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Lifestyle and 25-hydroxy-vitamin D among community-dwelling old adults with dementia, mild cognitive impairment, or normal cognitive function

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Abstract

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Statement of human and animal rights The study was approved by the National Bioethics Committee in Iceland (approval VSN-00-063), the Data Protection Authority, and by the National Institute on Aging Intramural Institutional Review Board.

Informed consent Written informed consent was obtained from all participants.

Conflict of interest Authors declare that they have no conflict of interest.

Background—Several studies have indicated that older adults with cognitive impairment have a poorer lifestyle than their healthy peers including lower 25-hydroxy-vitamin D levels (25OHD).

Aim—To investigate the associations between lifestyle and 25OHD depending on cognitive status among old adults.

Methods—Community-dwelling old adults (65–96 years) participated in this cross-sectional study based on the Age-Gene/Environment-Susceptibility-Reykjavik-Study. The analytical sample included 5162 subjects who were stratified by cognitive status, i.e., dementia ($n = 307$), mild cognitive impairment (MCI, $n = 492$), and normal cognitive status (NCS, $n = 4363$). Lifestyle variables were assessed and 25OHD was measured. The associations between lifestyle and 25OHD were calculated using linear models correcting for potential confounders.

Results—According to linear regression models, 25OHD was significantly lower in older people with dementia (53.8 ± 19.6 nmol/L) than in NCS participants (57.6 ± 17.7 nmol/L). Cod liver oil (7.1 – 9.2 nmol/L, $P < 0.001$) and dietary supplements (4.4 – 11.5 nmol/L, $P < 0.001$) were associated with higher 25OHD in all three groups. However, physical activity ≥ 3 h/week (2.82 nmol/L, $P < 0.001$), BMI < 30 kg/m² (5.2 nmol/L, $P < 0.001$), non-smoking (4.8 nmol/L, $P < 0.001$), alcohol consumption (2.7 nmol/L, $P < 0.001$), and fatty fish consumption ≥ 3 x/week (2.6 nmol/L, $P < 0.001$) were related to higher 25OHD in NCS only, but not in participants with dementia or MCI.

Discussion—Older people living in Iceland with dementia are at higher risk for 25OHD deficiency when compared to healthy individuals. Physical activity reported among participants with dementia, and MCI is low and is not significantly associated with 25OHD.

Conclusions—Lifestyle factors among NCS participants are associated with 25OHD levels. Importantly, healthy lifestyle should be promoted among individuals with MCI and dementia.

Keywords

Cognitive impairment; Healthy aging; Vitamin D; Physical activity; Dementia

Introduction

Vitamin D affects bone health and low levels of 25-hydroxy-vitamin D (25OHD) have been associated with disorders such as osteoporosis and osteomalacia in old adults [1]. In recent years, studies have suggested associations between 25OHD and several health-related outcomes beyond bone health [2]. The presence of vitamin D receptors [3] in many body tissues supports the evidence linking vitamin D deficiency to increased disease risk, e.g., cardiovascular disease, type 2 diabetes, and more recently, to neurodegenerative diseases [4].

Longitudinal studies have suggested that a healthy lifestyle, e.g., high physical activity, appropriate dietary intake, and normal body mass index (BMI), is associated with sufficient vitamin D levels in the general population [5, 6]. Further, several studies have indicated that older adults with mild cognitive impairment or dementia have a poorer lifestyle than their healthy peers, i.e., they are less physically active [7–9] and have lower vitamin D intake [10–12]. Additionally, they do not always get the appropriate health service with respect to

dementia [13] and consequently, there is a reason to believe that these individuals are at an increased risk for vitamin D deficiency.

A recent longitudinal study with a 12-year follow-up time, showed a twofold risk for developing all cause dementia in a nondemented population, when participants were either deficient or insufficient in vitamin D. The same study reported, among participants with mild stage of dementia, almost a triple risk for a progression to a more severe stage of dementia if participants were deficient (< 25 nmol/L) in vitamin D as compared to sufficient levels [14]. Also, in a retrospective study, analyzing the impact of vitamin D treatment in the progression of Alzheimer's disease, results showed that the time of progression to a more severe stage, was slower among those treated with vitamin D [15].

