Vitamin D Deficiency Associated With Cognitive Functioning in Psychotic Disorders

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ABSTRACT

Background: Cognitive dysfunctions are core features of psychotic disorders with substantial impact on daily functioning. Vitamin D deficiency has been found to be related to cognitive dysfunctions, but the associations between vitamin D deficiency and cognition in persons with a psychotic disorder are largely unknown.

Methods: This cross-sectional study included 225 patients with a *DSM-IV* psychotic disorder consecutively recruited from 2003 to 2014 and 159 randomly selected healthy controls, assessed by a cognitive test battery, a clinical protocol (including Structured Clinical Interview for *DSM-IV* Axis I Disorders and Positive and Negative Syndrome Scale), and a physical examination including vitamin D measurements. Multiple regression models were performed to evaluate the effect of vitamin D deficiency (defined serum 25-hydroxyvitamin D [25(OH)D] < 25 nmol/L) on key cognitive domains: processing speed, verbal learning, verbal memory, and executive functioning.

Results: Vitamin D deficiency was significantly associated with decreased processing speed (ie, Digit Symbol Coding) ($t = -2.6$, $P = .01$; total model: adjusted $R^2 = 0.40$, $F_{6, 374} = 43.8$, $P < .001$) and decreased fluency (ie, verbal fluency) ($t = -2.1$, $P = .04$; total model: adjusted $R^2 = 0.35$, $F_{6, 373} = 34.2$, $P < .001$) when the results were controlled for age, ethnicity, IQ, patient versus control status, and substance or alcohol abuse. Additional analyses indicated that negative symptoms diluted the association between vitamin D deficiency and processing speed ($t = -1.72$, $P = .09$) and verbal fluency ($t = -1.35$, $P = .18$) in patients.

Conclusion: The associations between vitamin D deficiency and processing speed and verbal fluency are good arguments for planning large-scale randomized controlled studies in target populations so conclusions can be made about the potential beneficial effect of vitamin D on cognition in psychotic disorders.

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Cognitive dysfunction is considered to be a core feature of psychotic disorders[1,2] with a substantial impact on daily functioning.[3,4] Impairments have been reported across cognitive domains and at the start of first treatment.[5–7] The most consistent findings include reduced processing speed, deficits in memory, and impaired executive functioning compared to healthy controls.[8,9] The neurobiology of cognitive dysfunctions is seen as part of underlying pathology in key dopaminergic and glutamatergic central nervous system (CNS) pathways.[10,11] Vitamin D is a neurosteroid hormone with a central role in CNS development and function,[12] and receptors for the active metabolite of vitamin D (vitamin D receptors) are widespread in the CNS.[13,14] The interaction between active vitamin D (1,25-dihydroxyvitamin D) and vitamin D receptors exerts modulating effects on brain function and CNS pathways,[12,15,16] which may affect cognitive function. There are high densities of vitamin D receptors in both the hippocampus and the dorsal striatum.[14] The hippocampus is involved in memory functions and has a central role in brain networks and in complex executive functions such as working memory.[17] The dorsal striatum's role is mainly to integrate and regulate motor behavior, but it is also involved in cognition,[18] especially in motivational learning as part of the reward system[19] and in inhibition.[20]

Low vitamin D levels, measured as serum 25-hydroxyvitamin D (25[OH]D), have been found to be associated with cognitive impairments in the elderly[21] and to be a predictor for cognitive decline (age > 70 years).[22,23] There are, however, few studies of the association between vitamin D and cognition in younger populations,[24] and these are mainly of participants with normal cognitive abilities and vitamin D levels within the normal range. In healthy adolescents and adults (aged < 65 years), no significant associations between vitamin D levels and cognitive performance have been found.[25–27] A randomized controlled trial[28] administering vitamin D supplements to young healthy adults found no effect on working memory, response inhibition, or cognitive flexibility. A study[29] including a sample with high prevalence of vitamin D deficiency found an association between higher vitamin D levels and better processing speed, although it was statistically significant only in older study participants. The association between vitamin D deficiency and reduced processing speed, however, appears as stable in a longitudinal study.[30] Another longitudinal study[31] found midlife vitamin D levels to be predictive of later fluency and working memory performance in a low-education group. However, no such association was found in people with higher education,[31] making the authors suggest that vitamin D has a modifying effect on cognitive reserves.

Clinical Points

- Cognitive impairments are core features in psychotic disorder, and few treatment options are available.
- Clinicians should measure vitamin D in patients with psychotic disorders and prominent cognitive impairments, especially impaired processing speed and fluency.
- Randomized controlled trials to investigate whether vitamin D has potential as an adjuvant treatment for cognitive impairments in psychotic disorder are encouraged.

In clinical studies[32–34] of disorders affecting cognition, especially in Alzheimer's disease, there are indications that vitamin D deficiency is associated with cognitive deficits. These deficits are mainly found in executive functions in terms of switching and updating information, and in processing speed.[33] In Parkinson's disease, vitamin D has been associated with better performance on category fluency and verbal memory tests.[35] In line with this, a study[36] of patients with multiple sclerosis found that higher vitamin D levels were associated with better long-term memory. In a sample of elderly subjects described as frail, vitamin D levels were associated with executive functions and, on a trend level, with processing speed.[37]

Despite the importance of cognitive deficits in psychotic disorders and the link between vitamin D deficiency and impaired cognition in other disorders with compromised CNS functioning, surprisingly few studies have investigated vitamin D deficiency and cognition in psychotic disorders. A small study[38] of patients with first-episode psychosis (N = 40) found an association between a cognitive summary score and low serum levels of vitamin D. A potential association between vitamin D deficiency and cognitive deficits in schizophrenia and other psychotic disorders will be of significant clinical importance. There are few treatment options for cognitive deficits, and vitamin D supplements could thus represent a possible treatment strategy.

