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The association between serum vitamin d level and cognitive function in older adults: Cooper Center Longitudinal Study

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ABSTRACT

Low blood level of vitamin D and low physical activity have been linked to the development of cognitive impairment in older adults. The purpose of the present study was to examine the relationship between serum vitamin D and cognition as measured via the Montreal Cognitive Assessment (MoCA) in a healthy, older population. The study sample consisted of 4358 patients from the Cooper Clinic in Dallas, TX. All participants underwent a maximal graded exercise test to determine cardiorespiratory fitness (CRF). Cognitive impairment was defined as a MoCA score < 25. Low vitamin D status was defined as serum 25-hydroxyvitamin D < 30 ng/mL. Multivariable logistic regression analysis was employed to evaluate the association between vitamin D blood level and MoCA score. A low MoCA score was directly associated with higher age (OR: 1.75, 95% CI: 1.53, 1.99), and inversely associated with female sex (OR: 0.63, 95% CI: 0.51, 0.77), and years of education (OR: 0.87, 95% CI: 0.84, 0.91). When controlling for significant predictors (age, sex, and education), the low vitamin D group had a significantly greater likelihood of having a low MoCA score (OR: 1.26, 95% CI: 1.04, 1.51). The vitamin D effect remained significant when CRF was added to the model (OR: 1.23, 95% CI: 1.02, 1.48). In conclusion, low vitamin D was shown to be associated with cognitive impairment. Therefore, preventive measures such as vitamin D supplementation may play a protective role in memory loss and/or age-associated cognitive decline.

1. Introduction

As mean life expectancy continues to rise (78.8 yr) in the United States (Statistics, 2016), there is an increasing need to identify modifiable risk factors that contribute to cognitive and physical deterioration associated with aging. Over the past decade, Vitamin D has gained much attention as numerous studies suggest its benefits expand far beyond bone health (Holick, 2007). Vitamin D status is best measured by serum 25-hydroxyvitamin D (serum vitamin D) levels. Though vitamin D deficiency (< 20 ng/mL) and insufficiency (21–29 ng/mL) is preventable, this condition affects more than a billion people worldwide (Holick, 2007). Significant evidence supports an impact of serum vitamin D on both the central and peripheral nervous systems (Mpandzou et al., 2016). Previous studies have shown an association between vitamin D deficiency/insufficiency and decreased cognitive function (Annweiler et al., 2010; Gschwind et al., 2014; Littlejohns et al., 2014; Llewellyn et al., 2011; Miller et al., 2015; Seamans et al., 2010; van Schoor et al., 2016; Wilkins et al., 2006; Wilson et al., 2014).

Additionally, several studies have shown that CRF is related to both serum vitamin D (Ardestani et al., 2011; Ellis et al., 2014; Farrell et al., 2011; Farrell and Willis, 2012) and cognitive function (Hayes et al., 2016; Pontifex et al., 2014). For example, in a previous Cooper Center Longitudinal Study (CCLS) analysis, vitamin D levels were positively associated with CRF in both men (Farrell et al., 2011) and women (Farrell and Willis, 2012).

Given the availability of serum vitamin D levels and measures of CRF in CCLS subjects, we analyzed the relationship between serum vitamin D and cognition, as measured by Montreal Cognitive Assessment (MoCA) scores. We hypothesized that in otherwise healthy older adults, low serum vitamin D concentration would be associated with lower MoCA scores (i.e. cognitive impairment) and that this relationship would be attenuated by CRF.

2. Methods

2.1. Sample

Patients from the Cooper Clinic in Dallas, Texas who gave consent

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Table 1
Descriptive characteristics based on serum vitamin D level within the Cooper Center Longitudinal Study population (Cooper Clinic, Dallas, TX).