Only few studies are available that have investigated vitamin D status among older adults with MCI or dementia and they indicate a higher prevalence of vitamin D deficiency compared to cognitively intact individuals [11, 16]. However, studies that examine the associations between lifestyle and vitamin D status in subjects with MCI or dementia are not available.

Given these considerations, we investigated 25OHD in different cognitive status groups among old adults from the Age Gene/Environment Susceptibility-Reykjavik Study (AGES-RS). The aims were to examine (1) vitamin D status among old adults with dementia, MCI and normal cognitive function, (2) whether participants with dementia and MCI have poorer lifestyle than cognitively intact individuals, (3) the associations between lifestyle and 25OHD in each cognitive status group using stratified, linear regression analysis.

Methods

Study population

The current cross-sectional analysis is based on data from the AGES-RS, which in general examined risk factors for diseases and disability in old age that includes environmental factors, genetic susceptibility, and their interactions. The AGES-RS is a continuation of the Reykjavik Study from the Icelandic Heart Associations (IHA). The Reykjavik Study was initiated in 1967 and included men and women born in the period 1907–1935 living in the Reykjavik area [17]. During 2002–2006, 5764 persons were chosen randomly from the survivors of the Reykjavik Study cohort and re-examined for the AGES-RS. Participants underwent a clinical examination, completed questionnaires, and completed a cognitive test battery. Details on the study design and the baseline AGES-RS assessments have been given elsewhere [18, 19]. In the current study, we used data from AGES-RS obtained between 2002 and 2006.

Mild cognitive impairment and dementia

Assessment of cognitive function was done following a three-step protocol to identify subjects with dementia or MCI. First, the Digit Symbol Substitution Test [20] and the Mini-Mental State Examination [21] were administered to the total sample. Participants who scored 23 or lower on the Mini-Mental State Examination or had a raw score of 17 or lower on the Digit Symbol Substitution Test were administered a second diagnostic

cognitive test battery. Participants who scored 8 or more on Trails B [22] that was the ratio of time taken for “Trails B/Trails A” (corrected for the number correct: $\frac{\{\text{time Trails B}/\text{number correct Trails B}\}}{\{\text{time Trails A}/\text{number correct Trails A}\}}$) or had lower than total score of 19 for the four immediate recall trials of the Rey Auditory Verbal Learning [23] went on to a third step. This step included a neurological examination and a proxy interview regarding medical history, social, cognitive, and daily functioning changes of the participant. Based on the three-step protocol, an assessment of dementia was made by a team composed of a geriatrician, neuroradiologist, neurologist, and neuropsychologist according to international guidelines from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [24].

The assessment for MCI was also made by the team, the criterion for having MCI was having degeneration in either memory or in one other cognitive domain, or having deficits in at least two cognitive domains without sufficiently severe cognitive function impairment or loss of activities of daily living to constitute dementia [25].

For the statistical analyses, participants were categorized into three groups: demented, MCI, and cognitively normal.

Serum 25-hydroxy-vitamin D measurement

The accredited laboratory from the Icelandic Heart Association conducted 25OHD measurements using the Liaison chemiluminescence immunoassay (DiaSorin Inc., Stillwater, Minnesota). The inter-assay coefficient of variation was < 6.5% when calculated data are from measurements using a frozen serum pool as the control sample and < 12.7% when calculated data is from measurements using liaison quality controls. Existing serum 25OHD levels were then standardized according to the international Vitamin D Standardization Program (VDSP) as previously described [19, 26]. For the analyses, standardized 25OHD were categorized into three groups based on Guidelines for Health Professionals from the National Institutes of Health (2014): deficient (< 30 nmol/L), insufficient (31–49 nmol/L), normal–high levels (≥ 50 nmol/L).

