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Vitamin D supplementation has no effect on cognitive performance after four months in mid-aged and older subjects

Rolf Jorde[a,b,*], Julia Kubiak[a], Johan Svartberg[a,b], Ole M. Fuskevåg[c], Yngve Figenschau[a,c,d], Ieva Martinaityte[a,b], Guri Grimnes[a,b]

[a] Tromsø Endocrine Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway
[b] Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway
[c] Division of Diagnostic Services, University Hospital of North Norway, Tromsø, Norway
[d] Department of Medical Biology, UiT The Arctic University of Norway, Tromsø, Norway

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ABSTRACT

Background: Low serum 25-hydroxyvitamin D (25(OH)D) levels are associated with impaired cognitive function, but the effect of vitamin D supplementation on cognitive function is uncertain.
Methods: 422 subjects were included in a randomized controlled trial with vitamin D (cholecalciferol) 100,000 IU given as a bolus dose followed by 20,000 IU per week versus placebo for four months. Cognitive function was evaluated with verbal recall test, coding test and tapping test.
Results: 374 subjects (mean age 52 years, 198 males) had complete cognitive tests both at baseline and at end of study. Mean baseline serum 25(OH)D level was 34 nmol/L. At baseline there were no significant associations between serum 25(OH)D and the three separate cognitive tests. At the end of the study mean serum 25(OH)D levels were 89 nmol/L and 31 nmol/L in the vitamin D and placebo groups, respectively. At the end of the study, there were no statistically significant differences between the two groups regarding change in the cognitive test scores. Nor did sub-group analyses based on gender, age, baseline serum 25(OH)D and cognitive test scores reveal significant differences between the two groups at the end of the study.
Conclusions: Vitamin D supplementation did not improve cognitive function during a four months intervention in mid-aged and older subjects.
Trial registration: ClinicalTrials.govNCT02750293

1. Introduction

Vitamin D is important for skeletal development, and vitamin D deficiency may lead to rickets in childhood and to osteomalacia in adults [1]. Vitamin D deficiency has also been associated with non-skeletal diseases like cardiovascular and immunological diseases, cancer and infections [1], as well as neurological diseases such as multiple sclerosis [2] and dementia [3]. This is plausible since the vitamin D receptor (VDR) and the enzymes necessary for hydroxylation of vitamin D to its active form 1,25-dihydroxyvitamin D (1,25(OH)$_2$D) are widely expressed throughout the body including most regions of the human brain [4–6].

It is therefore no surprise that there is an association between vitamin D status, as evaluated by serum 25-hydroxyvitamin D (25(OH)D), and cognitive function. This has been demonstrated in numerous cross-sectional studies [7–9] and in most [7,10], but not all [9] longitudinal studies. As with associations between vitamin D and diseases, the key question is whether there is a causal link between low serum 25(OH)D levels and cognition. This has to be answered by properly performed randomized controlled trials (RCTs), where the subjects included are vitamin D insufficient (serum 25(OH)D $<$ 50 nmol/L [11] and where the vitamin D dose given increase the serum 25(OH)D level to sufficient levels. However, there are only a few vitamin D and cognitive function RCTs published, and the results are non-conclusive [12–16].

The seventh survey in the Tromsø study in Northern Norway was performed in 2015/2016 and serum 25(OH)D was measured in 20,922 participants. We therefore had the opportunity to invite a large group of subjects with low serum 25(OH)D levels for evaluating the effect of

Abbreviations: BMI, body mass index; PTH, parathyroid hormone; RCT, randomized controlled trial; VDR, vitamin D receptor; 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D

* Corresponding author at: Tromsø Endocrine Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway.
E-mail address: rolf.jorde@unn.no (R. Jorde).

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vitamin D supplementation on cognitive function.

