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HIGHER VITAMIN D LEVELS ARE ASSOCIATED WITH BETTER ATTENTIONAL FUNCTIONS: DATA FROM THE NORCOG REGISTER

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Abstract: *Objectives:* The aim of this cross-sectional study was to evaluate which cognitive domains are mostly affected in persons with vitamin D insufficiency or deficiency, defined as 25(OH)D < 50 nmol/l and < 25 nmol/l, respectively. *Methods*: Data were collected from the Norwegian register for persons assessed for cognitive symptoms (NorCog). 580 persons aged ≥ 65 years were included. The following cognitive and neuropsychiatric tests were used: Mini Mental State Examination, Norwegian Revised Version (MMSE-NR), the Clock Drawing test, the Trail Making Test A and B, the 10-word memory test and the figure copying test from CERAD – immediate and delayed recall, The Controlled Oral Word Association Test -FAS and Boston Naming test. Neuropsychiatric symptoms were assessed by Neuropsychiatric Inventory–Questionnaire and Cornell Scale for Depression in Dementia. *Results*: Vitamin D-insufficiency was found in approx. 30 % of the study cohort. After adjustment for relevant covariates, higher serum 25(OH)D levels were associated with higher score on MMSE-NR (p=0.032) and 10-word Memory Test, immediate recall (p=0.038), as well as faster execution of Trail Making Test A and B (p=0.038 and p=0.021, respectively). Other tests were not significantly associated with 25(OH)D levels. *Conclusion:* Higher vitamin D levels appear to be associated with better cognition, especially in areas of executive function and mental flexibility.

Key words: Vitamin D, executive function, dementia, neurocognitive function.

Introduction

Although classified as a vitamin in the early 20th century, vitamin D is a group of steroid-like hormones. The major circulating form, 25(OH)D, is produced in the human skin from its precursor 7-dehydrocholesterol in the presence of sunlight and is a useful indicator of an individual's vitamin D-status because of its long half-life (1). Older people are at risk of developing low vitamin D values due to several factors, such as reduced skin thickness, less exposure to sunlight and decreased dietary intake of vitamin D (2). The current guidelines on vitamin D supplementation are based on levels needed to avoid rickets and osteomalacia, indirectly measured by the amount needed to suppress parathyroid hormone (PTH) (3). During the last decade, there has been an increased focus on the biological actions of vitamin D apart from the known effects on calcium and phosphate homeostasis (4). Part of this is driven by the discovery of the vitamin D receptor (VDR) in nearly every tissue in the human body, including the brain, especially in the areas affected by the neurodegenerative disorders (5), especially the hippocampus (6). Several animal studies have shown an association between higher levels of vitamin D and better performance on memory tasks and decrease in age-related amyloid burden (7-13), raising the question of whether vitamin D might be an important factor in preventing the development of dementia. This possibility is supported by findings that mutations in the VDR-gene correlate with development of Alzheimer's disease (14, 15).

Human cross-sectional and longitudinal studies have indicated a positive relationship between vitamin D deficiency and cognitive dysfunction or deterioration, depressive symptoms, lower amyloid-ß in cerebrospinal fluid (CSF), central brain atrophy and white matter lesions in older persons (16-19). Executive functions seem to be more affected than memory (20-22). Some of the studies found a consistent relationship between vitamin D status and performance on verbal fluency (23), as well as a slower rate of decline in the domain of verbal fluency (24). However, other studies have failed to show a consistent relationship between vitamin D and cognitive impairment (25-27). Intervention studies have been sparse (28), and shown conflicting results (29). The study limitations of cross-sectional, longitudinal and intervention studies have been small sample sizes, inclusion of patients with advanced dementia, use of divergent cognitive tests, reliance on medical record notes instead of a comprehensive diagnostic work-up, use of various vitamin D assays and inconsistent control for cofounders (26).

Vitamin D status is customarily measured as 25(OH)D in serum (which represents total concentration of both 25(OH) D2 and 25(OH)D3), considered the best indicator of vitamin D from both cutaneous synthesis and nutritional intake. The definition of adequate vitamin D status is still controversial.