Variable	All	Vitamin D < 30 ng/mL	Vitamin D ≥ 30 ng/mL	p-Value
Participants, n	4358	1434	2924	–
Age (SD), y	60.8 (5.9)	60.2 (5.3)	61.1 (6.2)	0.003
Female, n (%)	1193 (27.4)	341 (23.8)	852 (29.1)	< 0.001
Caucasian, n (%)	4061 (93.2)	1305 (91.0)	2756 (94.3)	< 0.001
Education (SD), y	16.4 (2.3)	16.3 (2.4)	16.4 (2.3)	0.046
History of MI, n (%)	28 (0.6)	10 (0.7)	18 (0.6)	0.840
History of stroke, n (%)	34 (0.8)	9 (0.6)	25 (0.9)	0.470
Current smoker, n (%)	274 (6.3)	125 (8.7)	149 (5.1)	< 0.001
Examined April–October, n (%)	2650 (60.8)	798 (55.6)	1852 (63.3)	< 0.001
Examined November–March, n (%)	1708 (39.2)	636 (44.4)	1072 (36.7)	< 0.001
Mean body mass index (SD), kg/m^2	27.0 (4.2)	28.3 (4.6)	26.4 (3.9)	< 0.001
Mean resting systolic blood pressure (SD), mm Hg	122.2 (13.6)	123.0 (13.5)	121.8 (13.6)	0.003
Mean total cholesterol (SD), mg/dL	187.8 (38.8)	197.0 (39.8)	183.4 (37.5)	< 0.001
Mean glucose level (SD), mg/dL	97.6 (15.0)	100.6 (19.8)	96.1 (11.7)	< 0.001
Mean thyroid-stimulating hormone (SD), uIU/mL	2.4 (1.7)	2.4 (1.6)	2.4 (1.8)	0.644
Mean serum vitamin D (SD), ng/mL	36.2 (13.7)	22.9 (5.0)	42.7 (11.8)	–
Mean cardiorespiratory fitness level (SD), MET	10.1 (2.1)	9.7 (2.1)	10.3 (2.1)	< 0.001
Mean MoCA score (SD)	26.9 (2.2)	26.9 (2.4)	27.0 (2.2)	0.456
MoCA ≥ 25, n (%)	3757 (86.2)	1212 (84.5)	2545 (87.0)	–
MoCA < 25, n (%)	601 (13.8)	222 (15.5)	379 (13.0)	0.025

Abbreviations: standard deviation (SD), myocardial infarction (MI), metabolic equivalent (MET), Montreal Cognitive Assessment (MoCA).

for their information to be entered in the CCLS, a database maintained by The Cooper Institute, were included in this study sample. The Cooper Institute's Institutional Review Board reviewed the overall study annually. The Cooper Clinic is a fee-for-service preventive medicine facility whose patients are typically well-educated, non-Hispanic whites (95%), and who have access to a preventive care exam through their employer or by self-referral.

The records of 6691 patients seen at the clinic from April 2009 to November 2016 were assessed. All participants completed a baseline examination including serum vitamin D level, CRF, and MoCA score. Excluded participants included those who were younger than 55 years (n = 1963), had missing variables of interest (n = 336), or had a body mass index (BMI) < 18.5 kg/m^2 (n = 34). The resulting study sample included 4358 patients (n = 1193 women, n = 3165 men).

2.2. Assessments and outcomes

Patients evaluated in this study completed an extensive self-reported medical history and underwent a physical examination. This examination included measurement of weight and height using a standard clinical scale and stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared. . Seated resting blood pressure was measured with a calibrated sphygmomanometer according to standard clinical procedures. Additionally, the blood chemistries were performed at the Cooper Clinic laboratory using standard automated techniques to determine cholesterol, glucose, thyroid stimulating hormone, and vitamin D levels.

2.2.1. Vitamin D

The Cooper Clinic uses serum 25-hydroxyvitamin D (25(OH)D) concentration as the measure of vitamin D status for its patients. As determined by a DiaSorin Liasion Chemiluminescence Analyzer, with test-retest coefficient of variation of 11%, serum vitamin D levels lower than 30 ng/mL were considered were considered “low vitamin D” level.

