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Brief Report

Vitamin D and behavioral disorders in older adults: results from the CLIP study

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ABSTRACT

Objectives: Vitamin D is involved in brain health and function. Our objective was to determine whether vitamin D deficiency was associated with behavioral disorders in geriatric patients.
Design: The observational cross-sectional CLIP (Cognition and LIPophilic vitamins) study. The report followed the STROBE statement.
Setting: Geriatric acute care unit in a tertiary university hospital in France for 3 months at the end of winter and beginning of spring.
Participants: 272 patients ≥65 years consecutively hospitalized or seen in consultation.
Measurements: Participants were separated into two groups according to vitamin D deficiency (i.e., serum 25-hydroxyvitamin D ≤25 nmol/L). Behavior was assessed using the reduced version of the Neuropsychiatric Inventory Scale (NPI-R) score and subscores. Age, sex, BMI, education level, comorbidities, MMSE and GDS scores, use psychoactive drugs and vitamin D supplements, and serum concentrations of calcium, parathyroid hormone, TSH and estimated glomerular filtration rate (eGFR) were used as potential confounders.
Results: Participants with vitamin D deficiency (n = 78) had similar NPI-R score (17.4 ± 20.3 versus 17.2 ± 16.1, p = 0.92) but higher (i.e., worse) subscore of agitation and aggressiveness (2.0 ± 3.3 versus 1.2 ± 2.4, p = 0.02) and higher (i.e., worse) subscore of disinhibition (0.99 ± 2.98 versus 0.38 ± 1.42, p = 0.02) than those without vitamin D deficiency (n = 194). In multiple linear regressions, vitamin D deficiency was inversely associated with the subscore of agitation and aggressiveness (β = 1.37, p = 0.005) and with the subscore of disinhibition (β = 0.96, p = 0.008).
Conclusion: Vitamin D deficiency was associated with more severe subscores of agitation and aggressiveness and of disinhibition among older adults. This provides a scientific basis to test the efficacy of vitamin D supplementation on behavioral disorders in older patients with vitamin D deficiency.

1. Introduction

Clinical importance of hypovitaminosis D is linked to its high prevalence, estimated at more than one billion people around the word [1], and its health manifestations. Vitamin D is classically known for its regulatory function in phosphocalcic metabolism [1,2]. A growing number of studies have also reported non-bone effects of vitamin D in the past decade, especially on brain health and function [2–5].

Hypovitaminosis D has been repeatedly associated with neurocognition [6], particularly with major neurocognitive disorders [7,8], accelerated cognitive decline [8,9] and delirium [10]. However, epidemiological associations reported thus far mainly implied cognitive performance rather than other manifestations accompanying neurocognitive disorders such as behavioral disorders.

Considering the neurocognitive effects of vitamin D, we hypothesized that vitamin D deficiency could participate to the onset of behavioral

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disorders among older adults. We had the opportunity to examine the association between vitamin D and behavioral performance in a sample of geriatric patients, the CLIP (Cognition and LIPophilic vitamins) cohort. The aim of the present study was to determine whether vitamin D deficiency was associated with behavioral disorders among geriatric patients.

2. Materials and methods

2.1. Participants

We studied in- and outpatients aged 65 and over consecutively recruited in the CLIP study. The CLIP study is an observational cross-sectional study designed to examine the relationships between neurocognition and lipophilic vitamins among all patients consecutively hospitalized or seen in consultation in the geriatric acute care unit of the University Hospital of Angers, France, from February to April 2014 [11]. After giving their informed consent for research, included participants received a full medical examination consisting of structured questionnaires, a standardized clinical examination and a blood test.

