



Original Article

Relationship of low vitamin D status with positive, negative and cognitive symptom domains in people with first-episode schizophrenia

K.A. Graham,¹ R.S. Keefe,² J.A. Lieberman,^{1*} A.S. Calikoglu,³ K.M. Lansing¹ and D.O. Perkins¹**Abstract**

Aim: Deficient vitamin D levels are very common among Americans of all ages and ethnicities, but little is known about its prevalence or associated problems among those with schizophrenia.

Methods: Stored plasma from 20 recent onset schizophrenia subjects and 20 matched healthy comparison subjects were analysed for 25 OH vitamin D, and related to measures of symptom severity and neurocognition.

Results: There was no significant difference in mean 25 OH vitamin D between the schizophrenia and the healthy comparison subjects (28.2 standard deviation (SD) 12.6 ng mL⁻¹ vs. 29.9 SD 14.3 ng mL⁻¹), and about half the subjects in each group had insufficient levels (<30 ng mL⁻¹). Among psychosis subjects, greater severity of negative symptoms was

correlated with lower vitamin D status ($r = -0.55$, $P = 0.012$); the correlations of overall symptom severity and positive symptom severity with 25 OH vitamin D levels approached significance ($r = -0.42$, $P = 0.07$ and $r = -0.36$, $P = 0.12$, respectively). There was no relationship of vitamin D with depressive symptoms. Among the schizophrenia subjects, lower 25 OH vitamin D levels were associated with more severe overall cognitive deficits ($r = 0.56$, $P = 0.019$).

Conclusion: This study found that lower vitamin D levels in schizophrenia subjects were associated with more severe negative symptoms and overall cognitive deficits. However, the cross-sectional design precludes any conclusions about whether low vitamin D status in fact causes more severe negative symptoms and cognitive impairments. No relationship was found between lower vitamin D levels and depressive symptoms.

Key words: complementary and alternative treatment, neurocognition, schizophrenia, symptoms, vitamin D.

Departments of ¹Psychiatry and ³Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, and ²Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA

Corresponding author: Dr Karen A. Graham, Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7160, USA. Email: karen_graham@med.unc.edu

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*Permanent address for J.A. Lieberman: Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York State Psychiatric Institute, NY 10032, USA.

INTRODUCTION

There is growing recognition of the importance of adequate vitamin D levels to overall health, including brain health. At the same time, there is recognition of a worldwide epidemic of vitamin D insufficiency.^{1,2} Although the importance of sunlight and vitamin D to bone health has been known for hundreds of years, it is only recently that they are being linked to other disease states, such as multiple sclerosis,³ prostate,⁴ breast and colorectal⁵ cancers,

Parkinson's disease,⁶ diabetes mellitus⁷ and the metabolic syndrome.⁸ Adequate vitamin D status is also needed for optimal muscular strength in youth (HELENA study) and the elderly.⁹ In addition to these diseases, vitamin D has also been linked to mental illnesses including Alzheimer's,¹⁰ premenstrual mood disorder,^{11,12} major depression¹³ and psychosis.¹⁴ However, the relationship of vitamin D status to the functions of the brain is also in its infancy,¹⁴ with some evidence of negative, cognitive¹⁵⁻¹⁷ and mood^{18,19} effects in people with insufficient vitamin

D levels. Neuroprotective qualities of vitamin D have been observed in animal studies, and recent reviews have suggested that vitamin D could play an important role in the central nervous system for healthy neural development and function.^{20,21} A correlation between schizophrenia and low prenatal and early life vitamin D status has been well demonstrated,^{22–24} and supplementation could be important for disease prevention.²¹ However, the influence of low vitamin D status on symptom severity in adults with schizophrenia, although hypothesized,²⁵ has only begun to be investigated. It has been found that patients with schizophrenia have lower vitamin D levels compared with healthy subjects or those with depression.²⁶ It has also been established that adolescent patients with lower vitamin D levels were 3.5 times more likely to have psychotic features than their unaffected counterparts and those that did not have psychotic features.¹³ In a sample of active duty military members, subjects with the highest suicide risk had the lowest vitamin D levels.²⁷ A recent meta-analysis also found that lower vitamin D levels are associated with greater risk for developing Alzheimer's and poorer cognitive performance.²⁸ Although recent studies have emerged showing that lower vitamin D levels are associated with symptoms common to schizophrenia, more research is needed to determine if vitamin D insufficiency contributes to symptom severity in schizophrenia. To this end, we assessed the relationship of vitamin D status with measures of positive, negative, cognitive and depressive symptoms in otherwise healthy young adults with schizophrenia.