2. Subjects and methods

2.1. Subjects

The main endpoint of the study was effects on cardiovascular risk factors, and the design of the study has previously been published in detail [17]. The Tromsø study is a repeated population based study conducted in the municipality of Tromsø, Norway, situated at 69°N [18]. In the seventh survey in 2015/2016 all citizens aged 40 years and above (32591) were invited to participate and 21,083 attended. Serum 25(OH)D was successfully measured in 20,922, and 1489 subjects with serum values < 42 nmol/L and < 80 years old were by mail invited to participate in the present study. Six-hundred and thirty-nine responded and were screened by phone by one of the study nurses at the Clinical Research Unit at the University Hospital of North Norway. Exclusion criteria were known granulomatous disease, diabetes, renal stones last five years, systolic blood pressure > 174 mmHg, diastolic blood pressure > 104 mmHg, serum craetinine > 130 μmol/L in males and > 120 μmol/L in females, clinical depression, clinical signs of vitamin D deficiency (muscle weakness), serious diseases that would make the subject unfit for participation (clinical evaluation by the first author if in doubt), use of vitamin D supplements exceeding 800 IU vitamin D per day, use of solarium on a regular basis, and planned holiday(s) in tropical areas during the study period. Women of childbearing potential without use of acceptable contraception (hormonal or intrauterine device) were excluded. Subjects with previous stroke or transitory ischemic attach (TIA) were included if no apparent mental of physical squelae. Subjects with other specific neurological diseases were not included. Information on alcohol intake/abuse was not recoded. Data on weight, height and smoking status reported by the subjects, as well as sex and vitamin D status in the Tromsø study, were sent to the randomization unit at the hospital's research department.

2.2. Study design

If eligible after the telephone screening, the participants met for a first visit at the Clinical Research Unit. At this visit the informed consent form was signed, clinical examinations performed, height and weight measured, medical history taken, life style questionnaires (smoking habits, sunny vacation or use of sunbed last three months) filled in and fasting blood samples drawn. If these examinations did not reveal any contraindication for participation, the next visit was performed within 2–5 days. At this second (non-fasting) visit, verbal recall, coding and tapping tests were performed, the subjects a filled in the Beck depression inventory II (BDI-II) [19], and the study drugs (vitamin D (cholecalciferol) capsules (20,000 IU (500 μg) Dekristol, Mibe, Jena, Germany) or identical looking placebo capsules containing arachis oil (Ayanda GmbH & CoKG, Falkenhagen, Germany) were dispensed. Five capsules were given as a loading dose followed by one capsule each week for four months. The weekly dose of 20,000 IU was used since this in previous studies has resulted in adequate serum 25(OH)D levels [20].

The randomization was stratified according to sex, smoking status, body mass index (BMI) above/below 27 kg/m^2 (self-reported height and weight used due to randomization logistics) and vitamin D status in the Tromsø study (serum 25(OH)D above/below 25 nmol/L). The BMI and 25(OH)D cut-offs were chosen as these were predicted to be the median values of those included. The randomization unit assigned the subject a randomization number using a block randomization procedure. This number was sent to the hospital's pharmacy who did have the randomization key and dispensed the medication accordingly. All others involved in the study, including nurses, doctors and study participants, were blinded throughout the study.

After two months the subjects were contacted by phone by one of the study nurses and asked about adverse events and were reminded to take the study medication. Two months thereafter, the third visit was performed with examinations identical to the first visit. The fourth visit followed a few days later, with return of study medication and examinations identical to the second visit. Compliance was calculated as the ratio between capsules used (capsules supplied minus capsules returned) and number of weeks between second and fourth visit.

The subjects were asked not to take any vitamin D supplements (including cod liver oil) during the four months intervention period.

2.3. Cognitive tests

Verbal recall, coding and tapping tests were performed at baseline and at end of study. The verbal recall test is a test of short-time verbal and visual memory [19]. The subjects are shown 12 nouns each written on a board and pronounced one at a time with 5-s intervals. The participants then had 2 min to recall the words. One point was given for each word correctly recalled.

The coding test (The Digit Symbol-Coding Test) is a part of the Wechsler Adult Intelligence Scale and used to examine psychomotor speed, attention and logical reasoning [22]. The test consists of 4 rows containing 96 small blank squares, each with a randomly assigned number from 1 to 9. A printed key shows which number to pair (code) with a different nonsense symbol. The subjects are asked to consecutively fill in as many as possible of the blank spaces with the corresponding nonsense symbol as quickly and accurately as possible over 90 s. One point was given for each square correctly coded.

The tapping test evaluates mainly psychomotor speed [21]. The subjects were instructed to tap as many times as possible in 10 s with their index finger on a computer, which registered the number of taps. The task was repeated four times with both hands, and the median score for the dominant hand was used in the analyses.

The participants were instructed regarding the cognitive tests by one of the nurses at the Clinical Research unit. All cognitive tests were performed in a silent room with only the tested subject and the nurse administering the test present. For each participant great care was taken to make the testing conditions (room, time of day, study nurse) as identical as possible on the two test occasions.

2.4. Biochemical analyses

Serum calcium and parathyroid hormone (PTH) were analysed as previously described [20]. Serum concentrations of 25(OH)D were measured by an in-house liquid chromatography–tandem mass spectrometry method that detects both 25(OH)D_3 and 25(OH)D_2 and the sum of these presented as 25(OH)D in the results [20].