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Vitamin D deficiency is traditionally defined as 25(OH)D < 25 nmol/l, based on the levels needed to prevent rickets (30). In 2003, the World Health Organization (WHO) defined vitamin D insufficiency as 25(OH)D < 50 nmol/l, based on the levels needed to prevent osteoporosis (31). In 2011, the Institute of Medicine recommended levels > 50 nmol/l for optimal bone health (32). Optimal vitamin D levels for extraskeletal functions, including brain health, are under discussion. Several expert groups recommend defining vitamin D insufficiency as 25(OH)D < 75 nmol/l and deficiency as < 50 nmol/l (30, 33). Circulating 25(OH)D concentrations vary substantially over the year (highest at the end of summer and lowest at the end of winter). Previous studies have shown marked seasonal variations in 25(OH)D (34), but relatively small variations at the same time of measurement after one year (35), indicating relatively stable values over time.

Vitamin D deficiency and insufficiency are considered to be a global health problem in all age groups (36), with old persons being at the highest risk (37). Previous Norwegian data from the population-based Oslo Health Study, 2000-2001, showed that home-dwelling elderly had as good vitamin D status as younger individuals (38) and higher levels of vitamin D than elderly persons in southern latitudes in Europe (39, 40). Another study of 73 patients with AD and 63 cognitively intact age-matched controls also found levels of mean vitamin D > 60 nmol/l in all groups (40). This is assumed to be due to high intake of fish and fish oil (41). Newer data of vitamin D status in a larger population of the elderly in Oslo and surrounding areas are lacking.

The aim of this cross-sectional study was to evaluate which cognitive domain is most affected in persons with vitamin D deficiency or insufficiency in a well-characterized cohort of elderly (≥ 65 years) persons presenting with cognitive symptoms.

Methods

Subjects

Data were collected from the Norwegian register for persons assessed for cognitive symptoms (NorCog). NorCog is a national quality and research register (42) that involves home-dwelling persons who are referred to a specialist for examination of cognitive symptoms and have the competence to consent. The register includes persons with both subjective cognitive impairment (SCI), mild cognitive impairment (MCI) and dementia. Registered data consist of, among others, age, sex, education (in years), comorbidity, prescribed medication, cognitive test performance in several domains, screening for depression and other neuropsychiatric symptoms, as well as clinical examination, radiological imaging, laboratory tests and clinical diagnosis.

The present study included persons registered in NorCog between 2011 and 2017 in 3 memory clinics: Oslo University Hospital, Ullevål, Diakonhjemmet Hospital and Lovisenberg Diaconal Hospital. The patients referred to these memory clinics are mostly from Oslo or the surrounding areas (South-Eastern region of Norway). As NorCog does not include patients not fluent in Norwegian language (defined as consultations with use of interpreter) because of use of alternative test batteries, nearly all the patients in the cohort are ethnic Norwegian. Inclusion criteria for the present study were age ≥ 65 years and available serum level of 25(OH)D for persons in the register. In total, 580 persons were included.

Measurements/ Assessment

25-hydroxyvitamin D

For the purpose of this study, vitamin D insufficiency was defined as 25(OH)D < 50 nmol/l and vitamin D deficiency as 25(OH)D < 25 nmol/l. 25(OH)D serum analysis was performed in all included persons. 460 out of 580 samples were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (reference level 50-150 nmol/l), which is considered the gold standard assay for the measurement of 25(OH)D (43, 44). The remaining 120 samples were analyzed using the Cobas 6000 Vitamin D assay (Roche) (reference level 45-161 nmol/l), an immunoassay. The two assays show acceptable agreement in comparison studies (45), but there is a certain analytical variability among methods, especially at very high and very low levels (45, 46).

Cognitive and neuropsychiatric assessments

Participants in the register were comprehensively assessed with several cognitive and neuropsychiatric tests according to a standardized protocol for evaluation of cognitive impairment and dementia in memory clinics in Norway. The following cognitive and neuropsychiatric tests were included: Mini Mental State Examination - Norwegian Revised Version, MMSE-NR (episodic and semantic memory, orientation, executive function, attention, language and visuospatial ability) (47), the Clock Drawing Test (visuospatial ability and executive functions) (47), the Trail Making Test A (attention, visual search and motor function) (47), the Trail Making Test B (processing speed, executive function, visual search and motor function) (48), the 10-word Memory Test and the Figure Copying Test from CERAD – immediate and delayed recall (verbal and visual memory) (49), the Controlled Oral Word Association Test (COWA)-FAS Phonemic Verbal Fluency Test (language and executive function) (50) and the Boston Naming Test (confrontation naming/language) (51). Neuropsychiatric symptoms were assessed by interview with caregiver informants using the Neuropsychiatric Inventory–Questionnaire (NPI-Q) and the Cornell Scale for Depression in Dementia (CSDD). The CSDD rates depressive symptoms and signs occurring during the week prior to the interview. The NPI-Q reviews 12 neuropsychiatric domains (present or absent within the last month) with severity of symptoms graded from 1 to 3. In this study, we dichotomized the results, including the number of symptoms present (0-12), not the severity.