METHODS

Subject characteristics

Outpatient subjects participating in two longitudinal first-episode schizophrenia research projects at the University of North Carolina at Chapel Hill consented to have blood drawn and stored in a biospecimen bank as approved by the University of North Carolina at Chapel Hill Investigational Review Board. Diagnosis in the schizophrenia subjects was made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID)²⁹ administered by an experienced masters-level clinician ($n = 17$ schizophrenia, $n = 2$ schizoaffective and $n = 1$ schizophreniform). For the remainder of this paper, all subjects with a psychotic disorder will be referred to as schizophrenia subjects. Duration of psychosis was less than 5 years, and subjects had not received more than 16 weeks of cumulative

antipsychotic treatment. Schizophrenia patients did not have clinically significant neurological or medical disorders that could influence the diagnosis, and did not have a history of or current diagnosis of substance dependence or current substance abuse. For each schizophrenia subject, a healthy control subject was matched for age, ethnicity and gender. For schizophrenia subjects, ages ranged from 19 to 26 for men and from 17 to 33 for women; for controls ages ranged from 19 to 26 for men and from 20 to 33 for women. Additionally, the month of blood draw was the same for the schizophrenia/healthy pair to control for the effects of sun exposure on vitamin D level. Healthy subjects did not have relevant current or past psychiatric or physical illness as determined by psychiatric and physical examination and laboratory testing including toxicology screening.

Procedures and evaluations

At the time that the blood specimen was obtained each subject underwent neurocognitive testing. There were some differences among the tests used in the two studies; however the five key domains of verbal fluency, attention, processing speed, visual working memory and executive functioning were evaluated with the same neurocognitive test in both studies (Table 1).^{30–36} These test procedures were identical for all study subjects, and supervision of test administration was conducted by the same study investigator (RSK). To create a summary cognitive score, the results of each test were standardized to the mean and standard deviation of the subject's group, and the standard scores averaged together.

All schizophrenia subjects had clinical evaluations that included the Positive and Negative Syndrome Scale (PANSS)³⁷ and the Calgary Depression Rating Scale (CDRS),³⁸ conducted by trained, experienced masters-level clinicians. The PANSS positive subscale was the sum of items delusions, conceptual disorganization, hallucinations, hyperactivity, grandiosity, suspiciousness and hostility. The PANSS negative subscale was the sum of items blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal, abstract thinking, lack of spontaneity and stereotyped thinking.

Vitamin D assay methods

All samples used in this analysis were drawn between November 2002 and November 2004, except one outlier comparison sample drawn in February 2006. All samples were biobanked at baseline, prior to any study procedures. Serum samples from

TABLE 1. Neurocognitive test battery

Domain	Test	Description
Verbal fluency	Controlled Oral Word Association Test (COWAT)	Subjects are asked to generate as many words as possible beginning with F, A and S in three separate trials of 60 s.
	Category Instance Generation (CIG)	Subjects are asked to name as many words as possible in 60 s within each of three categories (animals, fruits, vegetables).
Attention	Continuous Performance Test (CPT)	Subjects are asked to respond to a series of 450 two-digit numbers and then a second series of 450 four-digit numbers presented on a computer screen at a rate of one per second by lifting a finger from a mouse key whenever the number is identical to the previous number in the series.
Processing speed	WAIS-R Digit Symbol Test (Digit Symbol)	Each number (one through nine) is associated with a different simple symbol, and the subject is asked to copy as many symbols associated with the numbers as possible in 90 s.
Visual working memory	Computerized Task of Visuo-Spatial Working Memory (CTVSWM)	Subject focus on a cross on a computer screen. While the cross is fixated, a cue appears for 150 ms in one of 32 possible locations at a 4.5-inch radius from the cross. A delay period (5 or 15 s) is then imposed. During the delay, a series of geometric shapes appears in place of the fixation cross. The subject must press the space bar whenever the diamond shape appears. After the delay, the cross returns, and the subject must point on the computer screen to where they remember seeing the cue. Mean error in millimetres (distance between recall and actual target) is calculated for each subject for each type of trial.
Executive function	Wisconsin Card Sorting Task (WCST)	Subjects sort a series of stimulus cards that differ by shape, colour and number, with the correct sorting strategy changing after 10 consecutive correct responses. The number of perseverative errors, completed number of categories and additional consecutive cards in the final category is scored.