Covariates

The following covariates were assessed and used for statistical analysis: education (primary vs. at least secondary), BMI (both as kg/m^2 and categorical as underweight (< 20 kg/m^2), normal weight (20 to < 25 kg/m^2), overweight (25 to < 30 kg/m^2), and obese (≥ 30 kg/m^2), current smoking (yes vs. no), current alcohol consumption (yes vs. no), cod liver oil (daily vs. not daily), vitamin D supplements (yes vs. no), fatty fish consumption (< 3 vs. ≥ 3 times/week), leisure time physical activity (PA) (≤ 3 h vs. > 3 h), and medication (≤ 4 vs. > 4).

Type 2 diabetes mellitus (yes vs. no) was defined by a physician’s diagnosis of diabetes, use of diabetes medication and/or fasting blood glucose of > 7.0 mmol/L. Hypertension (yes vs. no) was defined by a physician’s diagnosis of hypertension, use of hypertension medications and/or blood pressure above 140/90 mm Hg.

Analytical sample

Of the total cohort ($N = 5764$), 5519 had measurement of 25OHD, and 5512 of those had data with complete assessment of cognitive status. Participants were categorized into three groups according to cognitive status. After excluding 350 participants with missing values on covariates, the number in each cognitive status group was 4363 (83.8%) with normal cognitive status, 492 (9.5%) with mild cognitive impairment and 307 (5.9%) with a dementia diagnosis after data cleansing. Therefore, the final analytical sample included 5162 participants.

Statistical analysis

Statistical analyses were carried out using IBM SPSS version 24.0 (SPSS, Chicago, IL, USA).

Baseline data

Differences in demographic and health characteristics among the three cognitive status groups were calculated using Chi-square test for categorical variables (with Bonferroni correction) and analysis of variance for continuous variables (with LSD post hoc test), crude and age adjusted. The level of statistical significance was set at $P < 0.05$ ($P < 0.016$ for the Bonferroni and LSD correction).

Linear regression models

Linear regression models (LEM) were used to address the research questions proposed initially by applying the continuous outcome of serum 25OHD levels as dependent variable throughout all calculations.

First, the differences in serum 25OHD levels were calculated among the cognitive status groups (all cognitive status groups in one model) using the normal cognitive status group as a referent group. Second, the associations between lifestyle and serum 25OHD levels were calculated using stratified analysis; therefore, calculating the associations separately in each cognitive status group.

The level of statistical significance was set at $P < 0.05$.

The differences in 25OHD levels among cognitive status groups—unstratified analysis

The differences in serum 25OHD levels among the three cognitive status groups were examined, by calculating the changes in beta between dementia group and MCI group as compared to the normal cognitive status group. The differences were calculated in two linear regression models (general linear model-univariate in SPSS): model 1: crude; model 2: additionally included age, gender, season, and education.

The associations between lifestyle and 25OHD-stratified analyses by cognitive status

The initially proposed research question, regarding associations between lifestyle and vitamin D levels, was examined through linear regression models (general linear model-univariate in SPSS), analyses were done separately for all three cognitive status groups

(dependent variable: serum 25OHD). Statistical correction for age, gender, season, and medication were applied.

Results

As shown in Table 1, most of the baseline characteristics were significantly different between the three groups and in general, the health characteristics of participants with dementia and MCI were worse than among cognitively intact participants. Both, the lowest mean 25OHD and highest prevalence of vitamin D deficiency were observed among dementia participants; however, the mean 25OHD of this group was still within the normal range (Table 1). Physical activity levels were low among the dementia group (63% reported no activity); however, the use of supplements was proportionally the highest among the same group (36%).

Table 2 shows the differences in 25OHD between the three groups using linear models accounting for potential confounders. Subjects with dementia had lower 25OHD levels by around 3.7 nmol/L when compared to subjects with normal cognitive function and neither lifestyle nor medicine use explained this difference (results not shown in table). MCI subjects had lower 25OHD levels in the crude analysis; however, this difference disappeared after statistical correction.