2.2.2. Cardiorespiratory fitness (CRF)

CRF was quantified as the duration of a maximal treadmill exercise test using a modified-Balke protocol as described elsewhere (Willis et al., 2011). There is a high correlation between exercise duration from this protocol and directly measured maximal oxygen uptake in men (r = 0.92) and women (r = 0.94) (Pollock et al., 1976; Pollock et al., 1972). To standardize exercise test performance, maximal MET (metabolic equivalents, 1 MET = 3.5 mL O_2 uptake/kg/min) levels of CRF were estimated based on the final treadmill speed and degree of elevation (Medicine, 2017).

2.2.3. Cognitive function

Cognitive function was assessed using the MoCA (Nasreddine et al., 2005), a brief assessment of eight cognitive domains with an emphasis on memory and executive function that is designed to detect mild levels of cognitive impairment. The MoCA was initially normed in a population similar to the CCLS (Smith et al., 2007). Routine screening with MoCA is performed at the Cooper Clinic among individuals over age 55 years and is repeated every 5 years until age 65 years, after which it is repeated every 3 years. MoCA scores range from 0 to 30 with a score of < 26 defined as possible mild cognitive impairment (Nasreddine et al., 2005). Based on previous findings, a score < 26 might be too stringent for our highly educated sample (Rossetti et al., 2011) and therefore, a total score of < 25 points was chosen as the threshold to ensure presence of impaired cognitive function.

2.3. Statistical analyses

Descriptive characteristics of the study sample were determined by serum vitamin D group and for the total sample. Multivariable logistic regression analysis was employed to evaluate the association between serum 25(OH)D and MoCA score. Results are presented for MoCA score regressed against serum 25(OH)D group (1) adjusted for age (years), sex, and education (Model 1); (2) adjusted for all covariates in Model 1 plus body mass index (BMI) and CRF in METs (Model 2); and (3) all covariates in Model 2 plus resting systolic blood pressure, glucose, total cholesterol, smoking status, season, ethnicity and previous history of cardiovascular disease (CVD) (Model 3). The potential effect modification of vitamin D and CRF was tested with the inclusion of an interaction term in Model 2. Analyses were performed using SAS/STAT® version 9.4. All significance testing was 2-sided with a p-value of < 0.05 considered statistically significant.

3. Results

3.1. Sample description

Baseline characteristics by serum vitamin D group are presented in Table 1. On average, subjects in the low serum vitamin D group

Table 2
Odds of having cognitive impairment (MoCA score < 25) in participants with low vitamin D levels (< 30 ng/mL) versus normal vitamin D levels (≥ 30 ng/mL) within the Cooper Center Longitudinal Study population (Cooper Clinic, Dallas, TX).

	Model 1[a]		Model 2[b]		Model 3[c]	
	n = 4358		n = 4358		n = 4247	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Age (years)	1.75	1.53–1.99	1.61	1.38–1.87	1.54	1.30–1.82
Sex (female)	0.63	0.51–0.77	0.53	0.41–0.69	0.55	0.42–0.73
Education (years)	0.87	0.84–0.91	0.88	0.84–0.91	0.88	0.84–0.91
Serum vitamin D (ng/mL)	1.26	1.04–1.51	1.23	1.02–1.48	1.24	1.01–1.51
CRF (METs)	–	–	0.94	0.89–0.99	0.94	0.89–0.99

[a] Model 1 adjusted for age, sex, and education.
[b] Model 2 adjusted for all covariates in Model 1 plus body mass index (BMI) and cardiorespiratory fitness (CRF) in metabolic equivalents (METs).
[c] Model 3 adjusted for all covariates in Model 2 plus resting systolic blood pressure, glucose, total cholesterol, smoking status, season, ethnicity and previous history of cardiovascular disease (CVD). 111 observations missing in Model 3 due to incomplete ethnicity information.

(< 30 ng/mL) had lower CRF and higher BMI values, along with higher blood levels of total cholesterol and fasting glucose when compared to the normal serum vitamin D group ($p < 0.001$). Although the mean MoCA score was similar between the groups, a larger percentage of individuals with a low MoCA score was observed among those with a low vitamin D level (15.5%) than among those with a normal vitamin D level (13.0), $p < 0.03$.