schizophrenia and control subjects were stored at -80°C . In November 2010, serum from 20 schizophrenia subjects and 20 matched controls were analysed for vitamin D status. Although we did not perform internal validation studies to verify the stability of the vitamin D samples, the literature clearly indicates that 25-hydroxy vitamin D (25OHD) is stable at least 40 years if samples are stored at -20°C or lower.³⁹ Serum vitamin D was measured by chemiluminescent immunoassay as 25OHD using the ISYS Autoanalyzer (Immunodiagnosics Systems, Inc., Scottsdale, AZ, USA) at the Clinical and Translational Research Lab of the Maine Medical Center Research Institute, Scarborough, Maine. Vitamin D levels were classified as insufficient if the value of 25OHD was $<30\text{ ng mL}^{-1}$ and sufficient if the value was $\geq 30\text{ ng mL}^{-1}$.^{40,41}

Statistical methods

Baseline characteristics were compared using Student *t*-tests for continuous variables and chi-

squared test for dichotomous variables. We compared mean 25OHD levels between schizophrenia and comparison subjects using a Student's *t*-test. We determined the relationship of 25OHD with neurocognitive function and symptom severity measures using general linear modelling, reporting unadjusted and age, sex and years of education adjusted results. Statistical analyses were conducted using SAS (Cary, NC, USA).

RESULTS

Comparison of first-episode schizophrenia and healthy control groups for demographic variables and 25OHD

There were no significant differences between the schizophrenia and the control groups for age, sex or ancestry (see Table 2). The mean 25OHD level of the two groups was also similar ($28.2 \pm 12.6\text{ ng mL}^{-1}$ for the schizophrenia group and $29.9 \pm 14.3\text{ ng mL}^{-1}$ for the control group). Caucasian subjects had

TABLE 2. Demographics and 25OHD levels for first-episode schizophrenia subjects and healthy control subjects

	Schizophrenia subjects (n = 20)	Healthy control subjects (n = 20)	P-value
Mean age (SD)	23 (3.8)	24.5 (3.9)	NS
% male (n)	60 (12)	60 (12)	NS
% Caucasian (n)	85 (17)	85 (17)	NS
Mean 25OHD (ng mL ⁻¹)	28.2 (12.6)	29.9 (14.3)	NS

NS, not significant; SD, standard deviation; 25OHD, 25-hydroxy vitamin D.

significantly higher 25OHD levels compared with African American subjects (32.07 ± 12.6 vs. 14.55 ± 5.7 ng mL⁻¹; $P < 0.0001$), and women had significantly higher levels compared with men (37.0 ± 13.3 vs. 23.8 ± 10.6 ng mL⁻¹; $P < 0.001$). When considering only Caucasian subjects the 25OHD levels were still significantly ($P = 0.03$) lower for men (27.5 ± 10.2 ng mL⁻¹) than women (37.0 ± 13.3 ng mL⁻¹). The level of 25OHD did not vary with age (range 17–30 years) or years of education.

Vitamin D status and symptom severity in first-episode schizophrenia subjects

Within the schizophrenia subjects, there was no relationship of age, sex or years of education with any measure of symptom severity, with the exception of sex and positive symptoms ($\chi^2 = 5.4$, $P = 0.02$). Within the schizophrenia group, more severe negative symptoms were associated with low vitamin D level (adjusted $\chi^2 = 4.78$, $P = 0.03$; age-, sex- and education-adjusted $\chi^2 = 7.36$, $P = 0.007$) (Fig. 1a) and total symptom severity (unadjusted $\chi^2 = 4.52$, $P = 0.03$; age-, sex- and education-adjusted $\chi^2 = 5.90$, $P = 0.02$) (Fig. 1b); positive symptom severity were associated with lower 25OHD at a trend level (unadjusted $\chi^2 = 3.73$, $P = 0.053$; age-, sex- and education-adjusted $\chi^2 = 2.05$, $P = 0.15$) (Fig. 1c). There was no relationship of 25OHD with depressive symptoms as measured by the CDRS. Schizophrenia subjects with insufficient vitamin D on average had significantly lower scores on the total PANSS and the negative symptom subscale, with a trend towards lower positive symptom subscale scores (see Table 3).