Table 1
Cognitive tests and informant-based interviews included in the analysis

Test name	Scoring
MMSE-NR[1]	0-30 points
Clock Drawing Test (CDR)	0-5 points
Trail Making Test A (TMT-A)	Measured in seconds
Trail Making Test B (TMT-B)	Measured in seconds[2]
Boston Naming Test	0-15 points
10-word Memory Test from CERAD[3]	Age and education dependent result
Figure Copying Test from CERAD[3]	0-11 points
COWA[4] FAS Phonemic Verbal Fluency Test	Age, sex and education dependent result
Neuropsychiatric Inventory (NPI-Q),	0-12; number of symptoms (present=1 or absent=0)
Cornell Scale for Depression in Dementia (CSDD).	0-38; 19 symptoms graded as not present =0, moderate=1, severe=2.

1. MMSE-NR = Mini Mental State Examination - Norwegian Revised Version; 2. Scored as 300 seconds if not completed in < 300 seconds; 3. CERAD = tests from the Consortium to Establish a Registry for Alzheimer's Disease; 4. COWA = Controlled Oral Word Association

Table 2
Descriptive characteristics of the study sample

Characteristic	Missing data N (%)	N (%)	Mean (SD)
Age, mean (SD)	0 (0)		76.6 (7.3)
Sex (women)	0 (0)	322 (55.5)	
Education (years)	58 (10)		12.4 (3.8)
BMI	96 (16.5)		24.7 (4.4)
Smoking (ever smoked)	58 (10.0)	314 (60.2)	
Alcohol consumption (moderate-high)[1]	78 (13.4)	87 (16.7)	
Cerebrovascular disease	59 (10.2)	116 (22.3)	
Cardiovascular disease (including hypertension)	54 (9.3)	314 (59.7)	
Diabetes	24 (4.1)	75 (13.5)	
Serum 25(OH)D in nmol/l	0 (0)		63.4 (25.0)
Vitamin D supplementation[2]	0 (0)	57 (9.8)	
MMS-NR (points)	30 (5.1)		24.1 (4.3)
Clock Drawing Test (points)	33 (5.7)		3.5 (1.5)
Trail Making Test A (seconds)	31 (5.3)		92.5 (70.5)
Trail Making Test B[3]	60 (10.3)		231.6 (92.6)
Boston Naming Test (points)	147 (25.3)		11.0 (3.2)
10-word Memory Test - Immediate	58 (10.0)		12.4 (4.9)
10-word Memory Test - Delayed	62 (10.7)		2.3 (2.4)
Figure Copying Test – Immediate	112 (19.3)		9.3 (1.9)
Figure Copying Test - Delayed	277 (39.1)		4.0 (3.7)
COWA – FAS	165 (28.4)		29.1 (14.1)
CSDD total score	201 (34.6)		6.8 (5.6)
NPI-Q, number of symptoms	124 (21.3)		3.3 (2.6)

1. Consume 4 or more units per week. Also includes former alcohol abuse; 2. Prescribed or patient reported; 3. Tests not finished within 300 seconds are scored as 300 seconds

The range of scores for each cognitive test is shown in Table 1. All participants were diagnosed according to the ICD-10 criteria for dementia and subtype, or to the Winblad criteria for MCI (52).