2.2. Data collection

2.2.1. Behavior

Behavior was assessed using the reduced neuropsychiatric inventory (NPI-R), a standardized caregiver self-questionnaire to collect information on the presence, severity and impact of 12 psycho-behavioral symptoms: delusions, hallucinations, agitation and aggressiveness, dysphoria, anxiety, euphoria, apathy, disinhibition, aberrant motor behaviors, irritability, night-time behavioral disturbance, appetite disturbances [12]. Each behavioral domain is assigned a severity score (/3) and a score of impact (/5); thus each NPI-R sub-score is finally scored out of 15 by multiplying the severity score by the score of impact, and the total NPI-R score is rated out of 180 (12 domains rated out of 15). The results of the NPI-R correlate with those of the longer version, but its administration time is considerably shortened, which makes it more accessible in clinical routine [13].

2.2.2. Serum 25-hydroxyvitamin D concentration

Serum concentrations of 25OHD effectively reflect the stock of vitamin D in the body. Serum concentrations of 25OHD were measured by radioimmunoassay (DiaSorin Inc., Stillwater, MN) in nmol/L (to convert to ng/mL, divide by 2.496). With this method, there is no interference with lipids, which is often observed in other non-chromatographic assays of 25OHD. The intra- and interassay precision was 5.2% and 11.3% respectively. Vitamin D deficiency was consensually defined using the threshold value of 25 nmol/L proposed by the World Health Organization and the National Institutes of Health definitions.

2.2.3. Covariates

Age, sex, body mass index (BMI), education level, comorbidities, Mini-Mental State Examination (MMSE; score 0–30, best) and Geriatric Depression Scale (GDS; score 0–4, worst) scores, use psychoactive drugs and vitamin D supplements, and serum concentrations of calcium, parathyroid hormone, Thyroid-stimulating hormone (TSH) and estimated glomerular filtration rate (eGFR) were used as potential confounders. Evaluation of education level was based on self-report. Participants who passed at least the Elementary School Recognition Certificate were considered to have high education level. Comorbidity burden was estimated with the Cumulative Illness Rating Scale-Geriatrics score (CIRS-G) (range 0–60, worst) [14]. Using psychoactive drugs (i.e., antidepressants or neuroleptics or anxiolytics) and vitamin D supplements were determined by a senior physician from drug prescriptions at the admission. All blood samples were analyzed using standardized laboratory methods at the University Hospital of Angers, France. eGFR was calculated using the Cockcroft-Gault formula ($[(140–age_{years}) \times weight_{kg}/creatinine_{\mu mol/L}] \times 1.04$ for women, and $\times 1.25$ for men).

2.3. Statistics

The participants' characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Firstly, comparisons of participants' characteristics according to vitamin D deficiency were performed using Student's *t*-test or the Chi-square test, as appropriate. Secondly, we examined the correlation between vitamin D

Table 1
Characteristics and comparison of the participants (n = 272) separated into two groups based on serum 25-hydroxyvitamin D concentration.

	Total cohort (n = 272)	Serum 25-hydroxyvitamin concentration (nmol/L)		P-Value *
		≤ 25 (n = 78)	> 25 (n = 194)	
Demographical and clinical measures				
Age, years	83.4 ± 7.1	84.5 ± 7.0	82.9 ± 7.1	0.10
Female sex, n (%)	175 (64.3)	47 (60.3)	128 (66.0)	0.37
Body mass index, kg/m^2	25.96 ± 5.44	26.66 ± 5.45	25.69 ± 5.42	0.22
High education level †, n (%)	203 (74.6)	60 (76.9)	143 (73.7)	0.58
CIRS-G score, /60	8.6 ± 4.4	7.9 ± 4.2	8.9 ± 4.4	0.13
MMSE score, /30	20.3 ± 6.4	19.8 ± 6.9	20.5 ± 6.2	0.44
GDS score, /4	0.9 ± 1.2	0.8 ± 1.1	0.9 ± 1.2	0.59
Use psychoactive drugs ‡, n (%)	146 (53.7)	32 (41.0)	114 (58.8)	**0.008**
Use vitamin D supplements, n (%)	110 (40.4)	13 (16.7)	97 (50.0)	**<0.001**
Inpatient, n (%)	168 (61.8)	59 (75.6)	109 (56.2)	**0.003**
Behavioural disorders				
NPI-R score, /180	17.3 ± 17.4	17.4 ± 20.3	17.2 ± 16.1	0.92
Subscore of agitation and aggressiveness, /15	1.39 ± 2.69	1.97 ± 3.32	1.16 ± 2.36	**0.02**
Subscore of disinhibition, /15	0.55 ± 2.01	0.99 ± 2.98	0.38 ± 1.42	**0.02**
Serum measures				
25-hydroxyvitamin D concentration, nmol/L	50.17 ± 31.15	16.45 ± 5.34	63.72 ± 26.59	**<0.001**
Parathyroid hormone concentration, pg/mL	35.63 ± 26.47	51.57 ± 35.99	29.20 ± 17.94	**<0.001**
Calcium concentration, mmol/L	3.14 ± 14.32	2.22 ± 0.18	3.50 ± 16.94	0.52
Estimated glomerular filtration rate, mL/min	52.37 ± 20.98	51.76 ± 19.12	52.61 ± 21.73	0.77
Thyroid Stimulating Hormone concentration, mUI/L	2.04 ± 6.23	1.85 ± 1.73	2.12 ± 7.27	0.75