Table 3 shows the associations between lifestyle and 25OHD using linear models stratified by cognitive status. Among subjects with dementia and MCI, cod liver oil intake and vitamin D supplements were the only lifestyle variables significantly associated with 25OHD. Those two variables showed the strongest results in heightening 25OHD levels, ranging from 7.12 to 9.18 nmol/L (cod liver oil-daily intake) and 4.41–11.52 nmol/L (supplement use).

Among participants with normal cognitive function, all the investigated lifestyle variables were significantly associated with 25OHD.

Among subjects with dementia, there was similar trend for positive associations between physical activity and 25OHD levels as seen among the normal cognitive function subjects, even though results did not reach statistical significance. The following three variables were associated with the highest 25OHD levels among normal cognitive function subjects; daily use of cod liver oil, body mass index ($< 30 \text{ kg/m}^2$), and no smoking.

Tables 2 and 3 was further recalculated with random sampling equalizing the three cognitive function groups matching the smallest group ($N = 307$). Random sampling changed the results only marginally and the new calculations were largely in agreement with previous analyses (results not shown in table).

Discussion

The current large cross-sectional study investigated the associations between lifestyle and 25OHD in community-dwelling old adults with dementia, MCI and normal cognitive function. According to age-adjusted analysis, participants with dementia and MCI had significantly lower 25OHD and they had poorer lifestyle than participants with normal

cognitive status, although the differences were small and not clinically relevant. Lifestyle was differentially associated with 25OHD in all three cognitive status groups, whereas the strongest associations were observed among the normal cognitive status group.

25OHD and cognitive status

In agreement with previous studies [10], we found lower 25OHD in participants with MCI and dementia. After statistical correction for lifestyle variables, the differences in 25OHD between MCI and normal group disappeared but remain significant in the dementia group.

It is possible that the lower vitamin D levels in participants with dementia are disease related [27] or a result of residual confounding, even though we controlled extensively for confounding factors. In general, lifestyle was related to 25OHD; however, there were some differences observed between the three cognitive status groups. Vitamin D supplements were associated with higher serum vitamin D levels in all three groups and we saw that they were used more frequently in participants with dementia than in the other two groups. Also, daily consumption of cod liver oil was positively associated with vitamin D levels in all three groups; however, the most frequent consumption was seen in the normal cognitive status group. High consumption of fatty fish was positively associated with 25OHD in the normal cognitive group only. The results indicate that individuals with dementia rely more on the use of supplements than cognitively intact individuals, possibly leading to sufficient 25OHD levels, thus explaining the small differences in 25OHD observed between the three groups.

Lifestyle and 25OHD levels among the cognitive status groups

As reported previously [28], we found that participants with dementia were less physically active. Studies suggest that individuals with dementia benefit from physical activity measured by overall health and well-being [8]. A study by van der Roest et al. revealed that in 40% of people with dementia, the needs for physical activity were not fulfilled [29]. In our study, majority of participants with dementia and MCI were physically inactive, 63% and 61%, respectively, which was a higher prevalence than in the group of people with normal cognitive function. This low physical activity among participants with dementia is alarming, since studies have shown that physical inactivity in individuals with dementia is associated with increased risk of cardiovascular disease, metabolic aberrations, and an accelerating progression of dementia [30, 31]. In the final analysis, there was a lack of a significant associations between physical activity and 25OHD in the dementia and the MCI group, this might be explained by several factors: a high proportion of participants with dementia and MCI was inactive, and the small proportion of active participants might have been more likely to participate in a supervised indoor activity without sufficient amount of sunlight exposure.