Analysis

Sample characteristics were presented as means and standard deviations (SD) or frequencies and percentages. As recruitment was performed at three memory clinics, data might exhibit hierarchical structure. The 25(OH)D levels in serum, adjusted for seasonal variations, were compared across diagnostic groups using linear mixed models with fixed effects for diagnostic group. To assess the association between the cognitive test results and 25(OH)D levels in serum, a linear mixed model was estimated for each of the 12 included tests (MMSE-NR, Clock Drawing Test, Trail Making Tests A and B, Boston Naming Test, 10-Word Memory Tests (immediate and delayed recall), Figure Copying Tests (immediate and delayed recall), FAS, NPI-Q and CSDD). The models contained fixed effects for 25(OH)D levels in serum unadjusted for seasonal variations, as the cognitive tests were performed within a month of blood draw. Random intercepts for clinic were included in all models to correctly adjust the results for within-clinic correlations. First, unadjusted models were estimated. The models were then adjusted for pre-defined confounders (sex, age, education (years), vascular burden (including cerebrovascular disease, coronary disease and high blood pressure), BMI, smoking (never smoker, former smoker, current smoker), and alcohol use (less that once a year, maximum 3 units per week, 4 units per week or more). Due to different laboratory methods, the models were also adjusted for 25(OH)D assay type. All regression models were estimated on subsamples of persons with no missing values on the covariates. Statistical analyses were performed in SPSS version 25 and SAS version 9.4. Results with p-values < 0.05 were considered statistically significant. No adjustment for multiple testing was implemented.

Ethics

The study was approved by The Regional Committee for Medical and Health Research Ethics (reference 2016/888/REK sør-øst C). All included participants had given valid written consent for inclusion in the NorCog register.

Results

Table 2 shows the demographic characteristics of the study group.

The sample included a total of 580 persons ≥ 65 years of age, 322 (55.5 %) of them women. Mean age was 76.6 years (SD 7.3). The distribution of diagnoses in the sample was as follows: Subjective cognitive impairment (SCI), n=45 (7.8 %); Mild cognitive impairment (MCI), n=226 (39.4 %); Alzheimer´s disease (AD) and mixed dementia with AD pathology, n=202 (35.2 %); Vascular dementia, n=21 (3.7 %), Other dementia types, n=62 (10.8 %), Depression, n=5 (0.9 %); and Other diagnoses, n=13 (2.3 %).

Mean serum-25(OH)D was 63.4 nmol/l (SD 25.0), ranging from 11 to 164 nmol/l. Only 4.1 % of the study population was found to be vitamin D deficient (defined as 25(OH)D < 25 nmol/l). Vitamin D insufficiency (defined as 25(OH) D < 50 nmol/l) was found in 30.7 % of the study sample. Pharmacological therapy containing vitamin D (with or without calcium) was reported by 9.6 % of the sample.

There was no significant difference in the prevalence of vitamin D deficiency between persons with SCI, MCI and dementia (Table 3).

Table 3

Linear mixed models assessing differences between diagnostic groups in seasonally-adjusted 25(OH)D in serum

Diagnosis	Mean difference[1] (95 % CI)	p-value
Subjective cognitive impairment (SCI)	4.21 (-3.87; 12.29)	0.306
Mild cognitive impairment (MCI)	2.03 (-2.55; 69.62)	0.383
Dementia	reference	-

1. Mean difference between SCI/MCI and Dementia (reference category in linear mixed models)

As shown in Table 2, not all outcome variables were available for all subjects. The regression analyses were performed on individuals with no missing covariates.

Results of the linear mixed models are presented in Table 4.

In the bivariate analyses, higher serum 25(OH)D levels were associated with higher MMSE-NR scores (p=0.048), higher Figure Copying Test scores, better immediate and delayed recall (p=0.042 and p=0.026, respectively), and faster execution of Trail Making Test B (p=0.024). After adjustment for relevant covariates (including age, sex and education), higher serum 25(OH)D levels were associated with higher scores on the MMSE-NR (p=0.032) and 10-word Memory Test, immediate recall (p=0.038), and faster execution of Trail Making Tests A and B (p=0.038 and p=0.021, respectively), while Figure Copying Tests were no longer significantly associated with 25(OH)D levels.