Data presented as mean ± standard deviation where applicable. CIRS-G: Cumulative Illness Rating Scale for Geriatrics; GDS: Geriatric Depression Scale; MMSE: Mini-Mental State Examination; NPI-R: reduced version of the Neuropsychiatric Inventory; *: between-group comparisons based on Chi-square test or t-test, as appropriate; †: at least Elementary School Recognition Certificate; ‡: benzodiazepines, antidepressants or neuroleptics; ||: score > 2 out of 15; P-value significant indicated in bold.

Table 2
Correlation matrix of vitamin D deficiency (i.e., serum 25-hydroxyvitamin D ≤25 nmol/L) and the subscores of the NPI-R (n = 272).

Characteristic	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. Vitamin D deficiency	-	0.04	−0.08	0.14*	−0.09	−0.08	−0.04	0.00	0.14*	−0.04	0.12	−0.04	0.03
2. Delusions		-	0.49***	0.40***	0.20**	0.21**	0.11	0.23***	0.32***	0.23***	0.34***	0.20**	0.23***
3. Hallucinations			-	0.33***	0.14*	0.13*	0.09	0.21**	0.06	0.20**	0.15*	0.09	0.12
4. Agitation and aggressiveness				-	0.22***	0.20**	0.25***	0.28***	0.56***	0.20**	0.69***	0.23***	0.29***
5. Dysphoria					-	0.45***	0.07	0.19**	0.13*	0.18**	0.34***	0.24***	0.28***
6. Anxiety						-	0.04	0.05	−0.03	0.12*	0.28***	0.22***	0.18**
7. Euphoria							-	0.12*	0.24***	−0.03	0.14*	−0.01	0.13*
8. Apathy								-	0.27***	0.14*	0.24***	0.04	0.26***
9. Disinhibition									-	0.20**	0.50***	0.13*	0.19***
10. Aberrant motor behavior										-	0.22***	0.03	0.08
11. Irritability											-	0.21***	0.23***
12. Nighttime behavioral disturbance												-	0.28***
13. Appetite/weight changes													-

*P < 0.05 (2-tailed); **: P < 0.01 (2-tailed); ***: P ≤ 0.001 (2-tailed).

deficiency and each subscore of the NPI-R. Thirdly, univariate and multiple linear regressions were used to examine the associations of vitamin D deficiency (independent variable) with the NPI-R subscores of agitation and aggressiveness and of disinhibition (dependent variables), while adjusting for potential confounders. Separate analyses were conducted for each dependent variable. P-values <0.05 were considered significant. All statistics were performed using SPSS (v19.0, IBM corporation, Chicago, IL).

2.4. Ethics

The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The entire study protocol was approved by the local Ethical Committee (No 2014-33).