2.5. Statistical analyses

Normal distribution was evaluated with skewness and kurtosis and visual inspection of histograms and found normal for the cognitive tests. At baseline comparisons between groups were performed with the Student's *t*-test or the chi-square test. Linear trend across serum 25(OH) D groups were evaluated with chi-square test (linear-by-linear association) or linear regression. A linear regression model with gender, age, BMI, serum calcium, serum PTH, serum 25(OH)D, smoking status, recent sunny vacation, BDI-II, education level and month at first visit (with the use of dummy variables) as covariates was used for evaluating predictors of the cognitive test scores. Comparisons between the two groups regarding change from baseline values (values at end of study minus value at baseline, delta values) were performed with a general linear model with gender and randomization status as fixed factors, and age and baseline value as covariates [23]. Interactions between gender, age and randomization status were tested in the same model and were not found significant.

A separate power calculation was not made for the cognitive function tests, and the number of subjects included was the result of power

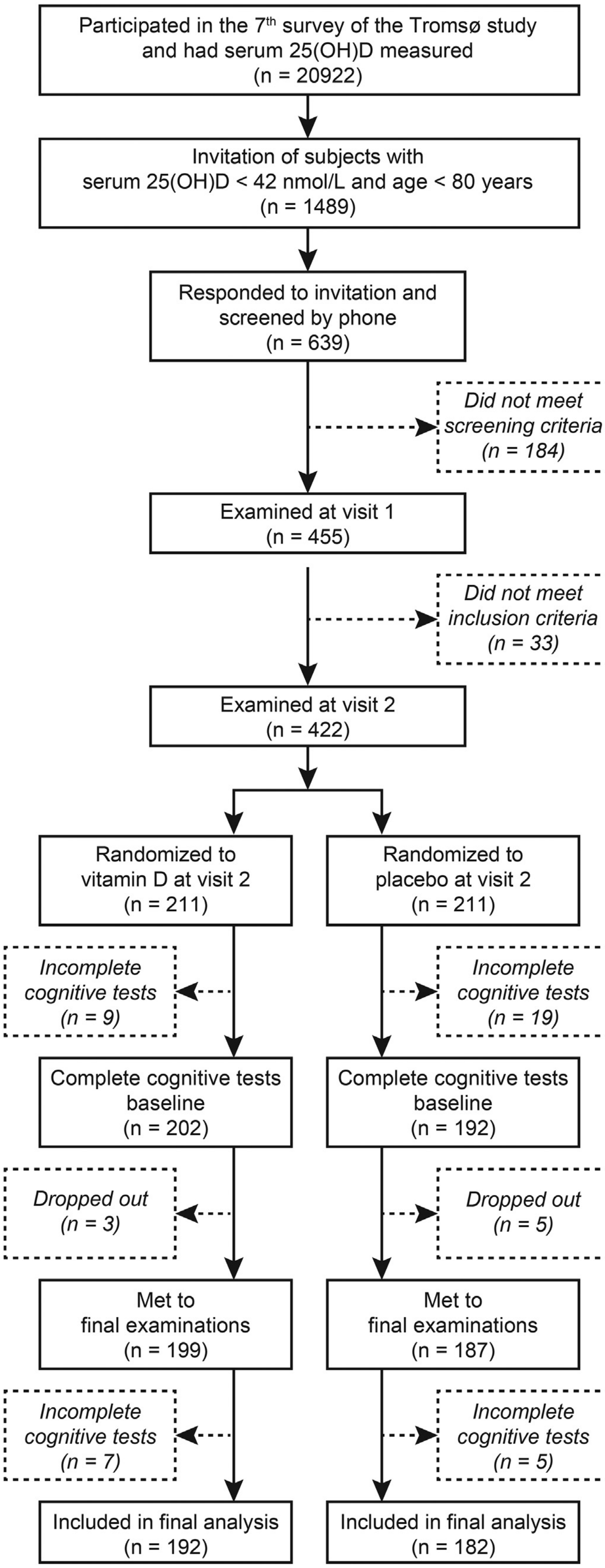

Fig. 1. Flowchart for the inclusion and performance of the study.

calculation for effects on cardiovascular risk factors [17].

$P < .05$ (two-tailed) was considered statically significant. All statistical analyses were performed using IBM SPSS version 22 software. The data are shown as mean ± SD unless otherwise specified.

2.6. Ethics

The study was approved by the Regional Committee for Medical Research Ethics (REK NORD 2013/1464) and by the Norwegian Medicines Agency (2013–003514-40). All subjects gave their written informed consent.