Mean levels of BMI were not significantly different between the groups in the age-adjusted analysis. When examining the BMI levels by group, participants with dementia had a somewhat higher proportion of underweight and normal weight compared to the group with normal cognitive status. Although, differences in the BMI levels were small, equaling around 3 kg body weight, they might be of importance, since studies have suggested that older adults who are overweight compared to those who are normal weight show better

cognitive performance [32] and weight loss may be a preclinical indicator of Alzheimer disease [33]. Further, weight loss is associated with a faster progression of dementia and with nursing home placement [34]. As previously observed [35], BMI was negatively associated with 25OHD, but we could observe this only in the normal cognitive status group and no significant relation between BMI and 25OHD was observed in the dementia or MCI groups.

In our study, smoking prevalence was low in all three groups. In the group with normal cognitive function, it was related to lower 25OHD by around 4 nmol/L which has been seen before [36]. A negative correlation between 25OHD levels and smoking could possibly be explained by the fact that smoking is usually accompanied by a less healthy lifestyle. However, in our analyses, the difference remained although we corrected for various lifestyle factors.

Participants with normal cognitive function reported more frequent alcohol consumption than the other two groups. For this group, we also observed a positive association between alcohol consumption and 25OHD. Similar results were reported previously in a Finish cross-sectional study [37]. However, a recently published review article on vitamin D and alcohol consumption found mixed results, indicating that the direction of the association between vitamin D and alcohol depends very much on the investigated population, e.g., alcoholic patients vs. moderate drinkers [38]. Newer experimental evidence actually does not support neither a positive nor a negative causal effect of moderated drinking on 25OHD [39].

Strength and limitations

The current study was of cross-sectional design which cannot differentiate cause and consequence of an observed association between lifestyle and vitamin D. The MCI ($N=492$) and dementia ($N=307$) groups had smaller statistical power associated with the total number of participants; therefore, a random sampling was applied equalizing the group size across cognitive function groups, and all analyses were recalculated. This procedure did not change the results significantly.

To our best knowledge, there are currently no studies available that compare serum vitamin D levels among different cognitive status groups and further examine the associations between different lifestyle factors and serum vitamin D levels. It is a strength of this study, that it comprised a variety of health-related, socioeconomic, and lifestyle variables so we could adjust for number of important confounders in the statistical analysis.

Conclusion

Community-dwelling adults with dementia in Iceland are at higher risk for vitamin D deficiency when compared to healthy individuals, although the majority has still vitamin D levels within the normal range. Older people with dementia seem to rely more on vitamin D supplements than their healthy counterparts. Physical activity reported among participants with dementia and MCI is low and is not associated with 25OHD levels in these groups. Although participants with dementia and MCI had poorer lifestyle than healthy participants,

differences in lifestyle did not fully explain the observed lower levels of 25OHD in the dementia group.

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Data availability

Data are not available due to laws of the Icelandic Data Protection Authority.

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Table 1

Demographic and health characteristics according to cognitive status among the participants (shown as mean \pm SD or as %)

	Dementia (<i>n</i> = 307)	Mild cognitive impairment (<i>n</i> = 492)	Normal cognition (<i>n</i> = 4363)	<i>P</i> value	<i>P</i> value ^a
Age (years)	81.7 \pm 5.5 *	80.4 \pm 5.7 *	75.8 \pm 5.2	<0.001	<0.001
Female	54% *	50% *	59%	<0.001	<0.001
Education (primary)	34% *	41% *	19%	<0.001	<0.001
Smoking (yes)	9%	10%	9%	0.51	0.012
Alcohol consumption (yes)	48% *	52% *	66%	<0.001	<0.001
25OHD (nmol/L)	53.8 \pm 19.6 *	55.8 \pm 19.0 *	57.6 \pm 17.7	<0.001	<0.001
Deficient (< 30 nmol/L)	16% *	12% *	7%	<0.001	<0.001
Insufficient (30–49 nmol/L)	24%	27%	25%		
Normal (\geq 50 nmol/L)	60%	61%	68%		
Weekly physical activity				<0.001	<0.001
No activity	63% *	61% *	44%		
3 h	29%	30%	40%		
> 3 h	8%	9%	16%		
BMI (kg/m ²)	26.3 \pm 4.3 *	26.8 \pm 4.4	27.1 \pm 4.4	0.01	0.86
Underweight	2% *	2%	1%		
Normal weight	38%	35%	31%		
Overweight	43%	41%	45%		
Obese	17%	22%	23%		
Cod liver oil (yes)	34% *	40%	42%	0.04	0.28
Vitamin D suppl. (yes)	36% *	31%	30%	<0.01	<0.001
Fatty fish (< 3x/week)	11%	12%	14%	0.82	0.09
Hypertension ^b	83%	85% *	80%	0.01	0.48
Type 2 diabetes ^c	18% *	14% *	11%	<0.001	<0.001
Medicine count	5	5	5	<0.001	<0.001
	58% *	46% *	38%	<0.001	<0.001