Vitamin D status and neurocognitive results in first-episode schizophrenia subjects and healthy control subjects

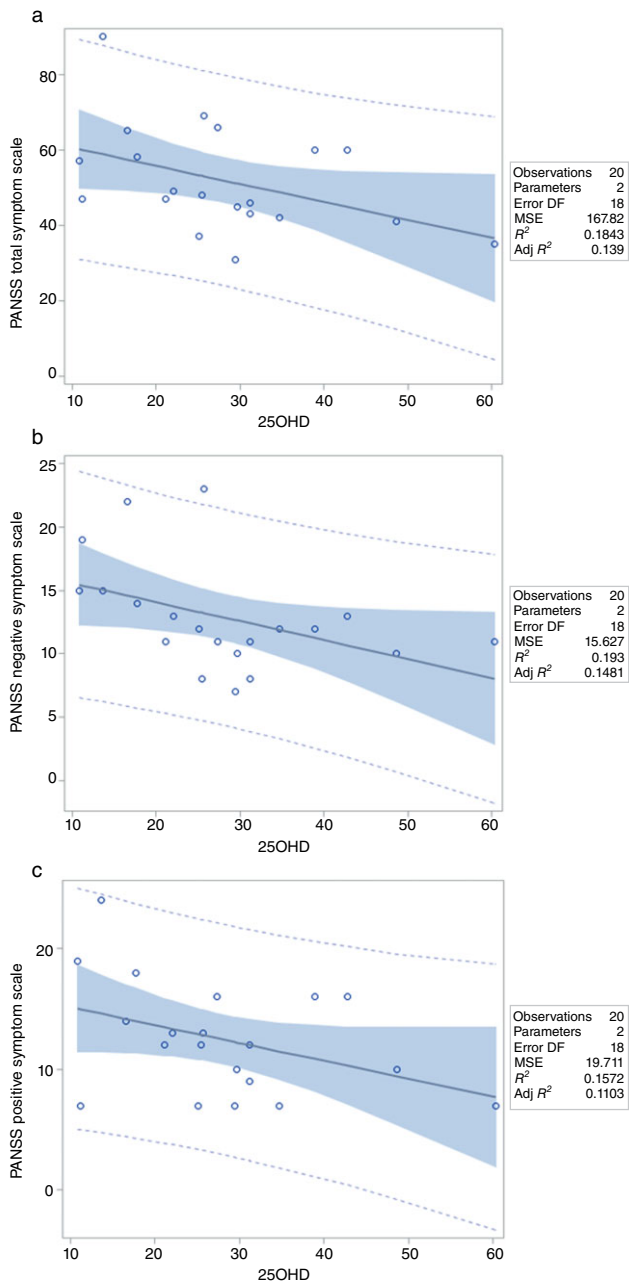
Among the schizophrenia subjects, lower 25OHD levels were associated with more severe cognitive deficits as measured by the cognition summary score (unadjusted $\chi^2 = 9.03$, $P = 0.003$; age-adjusted

$\chi^2 = 8.96$, $P = 0.003$; sex-adjusted $\chi^2 = 4.05$, $P = 0.04$; education-adjusted $\chi^2 = 5.53$, $P = 0.02$, full model-adjusted $\chi^2 = 2.0$, $P = 0.16$) (Fig. 2a). Within the individual test results, only lower verbal fluency scores were associated with low vitamin D status in this group, but this relationship did not remain after adjustment for sex (unadjusted $\chi^2 = 7.2$, $P = 0.007$). We did not find a relationship between 25OHD levels and cognitive function in healthy control subjects (Fig. 2b). Additionally, there was not a significant difference in performance on the neurocognitive summary score or individual domains for healthy control subjects with insufficient compared with sufficient vitamin D status.