3. Results

Among 272 included participants (mean ± standard deviation, 83.4 ± 7.1years; 64.3% women; 61.8% inpatient; 70.2% with MMSE score <25), 78 exhibited vitamin D deficiency (29%) (Table 1). The mean MMSE score was 20.3 ± 6.4, the mean GDS score was 0.9 ± 1.2, and the mean NPI-R score was 17.3 ± 17.4. There was no difference in NPI-R score between the participants with vitamin D deficiency and those without vitamin D deficiency (respectively, 17.4 ± 20.3 versus 17.2 ± 16.1, P = 0.92). There was also no difference regarding the NPI-R subscores, with the exception of the subscore of agitation and aggressiveness (respectively, 2.0 ± 3.3 versus 1.2 ± 2.4, P = 0.02) and the subscore of disinhibition (respectively, 0.99 ± 2.98 versus 0.38 ± 1.42, P = 0.02) that were higher (i.e., worse) in the case of vitamin D deficiency (Table 1).

Table 2 reports the correlations between vitamin D deficiency and the subscores of the NPI-R. Vitamin D deficiency correlated positively with the subscore of agitation and aggressiveness (r = 0.14, P = 0.02) and with the subscore of disinhibition (r = 0.14, P = 0.02), but not with all other NPI-R subscores (P > 0.05).

Finally, results of multiple linear regression models were reported in Table 3. We observed a positive adjusted association of vitamin D deficiency with the subscore of agitation and aggressiveness (β = 1.37, P = 0.005) and with the subscore of disinhibition (β = 0.96, P = 0.008). Higher TSH concentration was also associated with increased subscores of agitation and aggressiveness and of disinhibition, although higher MMSE score was associated with decreased subscores of agitation and aggressiveness and of disinhibition (Table 3).

4. Discussion

Vitamin D deficiency was not associated in geriatric patients with the NPI-score as a whole but was associated specifically with higher (i.e., worse) NPI-R subscores of agitation and aggressiveness and of disinhibition. This provides a scientific basis for conducting clinical trials to test the efficacy of vitamin D supplementation to prevent or improve the prognosis of behavioral disorders in older patients with initial serum 25OHD ≤ 25 nmol/L.

These findings are consistent with previous animal experimentation and neuropsychological literature in humans. Previous studies have reported that transgenic mice lacking functional vitamin D receptors (VDR) more often showed abnormal social behaviors compared to wild-type mice, in particular more often aggressiveness and a risk of cannibalism [15,16]. Interestingly, another animal model of Developmental vitamin D (DVD) deplete adult rats (i.e., rats subjected to transient low prenatal vitamin D) generated an animal model of schizophrenia [17]. In humans, the neuropsychoepidemiological literature found that individuals with hypovitaminosis D had increased risks of incidental depression [18], psychosis [18] and cognitive decline [7,8], notably an increased risk of Alzheimer disease [19]. Specifically, the cognitive risk appeared mainly as a decline of executive functions [20], in particular of cognitive inhibition [21]. Finally, in addition to chronic neurocognitive disorder, there is also a greater risk of acute decompensation in the form of delirium among those with hypovitaminosis D [10], which is usually expressed by disturbed behavior. Compared to previous literature, we provide here the first evidence that the cognitive risk is coupled with a risk of behavioral symptoms including agitation, aggressiveness and disinhibition in older adults with vitamin D deficiency. These novel findings suggest that the correction of vitamin D deficiency could represent an interesting therapeutic option to prevent and/or cure behavioral disorders in older adults. Consistently, an international expert consensus concluded that vitamin D supplementation should be administered to people with neurocognitive disorders [8], and previous randomized trials reported improved executive functioning in supplemented participants compared to those receiving a placebo [22]. Similarly, a pre-post study also found improved NPI score among older adults after 4 weeks of vitamin D2 supplementation [23].