3.2. Vitamin D, CRF, and MoCA

In Table 2, we show that a low MoCA score was directly associated with higher age (OR: 1.75, 95% CI: 1.53, 1.99), and inversely associated with female sex (OR: 0.63, 95% CI: 0.57, 0.77), and years of education (OR: 0.87, 95% CI: 0.84, 0.91).The low serum vitamin D group had a significantly greater likelihood of having cognitive impairment (OR: 1.26, 95% CI: 1.04, 1.51) when adjusted for age, sex, and education as compared to the normal serum vitamin D group. When CRF was added to the model, the relationship between low serum vitamin D and low MoCA score remained significant (OR: 1.23, 95% CI: 1.02, 1.48). CRF was significantly associated with reduced odds of a low MoCA score (OR: 0.94, 95% CI: 0.89, 0.99). In other words, for every 1 MET (3.5 mL/kg/min) increase in CRF, the likelihood of having a low MoCA score decreased by 6%. The inclusion of an interaction term in Model 2 was not significant ($p = 0.55$) and thus not included in the models. When fully adjusted for additional covariates that might affect cognition, including resting systolic blood pressure, glucose, total cholesterol, smoking status, season, ethnicity and previous history of cardiovascular disease, the association between vitamin D levels and low MoCA score remained significant (OR: 1.24, 95% CI: 1.01, 1.51, $p = 0.038$).

4. Discussion

In examining the relationship between serum vitamin D and cognitive function in healthy, older individuals, we observed a 26% increase in the likelihood of having a low MoCA score among those with a low serum vitamin D level. In addition, this association remained significant when CRF was added to the model. This study extends earlier findings by others as it examines the relationship between CRF on cognitive function in the setting of vitamin D deficiency.

While our study showed an association between serum vitamin D level and cognitive function, results from small clinical studies assessing this relationship have been somewhat inconsistent. Four population-based cross-sectional studies have examined the association between levels of serum 25(OH)D and cognitive function. In contrast with our findings, McGrath et al. (2007) found no association between serum vitamin D and a brief measure of verbal memory, executive function, processing speed, and sustained attention. However, Llewellyn et al. (2010) observed a significant association between low levels of 25(OH)D and increased odds of cognitive impairment as measured by the Mini-Mental State Examination. Similarly, Buell et al. (2009) observed a positive association between 25(OH)D levels and tests of executive function and processing speed, but not memory. Lastly, Lee et al. (2009) observed a significant positive association between serum vitamin D levels and a test of sustained attention. However, in this study, no significant associations were observed between 25(OH)D levels and memory or visuospatial ability. Taken together with these findings, our results suggest that low serum vitamin D level may be associated with cognitive dysfunction in a variety of domains.

Existing literature has shown that vitamin D has important effects on brain health. Vitamin D plays a neuroprotective role by regulation of calcium homeostasis (Brewer et al., 2001), attenuating accumulation of amyloid – β peptide (Masoumi et al., 2009), reversing age-related inflammatory changes in the hippocampus (Nissou et al., 2014) and having protective effects against neurodegenerative mechanisms associated with Alzheimer's disease (Annweiler et al., 2013). Furthermore, vitamin D deficiency has also been linked to brain changes such as decreased brain volume (Karakis et al., 2016), increased white matter abnormalities (Annweiler et al., 2015), decreased neuronal function in the cortex (Annweiler et al., 2014), and increased risk for ischemic stroke (Brondum-Jacobsen et al., 2013).

We also found that the association between vitamin D level and MoCA score was slightly abated by CRF, and for every 1 MET increase in CRF there was a 6% reduction in the likelihood of having a MoCA score < 25. These findings are not surprising as several studies have shown that CRF is related to both serum vitamin D (Ardestani et al., 2011; Ellis et al., 2014; Farrell et al., 2011; Farrell and Willis, 2012) and cognitive function (Hayes et al., 2016; Pontifex et al., 2014). Similar to our findings, Hayes et al. (2016) found that objectively measured CRF (VO_{2peak}) was positively associated with executive function and episodic memory in older adults. They concluded that increased CRF attenuated age-related cognitive decline. In younger adults, Pontifex et al. (2014) found that low CRF (VO_{2peak}) was associated with decreased implicit memory as well as decreased long-term memory retention.