The aim of the current study was to investigate the association between vitamin D deficiency and cognition in a large clinical sample of patients with psychotic disorders and healthy controls using a comprehensive test battery focusing on cognitive domains previously found to be associated with psychotic disorders and vitamin D levels, ie, processing speed, verbal learning, and memory and executive functions (including fluency, inhibition, set shifting, and working memory). Our hypothesis was that vitamin D deficiency would be associated with impaired cognitive function in these domains.

METHODS

Participants were recruited consecutively from May 2003 to September 2014 from inpatient and outpatient psychiatric units in the catchment areas of the 5 major hospitals in South Norway, as part of the larger Thematically Organized Psychosis (TOP) Study.[39] The regional committee for medical research ethics approved the study, and our research methodology followed the code of ethics of the World Medical Association, Declaration of Helsinki. Participation was based on informed consent.

Participants

For the current study, we included participants that had been assessed with a cognitive test battery and had available vitamin D measurements. To ensure that serum 25(OH)D reflected the serum level at the time of cognitive assessments, only participants with cognitive assessments and blood sampling within the same season (winter, including November–April, or summer, including May–October)[40] or with a maximum of 3 weeks' discrepancy were included. The rate of vitamin D deficiency is higher in migrants to Northern Europe, and some cognitive tests are culturally sensitive. To avoid cultural background from confounding the results, we included only participants with Norwegian as their mother's tongue or with all education in Norway. The exclusion criteria were traumatic brain injury, neurologic disorders, and mental retardation (IQ < 70). The healthy controls were randomly selected from the same geographic catchment area as the patients using national statistical records. Controls with a history of severe mental illness or mental disorders in close family or ongoing illicit drug abuse were also excluded. The final sample consisted of 384 participants: 225 patients and 159 healthy controls. The patients had following diagnostic distribution: schizophrenia (n = 91), schizophreniform (n = 14) and schizoaffective disorder (n = 17), major depressive disorder with psychotic features (n = 2), bipolar I disorder (n = 38), bipolar II disorder (n = 16), bipolar disorder not otherwise specified (NOS) (n = 3), and other psychosis (including delusional disorder and psychosis NOS) (n = 44). On the basis of recent studies showing a close relationship both in the genetic basis for disease and in cognitive dysfunction, we refer to the diagnoses as psychotic disorders in this article; however, 22 participants from the bipolar spectrum did not have a history of psychosis.

Clinical Assessment

Demographic and clinical variables and current medications were obtained by clinical interviews and reviewing medical records. Ethnicity was assessed by asking for country of birth; ethnic minorities involves participants born in Asian or African countries or with at least 1 parent from these continents. The Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition[41] was used for diagnostic purposes. Current symptomatology was assessed by the Positive and Negative Syndrome Scale (PANSS).[42] The PANSS scores were analyzed using the Wallwork 5-factor model.[43] The participants also underwent a physical examination including blood sampling.

Cognitive Assessment

The participants were assessed with 2 different neurocognitive test batteries over the study period.

Table 1. Overview of the Cognitive Tests

Test	Cognitive Test Battery[a]	N[b]	Mean ± SD
Processing speed	Combined *z* score	384	−0.65 ± 1.2
Digit Symbol Coding Test from the WAIS-III	1	108	59.8 ± 15.2
Brief Assessment of Cognition in Schizophrenia	2	276	54.1 ± 11.1
Verbal learning	Combined *z* score	338	−0.43 ± 1.3
CVLT, list A total correct	1	108	48.8 ± 10.6
HVLT-R, immediate recall	2	230	11.6 ± 0.8
Verbal memory	Combined *z* score	382	−0.47 ± 1.2
CVLT, long delay free recall	1	108	10.9 ± 3.2
HVLT-R, delayed recall	2	274	9.7 ± 2.0
Executive functions			
Verbal fluency	Combined *z* score	383	−0.56 ± 1.2
Category Fluency Test in the D-KEFS battery	1	107	39.7 ± 10.6
Category Fluency Test in the MCCB	2	276	26.4 ± 6.7
Working memory	Combined *z* score	365	−0.35 ± 1.0
Letter-Number Sequencing Test from the D-KEFS battery	1	91	9.3 ± 2.2
Letter-Number Sequencing Test from the MCCB	2	274	14. 5 ± 2.9
Inhibition			
The Color-Word Interference Test in the D-KEFS battery	1 + 2	384	54.3 ± 15.1
Set-shifting			
The Color-Word Interference Test in the D-KEFS battery	1 + 2	382	59.4 ± 13.8

[a]1 represents a version of the D-KEFS battery. 2 represents a version of the MCCB.
[b]Number of participants from the total sample assessed with the different cognitive tests.
Abbreviations: CVLT = California Verbal Learning Test, D-KEFS = Delis-Kaplan Executive Function System, HVLT-R = Hopkins Verbal Learning Test-Revised, MCCB = MATRICS Consensus Cognitive Battery, WAIS-III = Wechsler Adult Intelligence Scale-III.