Discussion

In this cross-sectional study, we examined the association between the results of cognitive test scores and 25(OH)D in serum in a cohort of persons with cognitive symptoms. All persons in the cohort were ≥65 years. The catchment area for the three hospitals consisted primarily of persons living in Oslo and the surrounding counties (latitude of approximately 60 degrees north). Nearly half of the study population (49.7 %) had dementia. The prevalence of vitamin D-deficiency in this group was low, but vitamin D insufficiency (defined as 25(OH)D < 50 nmol/l) was found in approximately 30 % of

Table 4

Associations between 25(OH)D in serum and tests of cognitive function and neuropsychiatric symptoms assessed through bivariate and multiple linear mixed models. The models were estimated for patients with no missing values on covariates. Due to varying number of missing values for each outcome variable, sample sizes were different in each model

Outcome variables	Bivariate model		Multivariable model [1]	
	Regression coefficient (95 % CI)	p-value	Regression coefficient (95 % CI)	p-value
Tests of cognitive function				
MMSE-NR (N=386)	0.02 (0.0002; 0.03)	0.048	0.02 (0.002; 0.04)	0.032
Clock Drawing Test (N=385)	0.002 (-0.004; 0.008)	0.601	0.002 (-0.004; 0.009)	0.462
TMT-A (N=378)	-0.26 (-0.54; 0.02)	0.067	-0.31 (-0.60; -0.02)	0.038
TMT-B (N=360)	-0.39 (-0.72; -0.05)	0.024	-0.39 (-0.73; -0.06)	0.021
10-word Memory Test - Immediate Recall (N=372)	0.02 (-0.003; 0.04)	0.094	0.02 (0.001; 0.04)	0.038
10-word Memory Test -Delayed Recall (N=370)	0.003 (-0.006; 0.01)	0.490	0.006 (-0.005; 0.02)	0.284
Figure Copying Test - Immediate Recall (N=334)	0.009 (0.0003; 0.02)	0.042	0.007 (-0.001; 0.02)	0.097
Figure Copying Test- Delayed Recall (N=257)	0.02 (0.003; 0.04)	0.026	0.02 (-0.001; 0.04)	0.066
COWA FAS Fluency Test (N=285)	0.05 (-0.009; 0.12)	0.093	0.04 (-0.02; 0.10)	0.169
Boston Naming Test (N=308)	-0.005 (-0.02; 0.009)	0.487	-0.005 (-0.02; 0.008)	0.448
Neuropsychiatric symptoms				
CSDD (N=273)	0.02 (-0.01; 0.04)	0.229	0.01 (-0.02; 0.04)	0.399
NPI-Q: number of symptoms (N=318)	0.002 (-0.009; 0.01)	0.719	0.002 (-0.01; 0.01)	0.768

1. Multivariable model is adjusted for sex, age, education, BMI, smoking, alcohol consumption, cerebrovascular disease, diabetes, hypertension and vitamin D-assay.

the study cohort. If the definition of vitamin D insufficiency as 25(OH)D < 75 nmol/l were to be used, 71.5 % of the study sample would be considered vitamin D insufficient. Vitamin D deficiency was equally prevalent in patients with and without dementia. The results of this study show lower prevalence of vitamin D insufficiency than previously reported in Norwegian populations of elderly persons (53). The possible explanation for this discrepancy might be a lower latitude, different population cohort, as well as the increased awareness of possible consequences of vitamin D deficiency both among doctors and the general population and increased use of diagnostic measures and supplements. Although less than 10 % of persons were recorded as using vitamin D supplements in this sample, the number is presumably somewhat higher as some persons do not report using over the counter supplements and 10-15 % of elderly in Norway regularly consume cod liver oil (54).

Our results show an association between vitamin D levels in serum (measured by 25(OH)D within 1 month of testing) and cognitive performance in several domains, assessed by standardized tests of cognitive function. Higher levels of vitamin D in serum were significantly associated with higher test scores on the MMSE-NR and 10-word Memory Test, immediate recall, as well as faster execution of Trail Making Tests A and B. The MMSE-NR is a frequently used screening tool that assesses several areas of cognition: concentration, working memory, attention, language and praxis, time and space orientation and memory, but contains no specific measurement of executive function. Trail Making Tests on the other hand are more specific tests that primarily evaluate executive function. In this study, higher levels of vitamin D in serum were also significantly associated with higher scores on the immediate recall part of the 10-word Memory Test (assessing concentration and verbal memory), but the association was not significant with the delayed recall portion of the test (mainly assessing memory). This supports our hypothesis that vitamin D is associated with attention and other areas of executive function more than memory. One explanation for these findings is possible non-genomic and genomic (through VDR) effects of vitamin D on the brain, especially in the areas affected by the neurodegenerative disorders (5), through among others, regulation of inflammation, calcium homeostasis and oxidative stress (55). Specifically, VDR is heavily distributed in the basal ganglia, substantia nigra and superficial/associative layer of the cortex, regions that are involved in executive function in the brain (6).