3. Results

The flow of inclusion and performance of the study is shown in Fig. 1. Out of the 639 subjects screened by phone, 455 passed the initial screening criteria and attended the first visit with clinical examination and blood samples. Among these, 422 subjects fulfilled all inclusion criteria and came to the second visit where all three cognitive tests were successfully performed in 394 subjects. These 394 subjects (206 males, 188 women) with mean age 51.8 years and mean serum 25(OH)D 34.0 nmol/L were included in the present analysis. In general, the subjects were healthy, but seven subjects had previous coronary disease (infarction and/or percutaneous coronary intervention (PCI)), ten had previous stroke or TIA, and twenty had been treated for cancer (Table 1).

Females had higher education level than the males and performed significantly better than males on the word recall test and coding tests. Males performed significantly better on the tapping test. Subjects with age < 50 years scored significantly better than those older on all three cognitive tests. Across the serum 25(OH)D groups < 30 nmol/L, 30–50 nmol/L, and > 50 nmol/L, there were a significant decrease in serum PTH and a significant increase in subjects who had recently been on a sunny vacation. The word, coding and tapping test scores were almost identical in the three serum 25(OH)D groups (Table 1).

Predictors of the cognitive test scores were evaluated in linear regression models. For all three tests, age was a significant negative predictor and education level a significant positive predictor. Females scored better on the coding test and males scored better on the tapping test. The serum 25(OH)D level, nor sun exposure (as evaluated by recent sunny vacation), were significant predictors for any of the three cognitive tests (Table 2).

Three hundred and eighty-six subjects with complete cognitive tests at baseline came to the final visit, and among these, 374 subjects successfully performed all cognitive test also at the last visit and were included in the intervention analyses. At baseline, the two groups were almost identical (Table 3). Most of the subjects were included during the autumn and winter months, equally in the two groups (Fig. 2). The compliance rate was high, 14.5% of the subjects had a compliance rate between 84.2 and 100%, and the rest had a compliance rate of 100%. During the intervention, the serum 25(OH)D levels in the vitamin D group ($n = 192$) increased from 32.8 ± 11.2 nmol/L to 88.9 ± 19.1 nmol/L, whereas there was a slight decrease in the placebo group ($n = 182$) from 35.3 ± 13.8 nmol/L to 30.8 ± 9.4 nmol/L. As compared to the placebo group, there was a significant increase in serum calcium and a decrease in serum PTH in the vitamin D group at the end of the intervention. There were no significant differences between the vitamin D and the placebo groups in change in any of three cognitive test scores from baseline to the end of the study (Table 3).

To explore whether there could be effects of vitamin D supplementation depending on sex, age, baseline serum 25(OH)D and cognitive test score levels, subgroup analyses were performed. However, no significant effects on cognitive function by the vitamin D supplementation as compared to placebo were found in males ($n = 198$) or females ($n = 176$) when analysed separately; if including only subjects with age above 50 years ($n = 187$) or above 60 years ($n = 66$); if

Table 1
Baseline characteristics in the subjects with complete cognitive tests at baseline in relation to gender, age and serum 25(OH)D levels.