Participants (N = 108) were tested with test battery 1,[44] a standardized test battery described by Simonsen et al.[45] Participants (N = 276) were tested with test battery 2, which is based on the MATRICS Consensus Cognitive Battery (MCCB).[46] We computed *z* scores based on a healthy control group for each of the corresponding subtests from the 2 different batteries to be able to merge the scores into the cognitive outcome variables processing speed, verbal learning, verbal memory, verbal fluency, and working memory. The 2 test batteries used the same tests to measure inhibition and set shifting (Table 1). Processing speed was measured with the Digit Symbol Coding Test from the Wechsler Adult Intelligence Scale-III (WAIS-III)[47] or Brief Assessment of Cognition in Schizophrenia.[46] Verbal learning and verbal memory were measured with the California Verbal Learning Test (CVLT)[48] or the Hopkins Verbal Learning Test-Revised.[46,49] Verbal fluency was measured with the Category Fluency Test in the Delis-Kaplan Executive Function System (D-KEFS) battery[50] or the Category Fluency Test from the MCCB.[46] Working memory was measured with the Letter-Number Sequencing Test from the D-KEFS battery[50] or the Letter-Number Sequencing Test from the MCCB.[46] Inhibition and set shifting were measured with the Color-Word Interference Test from the D-KEFS battery.[50] Current IQ was measured with the abbreviated scale Wechsler Abbreviated Scale of Intelligence.[51]

Biochemical Assessment

From September 2012, total serum 25(OH)D (a sum of $25[OH]D_2$ and $25[OH]D_3$) was determined using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method developed at the Hormone Laboratory (Oslo University Hospital, Aker, Norway).[52] Prior to September 2012, serum 25(OH)D was measured by radioimmunoassay (RIA [kit from Diasorin])[53] in the same laboratory. The regression equation LC-MS/MS = 1.16 × (RIA) − 9 was obtained at the laboratory during method comparison and was used to convert all serum 25(OH)D concentrations obtained by LC-MS to equivalent concentrations obtained by RIA, which were used in the analyses. Vitamin D deficiency was defined serum 25(OH)D < 25 nmol/L.[12]

Statistics

Statistical analysis was performed using IBM SPSS Statistics V22. The level of significance was preset to $P < .05$ (2-tailed). To investigate differences in cognitive domains between participants with and without vitamin D deficiency, we first performed a multivariate analysis of variance (MANOVA) with Bonferroni corrections, with vitamin D deficiency as fixed factor and the cognitive domains as dependent variables to ascertain that there were statistically significant differences across groups (data not shown). The MANOVA was then followed up by investigating group differences for each cognitive domain using *t* tests for normally distributed variables (processing speed, verbal fluency, and working memory) and Mann-Whitney *U* test for variables without normal distribution (verbal memory, inhibition, and set shifting).

After demonstrating group differences in cognitive domains, we performed a series of multiple linear analyses to investigate whether the association between vitamin D deficiency and cognitive domains was influenced by possible confounding variables. We performed a series of multiple linear analyses with the cognitive domains as dependents and vitamin D deficiency entered at the last step. The

variables inhibition and set shifting were log transformed to allow for use in linear regression. Model fit was evaluated by residual plots. Possible confounders were entered at the intermediate steps. These variables were chosen based on their theoretical and statistical possibility to mediate the relationship, ie, that they had an association ($P < .10$) with both the cognitive domain and vitamin D deficiency (using bivariate correlation analyses or *t* tests for continuous variables and χ^2 tests for dichotomous variables). We also included variables that were significantly different between patients and healthy controls (because of the significant difference in cognition) and between ethnic minorities and ethnic majorities (because of the significant difference in vitamin D status). Notably, sex was not significantly associated with vitamin D deficiency ($\chi^2 = 2.3$, $P = .13$), ethnic minority background ($\chi^2 = 0.08$, $P = .78$), or being a patient versus healthy control (see Table 2 for additional analyses). Season of the year was associated with vitamin D status but not with cognitive functioning, and use of psychotropic medication was completely congruent with being a patient (versus healthy control). None of these variables were thus entered in the final analyses. Also, educational status was not only substantially different between patients and healthy controls but also highly statistically significantly associated with IQ. Since length of education could be confounded with age at onset, we chose to enter IQ in the analyses. Age, ethnicity, current IQ, a history of substance or alcohol abuse, and patients versus control status were thus entered together with vitamin D deficiency as independent variables in the models. In the next step, we repeated the analyses in patients only (n = 255) to investigate the potential confounding effects of clinical symptoms. These follow-up analyses were done for only cognitive domains with statistically significant results in the previous analyses. The procedures were otherwise the same as described in text (see Table 3). For the dependent variables processing speed and verbal fluency, we thus redid the analyses with age, ethnicity, current IQ, substance or alcohol abuse, and vitamin D deficiency as independents before adding the negative symptom factor (log transformed) to evaluate whether this influenced the associations between vitamin D deficiency and the cognitive domains.