We did not find a significant association between serum vitamin D levels and cognitive tests of visuospatial function, visual memory or verbal fluency, after correction for covariates. Our results support the results from earlier studies, finding a stronger association between vitamin D levels and executive function than memory (22, 56-58), but do not support an

association between vitamin D and verbal fluency. Executive functions are a heterogeneous group of high-level processes including mental shifting and flexibility, information updating and inhibition. A previous study found the strongest association between vitamin D insufficiency and a decrease in mental shifting, but not other executive subfunctions (59). The possible explanation for our findings is that vitamin D might have strongest positive association with mental flexibility, within the area of executive function, as the association is consistently strongest with TMT-B in this and previous studies. A limitation of earlier studies on verbal fluency and vitamin D has been the small number of participants with vitamin D deficiency (23, 56).

Contrary to previous studies (18), we found no association between vitamin D status and neuropsychiatric symptoms. The possible explanation for this is a low number of persons with significant neuropsychiatric, including depressive symptoms (13.2 % with CSDD score > 12) and low prevalence of vitamin D deficiency in our sample. It is possible that vitamin D insufficiency has less influence on depressive and other neuropsychiatric symptoms than deficiency. Neuropsychiatric symptoms in this study were measured indirectly by interview of a caregiver. The accuracy of reports from caregivers might vary, but information obtained through informant interview is generally a strength, as persons with dementia can have reduced insight into their own symptoms. In contrast to the CSDD, which measured both the amount and severity of symptoms, we dichotomized the NPI-Q ratings into symptom present or not, and did not consider symptom severity, which might have influenced the results. Not all persons in the register had caregivers, which reduced the available data for these neuropsychiatric tests.

The optimal serum level of vitamin D required for brain health is still unclear. It is also uncertain whether 25(OH)D, routinely measured in serum as the barometer for vitamin D status, accurately reflects the amount of vitamin D available intracerebrally. There might be individual differences in vitamin D metabolism, supported by the studies finding VDR polymorphisms to be a risk factor for AD (55).

The study´s strengths

The strengths of this study include the use of a comprehensive battery of cognitive assessment scales, testing many different cognitive areas, and available high-quality data on comorbidity, education, BMI, smoking and alcohol use, allowing the models to be adjusted for known cofounders that influence both cognition and vitamin D levels. In addition, the cognitive tests used in this study are uniformly administered and explore a broad range of cognitive domains. Lastly, vitamin D was analyzed at the same time (within one month) that the cognitive test battery was administered to each patient.

The study´s limitations

In the regression models, complete covariate data were available for only about 65 % of the total study sample, thereby reducing the number of participants in the analysis and possibly introducing bias. Further, we chose to report the estimated p-values and confidence intervals, without adjusting them for multiple comparisons. Therefore, the results need to be interpreted with caution, as false positive findings are possible.

Two different vitamin D assays were used in the analysis. All regression models were adjusted for vitamin D assay type, even though only 6 % of the variation in 25(OH)D was accounted for by the laboratory method.

This being a cross-sectional study, it is not possible to draw a conclusion on causality, and it is possible that both lower vitamin D levels and cognitive impairment are simply markers of poor health. Neither can residual confounding be ruled out, even though potentially confounding variables identified in previous studies, were adjusted for in this analysis.

Conclusion

The results of this study show that higher vitamin D levels appear to be associated with better cognition, particularly in the areas of executive function and mental flexibility. Executive function is significantly impaired in dementia, and is strongly associated with activities of daily living (60). More research is needed on the intracerebral metabolism and dose-relationship of Vitamin D in this field.

The current study supports the recommendation that the routine testing of vitamin D status in elderly persons with cognitive symptoms should be considered, and vitamin D supplementation given in accordance with established clinical guidelines until more data are available.

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Conflict of interest: As potential conflicts of interest is to be mentioned that Anne-Brita Knapskog is the principal investigator in two drug trials (Roche BN29553 and Boehringer-Ingelheim 1346.0023) which are performed at the memory clinic, Department of Geriatric Medicine at Oslo University Hospital. The other authors declare no financial or other conflict of interest.

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