	All subjects	Gender		Age (years)		Serum 25(OH)D level (nmol/L)		
		Males	Females	< 50	> 49	< 30	30–49	> 49
	n = 394	*n* = 206	*n* = 188	*n* = 199	*n* = 195	*n* = 156	*n* = 193	*n* = 45
Males/females	206/188	206/0	0/188	107/92	99/96	85/71	93/100	28/17
Age (years)	51.8 ± 8.5	51.9 ± 8.7	51.7 ± 8.2	45.0 ± 3.1	58.8 ± 6.4	50.6 ± 8.0	52.7 ± 9.0	52.4 ± 7.9
BMI (kg/m^2)	27.8 ± 4.8	28.2 ± 4.6	27.3 ± 5.0	28.2 ± 5.1	27.4 ± 4.5	27.7 ± 4.9	28.1 ± 4.9	26.7 ± 4.3
Serum calcium (mmol/L)	2.27 ± 0.07	2.28 ± 0.07	2.26 ± 0.08	2.27 ± 0.07	2.28 ± 0.07	2.27 ± 0.07	2.27 ± 0.08	2.28 ± 0.07
Serum PTH (pmol/L)	6.7 ± 2.1	6.6 ± 1.9	7.0 ± 2.2	6.5 ± 2.1	7.0 ± 2.0[c]	7.2 ± 2.2	6.5 ± 2.0	6.1 ± 1.5[e]
Serum 25(OH)D (nmol/L)	34.0 ± 12.8	34.0 ± 13.0	34.0 ± 12.5	33.7 ± 14.3	34.3 ± 11.0	22.7 ± 5.0	37.1 ± 5.4	59.5 ± 9.1
Word recall test (score)	8.9 ± 1.8	8.7 ± 1.9	9.1 ± 1.7[a]	9.2 ± 1.8	8.5 ± 1.7[d]	8.9 ± 1.8	8.8 ± 1.8	9.1 ± 1.9
Coding test (score)	51.1 ± 11.5	47.8 ± 10.8	54.8 ± 11.3[b]	54.6 ± 9.7	47.5 ± 12.2[d]	51.1 ± 11.0	51.1 ± 12.3	51.3 ± 10.2
Tapping test (score)	62.5 ± 8.7	64.3 ± 9.1	60.5 ± 7.9[b]	65.3 ± 8.5	59.6 ± 8.1[d]	62.7 ± 8.9	62.3 ± 8.8	62.6 ± 8.2
BDI-II score	5.1 ± 5.4	5.1 ± 4.9	6.0 ± 5.9	5.5 ± 5.5	5.8 ± 5.3	5.6 ± 5.2	5.6 ± 5.6	4.3 ± 5.1
Previous coronary infarction and/or PCI (%)	1.8	2.0	1.6	0	3.6	0	2.1	6.6
Previous stroke or TIA (%)	2.5	3.4	1.6	0.5	4.6	3.2	2.6	0
Previous cancer (%)	5.1	4.4	5.9	3.0	7.2	3.8	7.3	0
Education (%)* (primary/secondary/university)	20/29/50	21/35/44	19/24/57[b]	17/31/52	24/28/48	21/33/46	18/27/54	24/27/48
Current smoker (%)	22.1	22.3	21.8	20.6	23.6	28.2	18.1	17.8
Sunny vacation last 3 months (%)	12.2	10.7	13.8	10.6	13.8	4.5	12.4	37.8[e]
Solarium last 3 months (%)	2.0	0	4.3	1.0	3.1	1.3	3.1	0

Abbreviations: BDI, Beck depression inventory; BMI, body mass index; PCI, percutaneous coronary intervention; PTH, parathyroid hormone; TIA, transitory ischemic attach; 25(OH)D, 25-hydroxyvitamin D.
[a] $P < .05$,
[b] $P < .001$ (vs males, Student's *t*-test or chi-quare test).
[c] $P < .01$,
[d] P < .001 (vs age < 50 years, Student's t-test).
[e] P < .001 (trend across 25(OH)D groups, chi-square test or linear regression).
* Education: Primary school up to ten years; Secondary school, additional three years; University or college education.

including only subjects with baseline serum 25(OH)D below 50 nmol/L ($n = 330$) or below 30 nmol/L ($n = 148$); if only including subjects with 100% compliance ($n = 320$) or if correlating change in cognitive scores versus change in serum 25(OH)D; nor if including only subjects who at baseline had a cognitive test score in the lower half of the subjects included ($n \sim 187$) (tested for each of the separate three tests) (data not shown).

Furthermore, if analysing those with cognitive function scores in the lower half of those included combined with serum 25(OH)D < 50 nmol/L or < 30 nmol/L, there still was no significant improvement in cognitive function scores in the vitamin D versus the placebo group (Table 4).

No serious side effects were recorded. Two subjects developed hypercalcemia (both had serum calcium = 2.57 mmol/L); one male whose serum calcium normalized upon retesting, and one female who were found to have developed primary hyperparathyroidism.

4. Discussion

In the present study we did not find a cross-sectional association between vitamin D status and cognition, nor did vitamin D supplementation improve any of the cognitive test scores even when restricting the analysis to those with vitamin D insufficiently (serum 25(OH)D < 50 nmol/L) or deficiency (serum 25(OH)D < 30 nmol/L) combined with a cognitive score in the lower half of those studied.

Our study mainly included subjects with low serum 25(OH)D levels and was therefore not designed to show cross-sectional relations. However, the association between vitamin D status and cognition has been shown convincingly in studies with an epidemiological design. Thus, in a previous study from Tromsø that included 4624 subjects, a high serum 25(OH)D level was significantly associated with better word recall, digit-symbol coding, finger tapping and Mini Mental State Examination, particularly in the elderly [7]. The participants in the upper quartile of serum 25(OH)D levels had approximately 5% better performance than those in the lower quartile. Furthermore, it was

Table 2
Standardized beta-coefficients in regression models with cognitive tests as dependent variables at baseline ($n = 394$)