RESULTS

The sample characteristics are summarized in Table 2. Vitamin D deficiency was bivariate-associated with a diagnosis of psychotic disorder ($\chi^2 = 13.9$, $P < .001$), ethnic minority ($\chi^2 = 24.7$, $P < .001$), a history of substance or alcohol abuse ($\chi^2 = 6.64$, $P = .01$), and lower current IQ ($t = 3.1$, $P = .002$).

Vitamin D deficiency was significantly associated with results for all the cognitive tests except verbal learning in bivariate analyses (Table 3). The results from the multiple regressions are shown in Table 4. The associations between vitamin D deficiency and decreased processing speed and verbal fluency remained significant after the results were controlled for possible confounding variables. The associations between vitamin D deficiency and working memory, verbal memory, inhibition, and set shifting did not remain significant after controlling for patient versus healthy control status and current IQ.

In patients (n = 225), both processing speed and verbal fluency were found to have a significant bivariate association with the negative symptom factor on the PANSS (Pearson $r = -0.18$, $P = .01$, and $r = -0.27$, $P < .001$, respectively). In a multiple regression model with processing speed as outcome

Table 2. Overview of the Sample

Variable	Patients (n = 225), n (%)	Healthy Controls (n = 159), n (%)	Test	*P* Value
Male sex	128 (56.9)	90 (56.6)	$\chi^2 = 0.003$	.96
Ethnic minority background	42 (18.7)	4 (2.5)	$\chi^2 = 23.0$	< .001
Vitamin D deficiency[a]	33 (14.7)	5 (3.1)	$\chi^2 = 13.9$	< .001
Substance or alcohol abuse[b]	57 (25.3)	0 (0)	$\chi^2 = 47.3$	< .001
Schizophrenia spectrum	122 (54.2)			
Outpatient	159 (70.6)			
	Mean (SD)	Mean (SD)		
Age, y	30.2 (10.0)	30.8 (7.9)	$t = -0.70$	.49
Current IQ	104.0 (13.9)	113.8 (10.9)	$t = -7.40$	< .001
Duration of illness, y	5.5 (6.3)			

[a]Vitamin D deficiency was defined serum 25-hydroxyvitamin D < 25 nmol/L.
[b]Having illicit substance or alcohol abuse or dependency as verified by the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Research Version, Patient Edition. Healthy controls with substance or alcohol abuse were excluded.

Table 3. Bivariate Associations With Vitamin D Deficiency[a]

Variable Score	Vitamin D < 25 nmol/L n	Vitamin D < 25 nmol/L Mean (SD)	Vitamin D ≥ 25 nmol/L n	Vitamin D ≥ 25 nmol/L Mean (SD)	Test	*P* Value
Processing speed[b]	38	−1.43 (0.92)	346	−0.56 (1.2)	$t = 4.20$	< .001
Fluency[b]	38	−1.35 (1.2)	345	−0.47 (1.2)	$t = 4.28$	< .001
Working memory[b]	34	−0.73 (1.1)	331	−0.31 (1.0)	$t = 2.25$	.03
		Median (range)		Median (range)		
Verbal learning[b]	28	−0.31 (−4.9 to 0.64)	310	0.41 (−8.5 to 1.8)	Mann-Whitney *U*	.20
Verbal memory[b]	37	−0.84 (−3.5 to 1.0)	345	−0.14 (−4.3 to 1.1)	Mann-Whitney *U*	.04
Inhibition	38	60.0 (33 to 92)	345	51.0 (31 to 160)	Mann-Whitney *U*	.003
Set-shifting	37	63.0 (42 to 98)	344	56.6 (32 to 132)	Mann-Whitney *U*	.004
		Mean (SD)		Mean (SD)		
PANSS						
Positive[c]	33	2.0 (1.1)	191	2.0 (1.0)	$t = -0.15$	.88
Negative[d]	33	2.1 (1.0)	191	1.9 (0.8)	$t = -1.74$	.08
Depressive[e]	33	2.5 (1.0)	191	2.4 (1.0)	$t = -0.40$	.69
Disorganized[f]	33	1.6 (0.5)	191	1.7 (0.8)	$t = 0.47$	.64
Excited[g]	33	1.2 (0.4)	191	1.3 (0.4)	$t = 0.78$	.44

[a]Vitamin D deficiency was defined serum 25-hydroxyvitamin D < 25 nmol/L. [b]Represents *z* scores. [c]Mean scores from items P1, P3, P5, and G9. [d]Mean scores from items N1, N2, N3, N4, N6, and G7. [e]Mean scores from items G2, G3, and G6. [f]Mean scores from items P2, N5, and G11. [g]Mean scores from items P4, P7, G8, and G14.
Abbreviation: PANSS = Positive and Negative Syndrome Scale—G = general psychopathology, N = negative, P = positive.