Mechanisms linking vitamin D to behavior are not fully elucidated. VDRs were found in neurons and glial cells from brain areas that are essential to cognitive function (temporal cingular and orbital cortex, thalamus, nucleus accumbens, stria terminalis and amygdala) [24]. By modifying the gene expression of various proteins, vitamin D modulates

Table 3
Univariate and multiple linear regressions showing the cross-sectional association of vitamin D deficiency* (independent variable) with the NPI-R subscore of agitation and aggressiveness and with the NPI-R subscore of disinhibition (dependent variables), adjusted for participants' characteristics (n = 272).

	Behavioral disorders							
	Subscore of agitation and aggressiveness				Subscore of disinhibition			
	Unadjusted model		Fully adjusted model		Unadjusted model		Fully adjusted model	
	Unadjusted β [95% CI]	P-Value	Fully adjusted β [95% CI]	P-Value	Unadjusted β [95% CI]	P-Value	Fully adjusted β [95% CI]	P-Value
Vitamin D deficiency*	**0.82 [0.11; 1.52]**	**0.02**	**1.37 [0.43; 2.31]**	**0.005**	**0.61 [0.08; 1.14]**	**0.02**	**0.96 [0.25; 1.66]**	**0.008**
Age	0.02 [−0.02; 0.07]	0.31	−0.01 [−0.07; 0.05]	0.76	0.02 [−0.02; 0.05]	0.34	0.02 [−0.03; 0.06]	0.52
Female sex	0.72 [0.06; 1.39]	**0.03**	0.63 [−0.20; 1.47]	0.14	0.47 [−0.03; 0.97]	0.06	0.40 [−0.23; 1.02]	0.21
Body mass index	−0.03 [−0.09; 0.04]	0.42	−0.05 [−0.13; 0.03]	0.25	0.00 [−0.04; 0.04]	1.00	0.04 [−0.03; 0.10]	0.27
High education level †	−0.46 [−1.20; 0.27]	0.22	−0.01 [−0.90; 0.90]	0.99	0.33 [−0.22; 0.88]	0.24	**0.81 [0.13; 1.48]**	**0.02**
CIRS-G score	0.01 [−0.07; 0.09]	0.89	0.01 [−0.09; 0.12]	0.79	−0.02 [−0.09; 0.04]	0.49	−0.06 [−0.14; 0.02]	0.12
MMSE score	**−0.12 [−0.17; −0.07]**	**<0.001**	**−0.12 [−0.18; −0.05]**	**<0.001**	**−0.07 [−0.11; −0.03]**	**<0.001**	**−0.11 [−0.16; −0.06]**	**<0.001**
GDS score	0.20 [−0.10; 0.50]	0.18	0.15 [−0.17; 0.46]	0.35	−0.04 [−0.27; 0.19]	0.73	−0.15 [−0.39; 0.09]	0.21
Use of psychoactive drugs ‡	0.54 [−0.10; 1.18]	0.10	0.23 [−0.64; 1.10]	0.60	0.23 [−0.25; 0.71]	0.35	0.31 [−0.34; 0.97]	0.34
Use of vitamin D supplements	−0.16 [−0.81; 0.50]	0.64	0.49 [−0.30; .128]	0.22	−0.15 [−0.64; 0.34]	0.55	0.39 [−0.20; 0.97]	0.20
Serum PTH concentration	0.01 [−0.01; 0.02]	0.45	−0.002 [−0.02; 0.02]	0.86	0.00 [−0.01; 0.01]	0.64	**−0.01 [−0.03; −0.01]**	**0.04**
Serum calcium concentration	−0.01 [−0.03; 0.02]	0.61	0.00 [−0.02; 0.02]	0.80	0.00 [−0.02; 0.02]	0.79	0.00 [−0.02; 0.01]	0.78
Estimated glomerular filtration rate	−0.01 [−0.02; 0.01]	0.46	0.01 [−0.01; 0.04]	0.25	0.00 [−0.01; 0.01]	0.95	0.01 [−0.01; 0.03]	0.31
Serum TSH concentration	**0.10 [0.05; 0.15]**	**<0.001**	**0.10 [0.05; 0.15]**	**<0.001**	**0.05 [0.01; 0.09]**	**0.008**	**0.04 [0.01; 0.08]**	**0.02**