	Word test score	Coding test score	Tapping test score
Age (years)	−0.253[b]	−0.392[b]	−0.358[b]
Gender (males = 1, females = 0)	−0.061	−0.249[b]	0.242[b]
BMI (kg/m^2)	−0.074	−0.096[a]	0.104[a]
Serum calcium (mmol/L)	0.046	−0.018	−0.061
Serum PTH (pmol/L)	0.082	0.054	−0.017
Serum 25(OH)D (nmol/L)	0.062	0.051	−0.007
Education (scale 1–3, 1 = lowest, 3 = highest)	0.241[b]	0.282[b]	0.115[a]
Current smoker (yes = 1, no = 0)	−0.003	−0.035	−0.049
Sunny vacation last 3 months (yes = 1, no = 0)	−0.078	0.013	0.062
BDI-II (score)	−0.029	−0.084	−0.019
Adjusted R^2	0.158	0.374	0.245

Abbreviations: BDI, Beck depression inventory; BMI, body mass index; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.
[a] $P < .05$;
[b] $P < .001$;

Table 3
Characteristics of the subjects in the vitamin D and placebo groups who had complete cognitive tests both at baseline and at end of study.

	Baseline		End of study		Change from baseline*	
	Vitamin D group	Placebo group	Vitamin D group	Placebo group	Vitamin D group	Placebo group
Males/females	101/91	97/85	101/91	97/85	101/91	97/85
Age (years)	51.1 ± 8.3	52.5 ± 8.5				
BMI (kg/m^2)	27.9 ± 5.0	27.8 ± 4.6	28.0 ± 5.1	27.9 ± 4.7	0.2 ± 0.7	0.1 ± 0.7
Serum calcium (mmol/L)	2.27 ± 0.07	2.27 ± 0.07	2.28 ± 0.08	2.27 ± 0.08	0.01 ± 0.06[a]	−0.00 ± 0.06
Serum PTH (pmol/L)	6.7 ± 2.2	6.8 ± 1.9	5.9 ± 1.9	7.4 ± 2.2	−0.8 ± 1.4[b]	0.5 ± 1.5
Serum 25(OH)D (nmol/L)	32.8 ± 11.2	35.3 ± 13.8	88.9 ± 19.1	30.8 ± 9.4	56.1 ± 22.2[b]	−4.5 ± 13.1
Word test (score)	8.8 ± 1.9	8.9 ± 1.8	9.4 ± 1.7	9.3 ± 1.8	0.6 ± 1.6	0.4 ± 1.6
Coding test (score)	51.0 ± 11.2	51.0 ± 11.9	53.7 ± 11.3	53.4 ± 12.5	2.6 ± 5.1	2.3 ± 5.8
Tapping test (score)	61.9 ± 8.2	63.3 ± 9.1	62.9 ± 7.8	64.0 ± 10.0	1.2 ± 4.1	0.6 ± 5.1
Previous coronary infarction and/or PCI (%)	2.1	1.6				
Previous stroke or TIA (%)	1.6	3.8				
Previous cancer (%)	5.7	4.9				
Education (%)** (primary/secondary/university)	19/30/50	22/28/50				
Current smoker (%)	21.4	22.0				
Sunny vacation last 3 months (%)	11.5	14.3				
Solarium last 3 months (%)	2.6	1.6				
BDI-II score	5.4 ± 5.2	5.6 ± 5.6				

Abbreviations: BDI, Beck depression inventory; BMI, body mass index; PCI, percutaneous coronary intervention; PTH, parathyroid hormone; TIA, transitory ischemic attach; 25(OH)D, 25-hydroxyvitamin D.
[a] $P < .05$.
[b] $P < .001$ versus placebo group; linear regression with adjustment for baseline value, age and gender.
* Value at end of study minus value at baseline.
** Education: Primary school up to ten years; Secondary school, additional three years; University or college education.

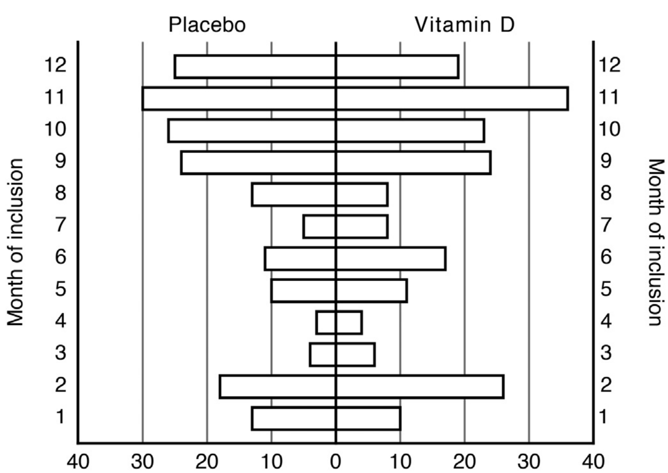

Fig. 2. Number of subjects in the vitamin D and placebo groups in relation to month of inclusion (1 = January, 2 = February, etc).