Table 4. Results From Multiple Regressions According to the Dependent Cognitive Domains and Vitamin D Deficiency Entered as Independent Variable Together With Other Potential Confounding Variables

	Processing Speed[a]				Verbal Memory			
Variable	*t*	*P* Value	B	95% CI	*t*	*P* Value	B	95% CI
Age	−5.5	<.001	−0.03	−0.04 to −0.02	−0.6	.51	−0.004	−0.02 to 0.01
Ethnic minority	1.4	.16	0.23	−0.1 to 0.57	−0.22	.82	−0.04	−0.42 to 0.33
Current IQ	9.3	<.001	0.04	0.03 to 0.05	8.1	<.001	0.04	0.03 to 0.05
Patient status	6.7	<.001	0.75	0.53 to 1.0	2.8	.005	0.36	0.11 to 0.61
Substance or alcohol abuse	−1.1	.26	−0.17	−0.47 to 0.13	−0.6	.53	−0.11	−0.44 to 0.23
Vitamin D deficiency[b]	−2.6	.01	−0.45	−0.79 to −0.11	−0.07	.94	−0.01	−0.39 to −0.37
	Total model: adjusted $R^2 = 0.40$, $F_{6, 374} = 43.8$, $P < .001$				Total model: adjusted $R^2 = 0.24$, $F_{6, 372} = 20.4$, $P < .001$			
Executive functions								
	Verbal Fluency[a]				Working Memory			
	t	*P* Value	B	95% CI	*t*	*P* Value	B	95% CI
Age	−0.5	.61	−0.003	−0.01 to 0.01	−0.9	.35	−0.01	−0.02 to 0.01
Ethnic minority	−1.01	.31	−0.18	−0.52 to 0.17	0.7	.47	0.11	−0.20 to 0.43
Current IQ	9.1	<.001	0.04	0.03 to 0.05	9.3	<.001	0.04	0.03 to 0.05
Patient status	4.5	<.001	0.53	0.30 to 0.76	2.0	.05	0.21	−0.01 to 0.42
Substance or alcohol abuse	−0.41	.68	−0.07	−0.38 to 0.25	0.73	.47	0.11	−0.18 to 0.40
Vitamin D deficiency[b]	−2.1	.04	−0.38	−0.73 to −0.02	−0.7	.48	−0.12	−0.45 to 0.21
	Total model: adjusted $R^2 = 0.35$, $F_{6, 373} = 34.2$, $P < .001$				Total model: adjusted $R^2 = 0.25$, $F_{6, 356} = 21.0$, $P < .001$			
	Inhibition				Set-Shifting			
	t	*P* Value	B	95% CI	*t*	*P* Value	B	95% CI
Age	1.6	.10	0.002	0.00 to 0.01	0.24	.81	<0.001	−0.002 to 0.003
Ethnic minority	1.2	.22	0.05	−0.03 to 0.12	1.3	.21	0.05	−0.03 to 0.12
Current IQ	−6.5	<.001	−0.01	−0.01 to −0.004	−5.0	<.001	−0.004	−0.01 to −0.003
Patient status	−4.3	<.001	−0.11	−0.16 to −0.06	−1.4	.17	−0.03	−0.08 to 0.01
Substance or alcohol abuse	−0.2	.87	−0.01	−0.07 to 0.06	1.6	.12	0.05	−0.01 to 0.11
Vitamin D deficiency[b]	0.6	.53	0.03	−0.05 to 0.10	1.1	.26	0.04	−0.03 to 0.11
	Total model: adjusted $R^2 = 0.23$, $F_{6, 373} = 19.4$, $P < .001$				Total model: adjusted $R^2 = 0.14$, $F_{6, 371} = 11.2$, $P < .001$			

[a]Significant contribution from vitamin D deficiency. [b]Vitamin D deficiency was defined serum 25-hydroxyvitamin D < 25 nmol/L.

and the same independent variables, vitamin D deficiency had a trend-level association ($t = -1.82$, $P = .06$). Adding negative symptoms in the model had an impact on the association between vitamin D deficiency and processing speed ($t = -1.72$, $P = .09$), while negative symptoms were significantly associated with processing speed ($t = -2.12$, $P = .04$) (total model adjusted $R^2 = 0.28$, $F_{6, 224} = 15.6$, $P < .001$). The same analyses were performed with verbal fluency as the outcome. The association between vitamin D deficiency and verbal fluency did not reach the level of significance in this smaller sample ($t = -1.54$, $P = .12$). Adding negative symptoms to the multiple regression model further diluted the association ($t = -1.35$, $P = .18$). Negative symptoms, however, were significantly associated with verbal fluency in the final model ($t = -3.12$, $P = .002$) (total model adjusted $R^2 = 0.28$, $F_{6, 218} = 15.5$, $P < .01$).

DISCUSSION

The current study shows an association between vitamin D deficiency and decreased processing speed (measured with Digit Symbol Coding Test) and between vitamin D deficiency and decreased verbal fluency (measured by Category Fluency Test) across patients with psychotic disorders and healthy controls.

The association between vitamin D deficiency and processing speed is in line with results from previous studies[29,37] of older individuals. However, our study is the first to show this association also in a younger population (mean ± SD age = 30 ± 10 years). Impairment in processing speed is a consistent finding in patients with psychotic disorder compared to healthy controls.[1,54] Processing speed is essential for all cognitive demands and for daily functioning and may be a specific marker for cognitive deficits in psychotic disorders, especially in schizophrenia,[55] that appear to be stable over time in longitudinal studies.[56] The association between reduced processing speed and vitamin D deficiency was, however, not patient specific, as the direction of the associations was similar in patients and in healthy controls and remained significant after controlling for patient versus control status.