DISCUSSION

This study is the first, to our knowledge, to report an association of vitamin D insufficiency and more severe negative symptoms and poorer neurocognitive function in patients with schizophrenia. These findings lead us to hypothesize that inadequate vitamin D status may account for some portion of the symptom burden experienced by persons with schizophrenia. As much of the disability experienced by persons with schizophrenia is related to severity of negative and cognitive symptoms⁴² and there are currently no approved pharmacologic methods to treat these symptoms, we hypothesize that correcting vitamin D insufficiency in schizophrenia could fill a critical role. It has been shown that dietary intake of vitamin D is associated with decreased risk of moderate and high-level psychotic symptoms in women from the general population in Sweden.⁴³ It is conceivable that vitamin D replacement could be a low-cost intervention that may reduce symptom burden in patients with schizophrenia who have low 25OHD levels. Even in the absence of definitive studies showing benefit of vitamin D supplementation for cognition and negative symptoms, correction of insufficient vitamin D status is strongly recommended for

FIGURE 1. The relationship of Positive and Negative Syndrome Scale (PANSS) total (a), negative (b) and positive (c) scales with 25OHD levels. (—) fit; (□) 95% confidence limits; (-----) 95% prediction limits.



prevention of osteoporosis,⁴⁴ and there is growing evidence for prevention of cancers, cardiovascular illness and diabetes.⁴⁵

There is convincing evidence that vitamin D has a role in healthy brain function. The vitamin D receptor and the enzyme needed for the hydroxylation of the precursor molecule 25OHD to the active form, 1- α -hydroxylase, have widespread expression in the adult human brain.⁴⁶ Many of these brain regions

are implicated in schizophrenia, including the hippocampus, thalamus, hypothalamus, amygdala, prefrontal cortex, cingulate gyrus and temporal lobe. Evidence of a correlation between development of schizophrenia and low prenatal and early life vitamin D status has been demonstrated in many studies. There is a highly significant peak in schizophrenia births in winter time,²² when risk of vitamin D deficiency is high. Incidence of schizophrenia is higher in immigrants, especially dark-skinned people moving to higher latitudes,²⁵ a scenario which promotes low vitamin D levels. A Finnish birth cohort study showed that vitamin D supplementation of at least 2000 IU per day in male infants during the first year of life reduced the risk of developing schizophrenia by 77% compared with those receiving less than 2000 IU per day.²³ Finally, low maternal vitamin D status may increase the subsequent risk of schizophrenia in the developing fetus.²⁴ A plausible role in schizophrenia pathology is also suggested by the finding that vitamin D acts to regulate transcription of many genes involved in pathways implicated in schizophrenia, including genes involved in synaptic plasticity, neuronal development and protection against oxidative stress.⁴⁷

In this study, those with schizophrenia were no more likely to have insufficient vitamin D than those in the healthy control group, indicating that low vitamin D status in late adolescence or early adulthood is unlikely to be causally related to schizophrenia risk in these subjects. We matched control subjects to patients based on sex, age and date of blood draw, three important factors affecting vitamin D level. Unfortunately, we were unable to control for body mass index (BMI), smoking status, dietary vitamin D intake and activity level that are other important factors affecting vitamin D status. Additionally, there was little ethnic diversity in the sample that will limit the ability to generalize results to different populations. A particular strength of this study is that all subjects did not receive more than 16 weeks of cumulative antipsychotic treatment, and duration of psychosis was less than 5 years. Despite this, exposures of this length of time may be sufficient to impact vitamin D status through increases in BMI. It is hypothesized that antipsychotic associated hyperprolactinaemia is a risk factor for osteoporosis by causing hypogonadism,⁴⁸ but it is not known whether there are direct effects of the antipsychotic medications on vitamin D status. Despite all of these risk factors for low vitamin D status, an equal percentage of the first-episode schizophrenia and healthy control subjects had insufficient 25OHD levels, roughly half. Two other