Others have also shown that CRF has a positive association with serum vitamin D levels in both men (Farrell et al., 2011) and women (Ellis et al., 2014; Farrell and Willis, 2012). In a clinical study, Ardestani et al. (2011) found that serum 25-hydroxyvitamin D concentration was positively related to CRF (VO_{2max}), even after adjusting for relevant predictors such as age, sex, and BMI. They also analyzed the association of serum vitamin D on VO_{2max} by percentiles of self-reported moderate to vigorous physical activity (MVPA), and found that for every one standard deviation increase in serum vitamin D level (13 ng/mL), VO_{2max} increased by 2.6 mL/kg/min when MVPA was low, 1.6 mL/kg/min when MVPA was moderate, and only 0.01 mL/kg/min when MVPA was high. They concluded that serum vitamin D levels

associated with CRF in adults and that the impact was greatest for those with low levels of physical activity. Lastly, aside from our study, one other study has examined the association of physical fitness and serum vitamin D levels with cognitive function (Ahn and Kang, 2015). They found that serum vitamin D levels, agility (measured via the eight-foot-up-and-go) and CRF (measured via the 6-minute walk test) were positively associated with cognitive performance. Taking all of the mentioned findings together, it appears that inadequate levels of vitamin D and exercise might contribute to cognitive decline in elders.

The mechanisms by which fitness impacts cognitive function are unclear. However, some studies have found a positive relationship between CRF and brain volume (Colcombe et al., 2006; Erickson et al., 2009; Erickson et al., 2010). For example, Erickson et al. (2009) found that CRF, measured via a maximal graded exercise test, was positively associated with both left and right hippocampal volume after controlling for age, sex, and education. Similarly, in participants with early Alzheimer's disease, Burns et al. (2008) found that CRF (VO_{2peak}) was positively associated with whole brain volume and white matter volume. Furthermore, Colcombe et al. (2006) found that 6 months of aerobic exercise training significantly increased brain volume in both gray and white matter regions. They also examined the impact of a 6-month stretching/toning program on brain volume and found no significant increases in either gray or white brain matter with nonaerobic exercise (Colcombe et al., 2006). Within the Cardiovascular Health Cognition Study cohort, Erickson et al. (2010) demonstrated that greater levels of physical activity predicted greater volumes of frontal, occipital, entorhinal, and hippocampal regions nine years later. Further, they found that 72 blocks of walking per week was associated with changes in gray matter volume. However, no further benefit was observed in those walking substantially > 72 blocks. The observed increase in gray matter volume with increased physical activity reduced the risk of cognitive impairment by 2-fold (Erickson et al., 2010).

Strengths of this study include a large sample of generally healthy older persons, so it is unlikely that our results were affected by other, unmeasured co-morbidities. The cohort was also well phenotyped. Serum vitamin D level was measured directly and CRF was determined objectively. Additionally, the MoCA was specifically designed for an educated population such as the one used for this study (Bernstein et al., 2011). An additional strength of this study is the utilization of objectively estimated CRF versus self-reported physical activity. A key limitation of this study is the unique and homogeneous, highly-educated preventive medicine population; thus, these results might not be generalizable to the population at large. Another limitation of this study is the use of a MoCA score rather than extensive neuropsychiatric testing. Lastly, this is a cross-sectional study, meaning that we can only identify an association instead of defining causality between low vitamin D and MoCA score.

5. Conclusions

In conclusion, in this generally healthy community-based sample, a significant relationship was observed between serum vitamin D levels and cognitive function. This association remained significant with the inclusion of CRF. Further research should determine if vitamin D supplementation slows cognitive decline in elders with low serum vitamin D levels.

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