Processing speed and verbal fluency, are 2 closely correlated cognitive tests (Pearson $r = 0.5$, $P < .001$, in the current sample). Fluency can be perceived as an executive task, but in the MCCB category, fluency is listed as a processing-speed task.[46] The association between vitamin D deficiency and impaired fluency is in line with findings from an aging multiethnic cohort[23] and a longitudinal study[57] of the general population that found very high vitamin D levels (> 100 nmol/L) to be significantly associated with

better fluency. The association between vitamin D and fluency has previously been shown in a small study[38] of patients with psychotic disorders, but in this other study involving 40 participants, it appeared to be confounded by sex differences. This was not the case in the current study, which included a larger sample. The association with vitamin D deficiency was not patient specific, indicating that the link between vitamin D deficiency and cognitive tasks is not directly influenced by disease mechanisms but instead may represent common physiological pathways. The effects on functioning might, however, be larger in groups with already compromised cognitive functioning.[31] Differences in the vitamin D metabolism and genetic polymorphism in vitamin D receptors could result in individual effects from available serum 25(OH)D, and further research on mechanisms is required.[58,59]

The current study did not find the expected associations between vitamin D deficiency and verbal memory. There was a bivariate association, but this was explained by differences in current IQ levels and patient versus control status. A link between vitamin D deficiency and impaired memory has been suggested, especially in clinical samples with impaired memory functions,[60] and high vitamin D levels have been found in relation with better memory performance in other clinical samples.[36] Very high vitamin D levels have, however, also been found to be related to poorer verbal memory in healthy populations.[27,61] Prospective studies have not found a consistent association between vitamin D levels and memory.[62] Our findings are in line with a comparable study[63] of psychiatric patients assessed by the Mini-Mental State Examination,[64] a cognitive test focusing on orientation and memory, in which no associations were found. Vitamin D deficiency has earlier been related to cognitive flexibility but not significantly associated with inhibition.[65] In a study[37] of frail elderly, executive function including a combined measure of interference tests, fluency, and a reaction time task was found associated with vitamin D levels. Our study indicates no significant associations between vitamin D deficiency and interference and set shifting.

The association between processing speed and verbal fluency with vitamin D deficiency in patients could be partly mediated by negative symptoms. The reduction of sample size, however, by removing the healthy controls reduced statistical power, thereby hampering interpretations. The negative symptom factor includes N6 (lack of spontaneity and flow of conversation) and G7 (motor retardation) from the PANSS.[43] The same phenomena could thus be covered by both the cognitive tests for fluency and processing speed and the PANSS symptom definitions. How these phenomena interact with each other, however, is difficult to disentangle. They might be based in common CNS processes, or the lack of motivation and motor retardation inherent in the negative symptom syndrome might disturb test performance in patients with prominent negative symptoms.

An overall limitation of this study was its cross-sectional design, which makes it impossible to investigate causality. Furthermore, we cannot rule out that the associations are influenced by confounding factors that were not measured in the current study. Another limitation is the use of 2 different methods for vitamin D measurements and 2 different cognitive test batteries over the length of the study period, even if we adjusted by using conversion equations for serum 25(OH)D measures and *z* scores for cognitive domains.

Uncontrolled clinical trials have shown that a few weeks of oral vitamin D supplements give an adequate increase in serum 25(OH)D.[66] Another open trial[67] found both an increase in serum 25(OH)D and a general improvement in cognition, especially in executive function, in a group of older outpatients with memory problems. A randomized placebo-controlled study,[28] however, reveal no effect of vitamin D supplementation on cognition, but the study participants in the latter did not have either cognitive deficits or vitamin D deficiency at baseline.

In conclusion, vitamin D is considered safe to use, is well tested, and is readily available. These benefits, combined with the substantial negative effects of cognitive dysfunctions on daily living are good arguments for planning large-scale randomized controlled studies in target populations to reach conclusions about the potential beneficial effect of vitamin D on cognition in psychotic disorders.

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REFERENCES

1. Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry*. 2006;67(10):e12.
2. Bortolato B, Miskowiak KW, Köhler CA, et al. Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatr Dis Treat*. 2015;11:3111–3125.
3. Mohamed S, Rosenheck R, Swartz M, et al. Relationship of cognition and psychopathology to functional impairment in schizophrenia. *Am J Psychiatry*. 2008;165(8):978–987.
4. Green MF. Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. *J Clin Psychiatry*. 2016;77(suppl 2):8–11.
5. Mesholam-Gately RI, Giuliano AJ, Goff KP, et al. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology*. 2009;23(3):315–336.
6. Demmo C, Lagerberg TV, Aminoff SR, et al. History of psychosis and previous episodes as potential explanatory factors for neurocognitive impairment in first-treatment bipolar I disorder. *Bipolar Disord*. 2016;18(2):136–147.
7. Haatveit B, Vaskinn A, Sundet KS, et al. Stability of executive functions in first episode psychosis: one year follow up study. *Psychiatry Res*. 2015;228(3):475–481.
8. Bora E, Yucel M, Pantelis C. Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *Br J Psychiatry*. 2009;195(6):475–482.
9. Kalkstein S, Hurford I, Gur RC.