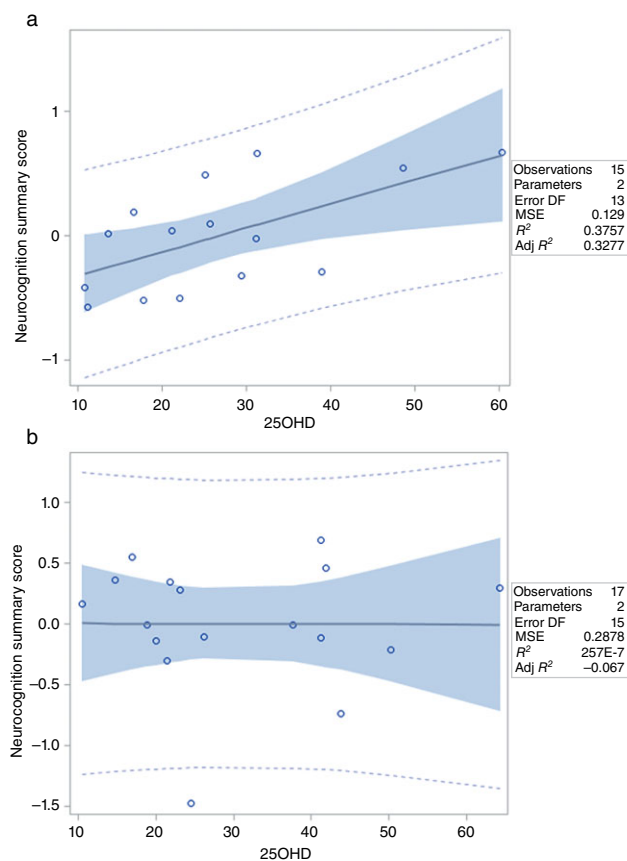
Vitamin D and schizophrenia symptoms

TABLE 3. Symptom scores (mean and SD) for first-episode schizophrenia subjects with insufficient (<30 ng mL⁻¹) and sufficient (≥30 ng mL⁻¹) 25OHD levels

	Insufficient 25OHD <i>n</i> = 11	Sufficient 25OHD <i>n</i> = 9	Adjusted <i>P</i> -value*	Unadjusted <i>P</i> -value
Total PANSS	57.6 (14.6)	44.8 (9.8)	0.06	0.02
PANSS negative subscale	14.8 (4.7)	10.4 (1.9)	0.04	0.006
PANSS positive subscale	14.1 (5.0)	10.4 (3.6)	0.20	0.054
Calgary Depression Rating Scale	11.5 (2.5)	10.4 (2.1)	0.36	0.30

NS, not significant; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; 25OHD, 25-hydroxy vitamin D.

FIGURE 2. (a) Relationship of 25-hydroxy vitamin D (25OHD) level and neurocognitive function: first-episode schizophrenia subjects. (—) fit; (■) 95% confidence limits; (---) 95% prediction limits. (b) Relationship of 25OHD level and neurocognitive function: healthy comparison subjects. (—) fit; (■) 95% confidence limits; (---) 95% prediction limits.



small studies from Europe similarly found low vitamin D levels in about half of adult schizophrenia patients.^{49,50} A recent study of 136 adolescents consecutively admitted to inpatient psychiatry units in France found an alarming 95.5% had 25OHD below the recommended 30 ng mL⁻¹, but with no correlation between use of antipsychotics, gender or BMI

and vitamin D status.⁵¹ Future studies to elucidate the impact of antipsychotic medications on vitamin D status are needed.

The relationship of vitamin D status to cognitive function has only been investigated in observational studies to date. Most recently, a large database analysis of 3325 American adults aged 65 years and older from the Third National Health and Nutrition Examination Survey (NHANES III) found that vitamin D deficiency was associated with increased odds of cognitive impairment.¹⁷ These results are in keeping with another population study of 752 women aged 75 years and older living in France. Those with vitamin D deficiency (<10 ng mL⁻¹) had lower scores on the Pfeiffer Short Portable Mental State Questionnaire compared with those with greater vitamin D levels ($P < 0.001$).¹⁶ The same investigators looked at a larger sample of 5596 community-dwelling women in France (mean age 80 years) and found that those with inadequate dietary intake of vitamin D (<35 μg week⁻¹) had significantly lower mean cognitive scores on the Pfeiffer Short Portable Mental State Questionnaire compared with those with adequate intake (>35 μg week⁻¹). This held after potential confounders were considered (age, BMI, sun exposure at midday, season, disability, number of chronic diseases, hypertension, depression, use of psychoactive drugs and education level).¹⁵ In a recent review, 4 out of 6 cross-sectional studies included found subjects with a lower vitamin D at baseline subsequently had higher cognitive decline over the course of 4–7 years compared with subjects with higher baseline vitamin D levels.⁵² However, Slinin and colleagues⁵³ did not find significant difference in cognitive functioning using the modified mini-mental state examination (MMSE), and lack of correlation between 25OHD and measures of executive and learning functions have also been reported.^{54,55} Similarly, low vitamin D levels were found to be common among geriatric inpatients, but there was no relationship between MMSE scores and vitamin