β: Coefficient of regression corresponding to a change in the behavioural subscore (/15); CI: confidence interval; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; GDS: Geriatric Depression Scale; MMSE: Mini-Mental State Examination; PTH: parathyroid hormone; TSH: Thyroid Stimulating Hormone concentration; *: Serum 25-hydroxyvitamin D $\leq$ 25 nmol/L; †: at least Elementary School Recognition Certificate; ‡: benzodiazepines, antidepressants or neuroleptics; β significant (i.e., $P < 0.05$) indicated in bold.

neurophysiology and neuroprotection [4]. Specifically, vitamin D regulates neurotrophic agents and controls cell differentiation and maturation [25], as well as the gene expression of various neurotransmitters including acetylcholine, dopamine and serotonin [6]. Vitamin D also limits inflammatory changes associated with aging in hippocampus [26], prevents the accumulation of Aβ peptides by stimulating phagocytosis [27] and blood-brain barrier efflux transport [28]. As a consequence, hypovitaminosis D is associated with changes in brain volume, vascularization and metabolism [4,5]; all changes that may explain the greater risk of behavioral disorders in the case of vitamin D deficiency. Nevertheless, causality could not be deducted from our observational study, and behavioral disorders may actually be the expression of an altered cognitive status responsible for hypovitaminosis D because of disability and subsequent decreased food intakes and sun exposure.

We found a positive association between TSH concentration and worse subscores of agitation and disinhibition, and an inverse association between MMSE score and NPI-R subscores. These associations are well-recognized [29], which strengthens the credibility of our primary result on the association of vitamin D deficiency with worse NPI-R subscores of agitation and aggressiveness and of disinhibition in geriatric patients.

Some limitations should be acknowledged. First, due to the limited number of 272 in. and outpatients from one single center, our study may lack power and the participants may be not representative of the population of all seniors. Second, our study is cross-sectional, which precludes inferring causality. Third, although we were able to control for important characteristics that could modify the associations, residual potential confounders such as the presence of psychotic symptoms or the determination of ApoE genotype, might still be present. Fourfth, limitations include the use of the MMSE and GDS tools, which may exhibit ceiling effects and limited sensitivity to subtle abnormalities. Finally, there is no reference in the literature specifying what the minimum clinically significant values are for the NPI subscores examined here. The DOMINO study suggests a minimum clinically significant value of 8 for the total NPI score [30]; it is therefore likely that the differences highlighted for each isolated subscore here may be considered as clinically relevant.

5. Conclusions

We report an association between vitamin D deficiency and increased risks of agitation, aggressiveness and disinhibition among geriatric patients. There is a strong need for novel effective preventive and therapeutic strategies for behavioral disorders. Further prospective studies and clinical trials are needed to clarify whether older adults with higher vitamin D concentrations are less likely to experience behavioral declines than the others, and whether vitamin D supplementation could improve, or prevent, this process.

Authors contributions

CA has full access to all data in the study, takes responsibility for the data, the analyses and interpretation, and has the right to publish any or all data, separate and apart from the attitudes of the sponsors. All authors have read and approved the final version of the manuscript.

Study concept and design: CA.

Acquisition of data: LG and AB.

Analysis and interpretation of data: LG, AB, SNK, DGA, ED and CA.

Drafting of the manuscript: LG and CA.

Critical revision of the manuscript for important intellectual content: AB, SNK, DGA and ED.

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Administrative, technical, or material support: CA.

Study supervision: CA.

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Conflicts of interest

The authors declare that the research was conducted with no commercial or financial relationships that could be considered as conflicts of interest.