found that the serum 25(OH)D level significantly predicted cognitive function 7–13 years later [7]. Similarly, van Schoor et al. found a significant association between serum 25(OH)D levels below 30 nmol/L and reduced cognitive function in 1320 elderly subjects [9], while Miller et al. found low vitamin D status associated with accelerated cognitive decline in a group of 381 older subjects [10]. These and other observational studies have been summarized in numerous review papers including > 26 studies with > 20,000 subjects, and all conclude that low serum 25(OH)D levels are associated with lower cognitive function, and that more intervention studies are needed [24–26].

The finding of an association between vitamin D and cognition is biologically plausible given the already mentioned presence of the VDR and vitamin D activating enzymes in the brain [4–6]. Furthermore, in animal studies vitamin D appears to slow down decline in cognitive function in rats and mice under various experimental conditions [27–31]. However, in the few proper RCTs where the effect of vitamin D on cognitive function has been tested, it has been difficult to show a positive effect. Thus, Dean et al. included 128 healthy young subjects (mean age 22 years) that were randomized to vitamin D 5000 IU per day versus placebo for six weeks. No effects on working memory, response inhibition, or cognitive flexibility were found which could be due to the high mean serum 25(OH)D level of 76 nmol/L at baseline [12]. In the Women's Health Initiative, development of cognitive impairment was followed in 4143 women with mean age 70 years, randomized to 1000 mg calcium carbonate plus 400 IU vitamin D daily versus placebo. During a mean observation period of 7.8 years, there was no difference between the groups regarding the main endpoint, development of cognitive impairment [15]. Serum 25(OH)D was only measured in a subgroup of 293 subjects who had a mean level of ∼ 50 nmol/L. In a subset of 1420 subjects, annual assessments were performed for domain-specific cognitive functions, but no significant differences between the two groups were found [15].

To our knowledge an effect of vitamin D supplementation has only been seen in one study, and in that study the subjects had low serum 25(OH)D levels at baseline. Thus, Dhesi et al. compared the effects of a single intramuscular injection of 600,000 IU ergocalciferol (vitamin D_2) vs placebo in 139 subjects with a history of falls. The subjects had a mean age of 77 years and a mean serum 25(OH)D level of 25 nmol/L at baseline. Compared to the placebo group, those given the vitamin D injection had after six months a significant improvement in psychomotor performance as evaluated by choice reaction time [13].

In our study we were not able to demonstrate a significant effect on any of the three cognitive test used, even in subgroups based on sex, age, serum 25(OH)D level or cognitive function level at baseline. Furthermore, Mendelian randomization studies do not support an effect of the serum 25(OH)D level on cognition. Based on risk alleles for low serum 25(OH)D synthesis, Maddock et al. formed a 25(OH)D synthesis score from single nucleotide polymorphisms (SNPs) related to the *DHCR7* and *CYP2R1* genes in 172,349 participants. However, no relation between this score and cognitive function was found, even though subjects with the highest synthesis score had approximately 9% lower serum 25(OH)D levels than those with none of the risk alleles [32]. However, in a study on 1024 Afro-Americans followed for a mean period of 4.4 years, SNPs related to the vitamin D receptor (*VDR*) and the *Megalin* gene (multifunctional endocytic receptor) were associated with age-related cognitive decline, which may support a role for vitamin D in this process [33].

Table 4
Characteristics of the subjects in the vitamin D and placebo groups who had complete cognitive tests both at baseline and at end of study and who had cognitive test score in the lower half for each test and with baseline serum 25(OH)D < 50 nmol/L or < 30 nmol/L.