Neurocognition in schizophrenia. *Curr Top Behav Neurosci*. 2010;4:373–390.
10. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull*. 2009;35(3):549–562.
11. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol*. 2015;29(2):97–115.
12. McGrath JJ, Burne TH, Féron F, et al. Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. *Schizophr Bull*. 2010;36(6):1073–1078.
13. Stumpf WE. Drugs in the brain—cellular imaging with receptor microscopic autoradiography. *Prog Histochem Cytochem*. 2012;47(1):1–26.
14. Eyles DW, Smith S, Kinobe R, et al. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat*. 2005;29(1):21–30.
15. Kalueff AV, Tuohimaa P. Neurosteroid hormone vitamin D and its utility in clinical nutrition. *Curr Opin Clin Nutr Metab Care*. 2007;10(1):12–19.
16. Kesby JP, Eyles DW, Burne TH, et al. The effects of vitamin D on brain development and adult brain function. *Mol Cell Endocrinol*. 2011;347(1–2):121–127.
17. Sigurdsson T, Duvarci S. Hippocampal-prefrontal interactions in cognition, behavior and psychiatric disease. *Front Syst Neurosci*. 2016;9:190.
18. Fuccillo MV. Striatal circuits as a common node for autism pathophysiology. *Front Neurosci*. 2016;10:27.
19. Schultz W. Dopamine reward prediction-error signaling: a two-component response. *Nat Rev Neurosci*. 2016;17(3):183–195.
20. Diamond A. Executive functions. *Annu Rev Psychol*. 2013;64:135–168.
21. Llewellyn DJ, Langa KM, Lang IA. Serum 25-hydroxyvitamin D concentration and cognitive impairment. *J Geriatr Psychiatry Neurol*. 2009;22(3):188–195.
22. Perna L, Mons U, Kliegel M, et al. Serum 25-hydroxyvitamin D and cognitive decline: a longitudinal study among non-demented older adults. *Dement Geriatr Cogn Disord*. 2014;38(3–4):254–263.
23. Miller JW, Harvey DJ, Beckett LA, et al. Vitamin D status and rates of cognitive decline in a multiethnic cohort of older adults. *JAMA Neurol*. 2015;72(11):1295–1303.
24. Anastasiou CA, Yannakoulia M, Scarmeas N. Vitamin D and cognition: an update of the current evidence. *J Alzheimers Dis*. 2014;42(suppl 3):S71–S80.
25. Jorde R, Mathiesen EB, Rogne S, et al. Vitamin D and cognitive function: the Tromsø Study. *J Neurol Sci*. 2015;355(1–2):155–161.
26. Tolppanen AM, Williams D, Lawlor DA. The association of circulating 25-hydroxyvitamin D and calcium with cognitive performance in adolescents: cross-sectional study using data from the third National Health and Nutrition Examination Survey. *Paediatr Perinat Epidemiol*. 2011;25(1):67–74.
27. McGrath J, Scragg R, Chant D, et al. No association between serum 25-hydroxyvitamin D3 level and performance on psychometric tests in NHANES III. *Neuroepidemiology*. 2007;29(1–2):49–54.
28. Dean AJ, Bellgrove MA, Hall T, et al. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults—a randomised controlled trial. *PLoS One*. 2011;6(11):e25966.
29. Darwish H, Zeinoun P, Ghusn H, et al. Serum 25-hydroxyvitamin D predicts cognitive performance in adults. *Neuropsychiatr Dis Treat*. 2015;11:2217–2223.
30. van Schoor NM, Comijs HC, Llewellyn DJ, et al. Cross-sectional and longitudinal associations between serum 25-hydroxyvitamin D and cognitive functioning. *Int Psychogeriatr*. 2016;28(5):759–768.
31. Assmann KE, Touvier M, Andreeva VA, et al. Midlife plasma vitamin D concentrations and performance in different cognitive domains assessed 13 years later. *Br J Nutr*. 2015;113(10):1628–1637.
32. Wood JM, Gupta S. Vitamin D and neurocognitive disorder due to Alzheimer's disease: a review of the literature. *Ann Clin Psychiatry*. 2015;27(2):e1–e7.
33. Annweiler C, Montero-Odasso M, Llewellyn DJ, et al. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. *J Alzheimers Dis*. 2013;37(1):147–171.
34. Brouwer-Brolsma EM, de Groot LC. Vitamin D and cognition in older adults: an update of recent findings. *Curr Opin Clin Nutr Metab Care*. 2015;18(1):11–16.
35. Peterson AL, Murchison C, Zabetian C, et al. Memory, mood, and vitamin D in persons with Parkinson's disease. *J Parkinsons Dis*. 2013;3(4):547–555.
36. Koven NS, Cadden MH, Murali S, et al. Vitamin D and long-term memory in multiple sclerosis. *Cogn Behav Neurol*. 2013;26(3):155–160.
37. Brouwer-Brolsma EM, van de Rest O, Tieland M, et al. Serum 25-hydroxyvitamin D is associated with cognitive executive function in Dutch prefrail and frail elderly: a cross-sectional study exploring the associations of 25-hydroxyvitamin D with glucose metabolism, cognitive performance and depression. *J Am Med Dir Assoc*. 2013;14(11):852.e9–852.e17.
38. Graham KA, Keefe RS, Lieberman JA, et al. Relationship of low vitamin D status with positive, negative and cognitive symptom domains in people with first-episode schizophrenia. *Early Interv Psychiatry*. 2015;9(5):397–405.