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References

[1] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81, doi:http://dx.doi.org/10.1056/NEJMra070553.
[2] Charoenngam N, Shirvani A, Holick MF. Vitamin D for skeletal and non-skeletal health: what we should know. J Clin Orthop Trauma 2019;10:1082–93, doi:http://dx.doi.org/10.1016/j.jcot.2019.07.004.
[3] Annweiler C, Allali G, Allain P, Bridenbaugh S, Schott AM, Kressig RW, et al. Vitamin D and cognitive performance in adults: a systematic review. Eur J Neurol 2009;16:1083–9, doi:http://dx.doi.org/10.1111/j.1468-1331.2009.02755.x.
[4] Annweiler C. Vitamin D in dementia prevention. Ann N Y Acad Sci 2016;1367:57–63, doi:http://dx.doi.org/10.1111/nyas.13058.
[5] Landel V, Annweiler C, Millet P, Morello M, Féron F. Vitamin D, cognition and alzheimer's disease: the therapeutic benefit is in the D-tails. J Alzheimers Dis 2016;53:419–44, doi:http://dx.doi.org/10.3233/JAD-150943.
[6] Annweiler C, Schott AM, Berrut G, Chauviré V, Le Gall D, Inzitari M, et al. Vitamin D and ageing: neurological issues. Neuropsychobiology 2010;62:139–50, doi:http://dx.doi.org/10.1159/000318570.
[7] Etgen T, Sander D, Bickel H, Sander K, Förstl H. Vitamin D deficiency, cognitive impairment and dementia: a systematic review and meta-analysis. Dement Geriatr Cogn Disord 2012;33:297–305, doi:http://dx.doi.org/10.1159/000339702.
[8] Annweiler C, Dursun E, Féron F, Gezen-Ak D, Kalueff AV, Littlejohns T, et al. 'Vitamin D and cognition in older adults': updated international recommendations. J Intern Med 2015;277:45–57, doi:http://dx.doi.org/10.1111/joim.12279.
[9] Tilvis RS, Kähönen-Väre MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. J Gerontol A Biol Sci Med Sci 2004;59:268–74, doi:http://dx.doi.org/10.1093/gerona/59.3.m268.
[10] Chouët J, Sacco G, Karras SN, Llewellyn DJ, Sánchez-Rodríguez D, Annweiler C. Vitamin D and delirium in older adults: a case-control study in geriatric acute care unit. Front Neurol 2020;11:1034, doi:http://dx.doi.org/10.3389/fneur.2020.01034.
[11] Chouet J, Ferland G, Féart C, Rolland Y, Presse N, Boucher K, et al. Dietary vitamin K intake is associated with cognition and behaviour among geriatric patients: the CLIP study. Nutrients 2015;7:6739–50, doi:http://dx.doi.org/10.3390/nu7085306.
[12] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14, doi:http://dx.doi.org/10.1212/wnl.44.12.2308.
[13] Michel E, Robert P, Boulhassass R, Lafont V, Baudu C, Bertogliati C, et al. Validation de la version réduite de l'inventaire neuropsychiatrique (NPI-R). La Revue de Gériatrie 2005;30:385–90.
[14] Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968;16:622–6, doi:http://dx.doi.org/10.1111/j.1532-5415.1968.tb02103.x.
[15] Burne TH, McGrath JJ, Eyles DW, Mackay-Sim A. Behavioural characterization of vitamin D receptor knockout mice. Behav Brain Res 2005;157:299–308, doi:http://dx.doi.org/10.1016/j.bbr.2004.07.008.
[16] Kalueff AV, Keisala T, Minasyan A, Kuuslahti M, Miettinen S, Tuohimaa P. Behavioural anomalies in mice evoked by "Tokyo" disruption of the Vitamin D receptor gene. Neurosci Res 2006;54:254–60, doi:http://dx.doi.org/10.1016/j.neures.2005.12.008.
[17] Kesby JP, Burne TH, McGrath JJ, Eyles DW. Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: an animal model of schizophrenia. Biol Psychiatry 2006;60:591–6, doi:http://dx.doi.org/10.1016/j.biopsych.2006.02.033.
[18] Roy NM, Al-Harthi L, Sampat N, Al-Mujaini R, Mahadevan S, Al Adawi S, et al. Impact of vitamin D on neurocognitive function in dementia, depression, schizophrenia and ADHD. Front Biosci (Landmark Ed) 2021;26:566–611, doi:http://dx.doi.org/10.2741/4908.
[19] Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, Chaves PH, et al. Vitamin D and the risk of dementia and Alzheimer disease. Neurology 2014;83:920–8, doi:http://dx.doi.org/10.1212/WNL.0000000000000755.
[20] Annweiler C, Montero-Odasso M, Llewellyn DJ, Richard-Devantoy S, Duque G, Beauchet O. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. J Alzheimers Dis 2013;37:147–71, doi:http://dx.doi.org/10.3233/JAD-130452.
[21] EMAS study group. Lee DM, Tajar A, Ulubaev A, Pendleton N, O'Neill TW, O'Connor DB, et al. Association between 25-hydroxyvitamin D levels and cognitive performance