25OHD 25 hydroxy-vitamin D, BMI body mass index

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* Significantly different from the normal cognitive function group

^a Age-adjusted P value

^b Hypertension, those with systolic BP over 140 mmHg, diastolic BP > 90 mmHg or on hypertensive medication

^c Diabetes mellitus was defined by physician's diagnosis of diabetes or use of diabetes medication

Table 2

Differences* in 25-hydroxy-vitamin D levels among dementia and mild cognitive-impaired participants using liner regression

Dependent variable: 25OHD	Model 1			Model 2		
	β	95%CI	<i>P</i> value	β	95%CI	<i>P</i> value
Dementia (<i>n</i> = 307)	- 3.733	- 5.748 - 1.717	< 0.01	- 3.880	- 5.968 - 1.791	< 0.01
MCI (<i>n</i> = 492)	- 1.785	- 3.429 - 0.141	0.033	- 1.483	- 3.196 - 0.230	0.090
Normal Cognition** (<i>n</i> = 4346)						
Age (years)				0.085	- 0.006 - 0.176	0.067
Male ^a				4.077	3.081 - 5.074	< 0.01
Season (summer) ^b				2.824	1.353 - 4.295	< 0.01
Education (primary) ^c				- 4.284	- 6.096 - - 2.472	< 0.01

β β Coefficient; model 1: crude. model 2: corrected for age, sex, season, and education

* Based on univariate general linear model

** Reference group

Compared to

^a female,

^b winter,

^c university degree

Table 3

Associations* between lifestyle and 25-hydroxy-vitamin D levels** in the three groups of cognitive status

Dependent variable: 25OHD	Dementia (n = 307)			Mild cognitive impairment (n = 492)			Normal cognition (n = 4363)					
	β	95%CI	P value	β	95%CI	P value	β	95%CI	P value			
Physical activity (> 3 h/week)	1.77	3.078	6.626	0.47	3.38	6.95	0.07	2.82	1.73	3.79	<0.01	
BMI (<30 kg/m ²)	2.68	- 3.134	8.384	0.36	0.99	5.32	0.63	5.24	4.43	6.80	<0.01	
Cod liver oil (daily)	7.12	2.908	12.582	<0.01	8.91	5.25	12.79	<0.01	9.18	7.99	10.37	<0.01
Supplements (yes)	11.52	6.825	15.810	<0.01	6.37	3.82	11.01	<0.01	4.41	3.32	5.49	<0.01
Smoking (no)	0.59	- 6.21	7.41	0.86	4.31	9.78	0.21	4.79	3.26	6.69	<0.01	
Alcohol (yes)	2.11	- 6.13	2.73	0.32	1.25	4.58	0.79	2.67	1.59	3.74	<0.01	
Fatty fish (> 3x/week)	2.35	3.86	8.56	0.11	4.55	9.52	0.07	2.63	1.21	4.10	<0.01	

The statistical model additionally includes age, gender, season, and medication β Coefficient, *BM*/body mass index

* Based on univariate general linear model

** 25OHD as the dependent variable