39. Thematically Organized Psychosis (TOP) Study. NORMENT: Norwegian Centre for Mental Disorders Research.http://www.med.uio.no/norment/english/.
40. Porojnicu AC, Robsahm TE, Dahlback A, et al. Seasonal and geographical variations in lung cancer prognosis in Norway: does vitamin D from the sun play a role? *Lung Cancer*. 2007;55(3):263–270.
41. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)*. [Norwegian version; Vogel E, Vogel P, Kardel I, et al. Psychological Institute, University of Oslo; Oslo, Norway: 1996].
42. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
43. Wallwork RS, Fortgang R, Hashimoto R, et al. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. *Schizophr Res*. 2012;137(1–3):246–250.
44. Delis DC, Kaplan E, Kramer JH. *The Delis-Kaplan Executive Function System (D-KEFS): Norwegian Manual*. Stockholm, Sweden: Pearson Assessment; 2005.
45. Simonsen C, Sundet K, Vaskinn A, et al. Psychosocial function in schizophrenia and bipolar disorder: relationship to neurocognition and clinical symptoms. *J Int Neuropsychol Soc*. 2010;16(5):771–783.
46. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165(2):203–213.
47. Wechsler D. *Wechsler Adult Intelligence Scale* [Norwegian manual]. 3rd ed (WAIS-III). Stockholm, Sweden: Pearson Assessment; 2003.
48. Delis DCKJ, Kaplan E, Ober BA. *California Verbal Learning Test: CVLT-II*. Stockholm, Sweden: Pearson Assessment; 2004.
49. Benedict RHBSD, Groninger L, Brandt J. The Hopkins Verbal Learning Test-Revised: normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychol*. 1998;(12):43–55.
50. Delis DCKE, Kramer JH. *The Delis-Kaplan Executive Function System: D-KEFS*. Stockholm, Sweden: Pearson Assessment; 2005.
51. Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI)* [Norwegian manual supplement]. Stockholm, Sweden: Pearson Assessment; 2007.
52. Nerhus M, Berg AO, Dahl SR, et al. Vitamin D status in psychotic disorder patients and healthy controls—the influence of ethnic background. *Psychiatry Res*. 2015;230(2):616–621.
53. Holvik K, Meyer HE, Haug E, et al. Prevalence and predictors of vitamin D deficiency in five immigrant groups living in Oslo, Norway: the Oslo Immigrant Health Study. *Eur J Clin Nutr*. 2005;59(1):57–63.
54. Schaefer J, Giangrande E, Weinberger DR, et al. The global cognitive impairment in schizophrenia: consistent over decades and around the world. *Schizophr Res*. 2013;150(1):42–50.
55. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry*. 2007;64(5):532–542.
56. Bonner-Jackson A, Grossman LS, Harrow M, et al. Neurocognition in schizophrenia: a 20-year multi-follow-up of the course of processing speed and stored knowledge. *Compr Psychiatry*. 2010;51(5):471–479.
57. Pettersen JA. Vitamin D and executive functioning: are higher levels better? *J Clin Exp Neuropsychol*. 2016;38(4):467–477.
58. Cui X, Gooch H, Groves NJ, et al. Vitamin D and the brain: key questions for future research. *J Steroid Biochem Mol Biol*. 2015;148:305–309.
59. Łaczmański Ł, Jakubik M, Bednarek-Tupikowska G, et al. Vitamin D receptor gene polymorphisms in Alzheimer's disease patients. *Exp Gerontol*. 2015;69:142–147.
60. Vicente P, Herr M, Mahieux F, et al. Vitamin D and neuropsychological assessment of cognitive functions: a study of their relationships in a sample of 244 patients attending a memory clinic [in French]. *Geriatr Psychol Neuropsychiatr Vieil*. 2015;13(4):452–461.
61. Lam V, Albrecht MA, Takechi R, et al. Serum 25-hydroxyvitamin D is associated with reduced verbal episodic memory in healthy, middle-aged and older adults. *Eur J Nutr*. 2016;55(4):1503–1513.
62. Kuźma E, Soni M, Littlejohns TJ, et al. Vitamin D and memory decline: two population-based prospective studies. *J Alzheimers Dis*. 2016;50(4):1099–1108.
63. Leedahl DD, Cunningham JL, Drake MT, et al. Hypovitaminosis D in psychiatric inpatients: clinical correlation with depressive symptoms, cognitive impairment, and

prescribing practices. *Psychosomatics*. 2013;54(3):257–262.
64. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
65. Annweiler C, Maby E, Meyerber M, et al. Hypovitaminosis D and executive dysfunction in older adults with memory complaint: a memory clinic-based study. *Dement Geriatr Cogn Disord*. 2014;37(5–6):286–293.
66. Przybelski R, Agrawal S, Krueger D, et al. Rapid correction of low vitamin D status in nursing home residents. *Osteoporos Int*. 2008;19(11):1621–1628.
67. Annweiler C, Fantino B, Gautier J, et al. Cognitive effects of vitamin D supplementation in older outpatients visiting a memory clinic: a pre-post study. *J Am Geriatr Soc*. 2012;60(4):793–795.