	Baseline		End of study		Change from baseline*	
	Vitamin D group	Placebo group	Vitamin D group	Placebo group	Vitamin D group	Placebo group
Word test score < 9 and serum 25(OH)D < 50 nmol/L						
N	75	67	75	67	75	67
Serum 25(OH)D (nmol/L)	31.6 ± 8.9	30.1 ± 8.4	91.5 ± 20.1	28.9 ± 8.4	60.0 ± 21.7[a]	−1.2 ± 8.8
Word test score	7.0 ± 0.9	7.2 ± 0.9	8.4 ± 1.5	8.4 ± 1.8	1.4 ± 1.6	1.2 ± 1.5
Word test score < 9 and serum 25(OH)D < 30 nmol/L						
N	31	30	31	30	31	30
Serum 25(OH)D (nmol/L)	23.2 ± 5.0	22.6 ± 4.6	94.8 ± 23.0	25.4 ± 7.4	71.6 ± 20.9[a]	2.9 ± 7.4
Word test score	7.1 ± 1.0	7.1 ± 1.0	8.5 ± 1.2	8.2 ± 1.6	1.5 ± 1.4	1.1 ± 1.5
Coding test score < 52 and serum 25(OH)D < 50 nmol/L						
N	89	73	89	73	89	73
Serum 25(OH)D (nmol/L)	31.1 ± 9.3	30.1 ± 7.9	87.3 ± 19.0	27.6 ± 7.6	56.3 ± 21.1[a]	−2.5 ± 8.6
Coding test score	42.1 ± 7.4	41.1 ± 8.4	45.6 ± 8.4	43.9 ± 9.8	3.5 ± 4.9	2.9 ± 6.1
Coding test score < 52 and serum 25(OH)D < 30 nmol/L						
N	34	34	34	34	34	34
Serum 25(OH)D (nmol/L)	21.6 ± 5.8	23.3 ± 4.5	89.9 ± 21.9	24.5 ± 8.2	68.2 ± 20.9[a]	1.2 ± 8.4
Coding test score	42.6 ± 6.1	41.3 ± 8.0	46.4 ± 5.9	44.4 ± 8.9	3.8 ± 4.7	3.1 ± 5.8
Tapping test score < 62.3 and serum 25(OH)D < 50 nmol/L						
N	93	69	93	69	93	69
Serum 25(OH)D (nmol/L)	31.3 ± 8.6	30.8 ± 8.5	89.6 ± 20.9	27.9 ± 8.1	58.3 ± 22.3[a]	−2.9 ± 8.1
Tapping test score	56.0 ± 5.1	55.5 ± 4.6	58.1 ± 4.9	56.4 ± 6.2	2.2 ± 4.1	0.9 ± 3.6
Tapping test score < 62.3 and serum 25(OH)D < 30 nmol/L						
N	39	30	39	30	39	30
Serum 25(OH)D (nmol/L)	23.1 ± 4.5	23.0 ± 4.9	91.2 ± 22.7	23.7 ± 6.9	68.2 ± 21.0[a]	0.7 ± 6.7
Tapping test score	56.4 ± 3.6	55.3 ± 4.8	57.5 ± 3.7	56.0 ± 6.7	1.1 ± 3.0	0.8 ± 3.5

Abbreviations: 25(OH)D, 25-hydroxyvitamin D.
[a] $P < 0.001$versus placebo group (linear regression with adjustment for baseline value, age and gender).
* Value at end of study minus value at baseline.

Our study has several shortcomings. The subjects were followed for a short period of time, and it is likely that a longer lasting study in older subjects at risk of cognitive decline would have been better for showing a preventive effect. We did not record sun exposure except for sunny vacations, we did not have data on diet pre- and post-intervention, and except for education level, we did not have information on socio-economic factors. Vitamin D was given in weekly doses while daily doses might be more efficient [34]. We only used three cognitive tests, which examined only a few cognitive domains. Had we included more tests, a composite cognitive test score could have been made, which might have been better suited for picking up minor changes. Although we included a large number of vitamin D insufficient subjects (serum 25(OH) D < 50 nmol/L), only 148 subjects were truly vitamin D deficient (serum 25(OH)D < 30 nmol/L) [11]. We therefore cannot rule out that the study was underpowered and that subtle effects were missed.

On the other hand, our study do have strengths as the vitamin D dose increased the serum 25(OH)D to sufficient levels, the effects on serum calcium and PTH were as expected giving the study internal validity, the study was performed at a clinical research unit with strict adherences to good clinical practice rules, and the compliance rate was high.

In conclusion, we did not find a positive effect by vitamin D supplementation on cognitive function even in vitamin D deficient subjects. We therefore believe that to show an effect of vitamin D on cognitive function (if there is one), one would have to include a much larger group of subjects with more severe vitamin D deficiency and at a higher risk of cognitive decline, and preferably use a battery of tests to create a composite cognitive test score. Regardless of other potential benefits, such subjects should be given vitamin D supplementation for maintaining bone health. Randomization to placebo for a longer period of time, which probably is needed to show an effect on cognitive function, could therefore be ethically questionable.

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Disclosure statement

The authors have nothing to disclose.

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