Beta	95% Confidence interval	Adjusted R ²	
Dependent variable: MoCA				
Step 5				
Age	−0.366**	(−0.013, −0.007)	0.424	
Education				
Illiterate	−0.24**	(−0.731, −0.281)		
1–8 years	−0.33**	(−0.489, −0.247)		
9–11 years	−0.06	(−0.254, 0.067)		
12–13 years	0.02	(−0.094, 0.145)		
More than 13 years	1			
Alcohol	0.10*	(0.003, 0.197)		
Physical exercise	0.07	(−0.025, 0.144)		
25(OH)D	−0.00	(−0.003, 0.003)		
Dependent variable: RCFT immediate recall				
Step 5				
Age	−0.39**	(−0.222, −0.128)	0.406	
Education				
Illiterate	−0.25**	(−12.64, −5.16)		
1–8 years	−0.25**	(−6.22, −2.38)		
9–11 years	−0.08	(−4.524, 0.524)		
12–13 years	0.08	(−0.337, 3.372)		
More than 13 years	1			
Alcohol	0.02	(−1.187, 1.826)		
Physical exercise	0.041	(−0.796, 1.890)		
25(OH)D	0.103*	(0.002, 0.106)		
Dependent variable: RCFT delayed recall				
Step 5				
Age	−0.416**	(−0.238, −0.142)	0.427	
Education				
Illiterate	−0.235**	(−12.483, −4.876)		
1–8 years	−0.258**	(−6.552, −2.647)		
9–11 years	−0.064	(−4.248, 0.992)		
12–13 years	0.041	(−1.140, 2.636)		
More than 13 years	1			
Alcohol	0.115*	(0.247, 3.314)		
Physical exercise	0.011	(−1.214, 1.524)		
25(OH)D	0.094	(−0.002, 0.104)		
Dependent variable: SDMT				
Step 6				
Age	−0.575**	(−0.777, −0.524)	0.672	
Education				
Illiterate	−0.245**	(−47.852, −19.898)		
1–8 years	−0.351**	(−18.183, −8.838)		
9–11 years	−0.190**	(−16.601, −4.217)		
12–13 years	−0.047	(−6.809, 2.687)		
More than 13 years	1			
Alcohol	0.155**	(1.916, 10.175)		
Physical exercise	0.004	(−3.583, 3.839)		
25(OH)D	0.125**	(0.040, 0.394)		

Notes: * $P < 0.05$. ** $P < 0.01$.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MoCA, Montreal Cognitive Assessment; RCFT, Rey Complex Figure and Recognition Trial Test; SDMT, Symbol Digit Modalities Test.

RCFT-IR and the SDMT but not the MoCA, after controlling for age and years of education and alcohol (Table 4).

There was a significant relationship between years of education and 25(OH)D levels; those with ≥ 12 years of education had significantly higher 25(OH)D levels than did those with < 12 years of education (25.04 ± 13.62 ng/dL vs 20.32 ± 9.8 ng/dL, $P < 0.005$; respectively) ($r = 0.175$ $P = 0.005$). We attributed this difference to the intake of vitamin D

supplements, since the correlation disappeared after removing subjects taking supplements from the analysis (Table 4).

Discussion

In this study, we explored the relationship of 25(OH)D levels and cognitive performance in younger and older adults. Our data showed a high prevalence of 25(OH)D deficiency that was significantly associated with poor cognitive

performance in younger and older adults. Interestingly, we found that a moderate amount of alcohol consumption was associated with better cognitive performance.

The positive association between low 25(OH)D and cognitive impairment has been previously reported.^{11,29–32} In this study, we found that this association was significant in younger adults as early as 30 years of age. This observation suggests that early correction of vitamin D levels may control one of the factors associated with cognitive impairment and delay the onset of age-related cognitive impairment. Longitudinal studies examining the effect of early vitamin D supplementation on cognitive performance over time is therefore needed.

The high prevalence of hypovitaminosis D found in this study is in line with previous results.³³ Genetic and environmental factors could be behind this widespread low vitamin D in this population.³⁴ The significant association between age, years of education, and cognitive performance is well known.³⁵ When controlling for age and years of education, 25(OH)D was a significant predictor of cognitive performance, in line with the previous studies in older adults.³⁶

In this study, we could not demonstrate a correlation between 25(OH)D and the MoCA scores in either the whole group or the older adult subgroup. Moreover, 25(OH)D did not predict the MoCA score after controlling for age and education, and adjusting for verbal fluency. Given that the other cognitive tests coherently showed a correlation between 25(OH)D and cognitive performance, this suggests that the cutoffs and items of the MoCA are not appropriate for the population being tested. The MoCA scores may not account for education. The majority, across all age groups, were unable to complete the verbal fluency section. It is possible that the letter “f” used in the verbal fluency section of the MoCA-Arabic in Lebanon is not representative of verbal fluency due to low frequency of words in Lebanese spoken dialect. The MoCA has many verbal sections, therefore requires cultural adaptability, which is not the case for the SDMT and the RCFT. It may be too broad as a measure of cognitive performance compared with the RCFT that targets one cognitive function, namely visuospatial memory. In this study, we showed that the SDMT is a sensitive screening measure of cognitive performance, and the RCFT a good measure for in-depth evaluation.

The main advantage of using the RCFT and SDMT is that neither requires translation. However, these tests have not been used before in Lebanon or in other Arab countries, therefore, we lack the normative values of this population. Nonetheless, the visuospatial performance and speed of processing of older adults by age group is in line with previous studies of the same age and similar years of education.^{37,38}

Wearing the veil has been suggested as a cause of low vitamin D in women in Middle-Eastern countries. In this study, although the majority of women did not wear the veil, the vitamin D level was lower in women who wore the veil than in men and women who did not wear a veil, in line with findings of previous study.³⁹

In our sample, the ratio of women to men was higher among older and younger adults – this may suggest that women are more likely to volunteer in research studies.

Our data revealed an association with alcohol intake; moderate alcohol intake was a positive predictor of cognitive performance. Recent studies have shown that moderate alcohol consumption is associated with smaller decline in cognitive impairment.^{28,40} Only 26.7% of our sample consumed any alcohol. Nonetheless, the positive alcohol consumption effect could be demonstrated. This association between alcohol and cognitive performance needs to be explored further in a larger sample.

In summary, this study showed that a low vitamin D level is associated with greater risk of cognitive impairment in older as well as younger adults. Moderate alcohol consumption improved cognitive performance. These findings suggest that there are areas of possible intervention to prevent cognitive impairment. Prospective longitudinal studies are needed to ascertain the effect of such interventions.

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Disclosure

The authors report no conflicts of interest in this work.

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