in middle-aged and older European men. J Neurol Neurosurg Psychiatry 2009;80:722–9, doi:http://dx.doi.org/10.1136/jnnp.2008.165720.
[22] Dhesi JK, Jackson SH, Bearne LM, Moniz C, Hurley MV, Swift CG, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing 2004;33:589–95, doi:http://dx.doi.org/10.1093/ageing/afh209.
[23] Przybelski R, Agrawal S, Krueger D, Engelke JA, Walbrun F, Binkley N. Rapid correction of low vitamin D status in nursing home residents. Osteoporos Int 2008;19:1621–8, doi:http://dx.doi.org/10.1007/s00198-008-0619-x.
[24] Kalueff AV, Tuohimaa P. Neurosteroid hormone vitamin D and its utility in clinical nutrition. Curr Opin Clin Nutr Metab Care 2007;10:12–9, doi:http://dx.doi.org/10.1097/MCO.0b013e328010ca18.
[25] Brown J, Bianco JI, McGrath JJ, Eyles DW. 1,25-dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. Neurosci Lett 2003;343:139–43, doi:http://dx.doi.org/10.1016/s0304-3940(03)00303-3.
[26] Nissou MF, Guttin A, Zenga C, Berger F, Issartel JP, Wion D. Additional clues for a protective role of vitamin D in neurodegenerative diseases: 1,25-dihydroxyvitamin D3 triggers an anti-inflammatory response in brain pericytes. J Alzheimers Dis 2014;42:789–99, doi:http://dx.doi.org/10.3233/JAD-140411.
[27] Masoumi A, Goldenson B, Ghirmai S, Avagyan H, Zaghi J, Abel K, et al. 1alpha,25-dihydroxyvitamin D3 interacts with curcuminoids to stimulate amyloid-beta clearance by macrophages of Alzheimer's disease patients. J Alzheimers Dis 2009;17:703–17, doi:http://dx.doi.org/10.3233/JAD-2009-1080.
[28] Ito S, Ohtsuki S, Nezu Y, Koitabashi Y, Murata S, Terasaki T. 1α,25-Dihydroxyvitamin D3 enhances cerebral clearance of human amyloid-β peptide(1-40) from mouse brain across the blood-brain barrier. Fluids Barriers CNS 2011;8:20, doi:http://dx.doi.org/10.1186/2045-8118-8-20.
[29] Chen G, Gao W, Xu Y, Chen H, Cai H. Serum TSH levels are associated with hyperactivity behaviors in children with attention deficit/hyperactivity disorder. Neuropsychiatr Dis Treat 2023;19:557–64, doi:http://dx.doi.org/10.2147/NDT.S402530.
[30] Howard R, Phillips P, Johnson T, O'Brien J, Sheehan B, Lindesay J, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. Int J Geriatr Psychiatry 2011;26:812–7, doi:http://dx.doi.org/10.1002/gps.2607.