D levels.⁵⁶ Another cross-sectional study looking at healthy subjects representative of the US population found no association between cognitive functioning and vitamin D levels; in fact their study found that elderly subjects with the highest vitamin D levels were the poorest performers in neurocognition.⁵⁶ In our study, we found that among young adults with schizophrenia lower 25OHD levels were associated with more severe cognitive deficits as measured by the cognition summary score and lower verbal fluency scores. This relationship was not found in our matched healthy control subjects, which is in keeping with results of an analysis of NHANES data for healthy adolescents and adults less than 60 years of age.⁵⁵ It is possible that schizophrenia patients with more severe negative and/or cognitive symptoms would have lifestyles that lead to lower vitamin D status. These symptoms, including social isolation and amotivation, would be associated with lower overall level of functioning potentially leading to poorer nutrition and less time spent outdoors that would contribute to lower 25OHD. Additionally, subjects with more severe negative symptoms would be expected to initiate action less quickly or competently, which may lead to lower verbal fluency scores, falsely lowering cognitive results.

Vitamin D deficiency has been investigated as a mediator of depression. Another analysis of the NHANES III database found that young adults deficient in vitamin D had significantly higher likelihood of depression compared with those who were not.¹⁹ Also, a randomized clinical trial investigated the effects of a 1 year course of vitamin D or placebo on mood. Subjects with insufficient vitamin D status had significantly lower Beck Depression Inventory scores at baseline. Subjects receiving 40 000 IU vitamin D₃ had greatest improvement in this measure of depression, with lesser improvement when 20 000 IU vitamin D₃ was given, and no change when placebo was given.¹⁸ In patients with seasonal affective disorder randomized to either phototherapy or vitamin D supplementation, the patients who received vitamin D treatment showed improvement in psychological tests whereas the phototherapy group remained the same.⁵⁷ On average our schizophrenia subjects were experiencing mild depression as measured by the CDRS, and there was no relationship between scores on this scale and vitamin D status.

The current US guidelines for optimal vitamin D levels were developed for the prevention of significant bone pathology, especially rickets in children. Recently, the Institute of Medicine recommended that 25OHD levels below 12 ng mL⁻¹ be considered

indicative of deficiency and between 12 and 20 ng mL⁻¹ indicative of insufficiency.⁵⁸ However, these recommendations are very controversial as levels in this range have been implicated in numerous human disorders including cardiovascular disease, diabetes, cancer, multiple sclerosis, allergy, asthma and obesity.^{33,34} For these reasons, a 25OHD level at or above 30 ng mL⁻¹ is recommended by many clinicians and researchers⁵⁹ as optimal for good health and disease prevention, and with some finding additional benefits up to 60 ng mL⁻¹.⁶⁰ Our preliminary findings are consistent with the vast majority of published work that supports a need for higher vitamin D intake for most persons living in temperate climates. Oral supplementation with vitamin D₃ is inexpensive and toxicity occurs only with very high doses.^{60,61}

Our study involves only 20 subjects early in the course of schizophrenia and 20 matched healthy comparison subjects. With this small sample size, there may be both Type I errors, as we did not correct for multiple comparisons, and Type II errors, that is, missing more subtle adverse effects of insufficient vitamin D status on schizophrenia symptoms. In addition, the question of reverse causality (worse negative and cognitive symptoms leading to lower vitamin D status) can never be conclusively answered in a cross-sectional study such as this one. Although the results of our pilot study raise important questions for patients with schizophrenia, it is premature to draw any conclusions regarding whether vitamin D supplementation can improve schizophrenia symptoms. Treatment recommendations for schizophrenia cannot be made based on these findings, but require well-designed placebo controlled clinical trials.

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