Serum Vitamin D Levels in Relation to Schizophrenia: A Systematic Review and Meta-Analysis of Observational Studies

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Introduction: Although several observational studies have investigated the association between vitamin D status and schizophrenia, we are aware of no comprehensive meta-analysis in this regard.

Objective: We aimed to conduct a systematic review and a meta-analysis of observational studies to summarize the available data on the association between serum vitamin D levels and schizophrenia.

Methods: A systematic research on all published articles until October 2013 was conducted in PubMed, ISI (Web of science), SCOPUS, and Google Scholar. All observational studies that had measured serum vitamin D levels in schizophrenic patients were included in the systematic review. After considering exclusion criteria, we had 19 studies for the systematic review that were included in three separate meta-analyses: 1) a meta-analysis on mean levels of 25-hydroxyvitamin D [25(OH)D] (n = 13); 2) a meta-analysis on the prevalence of vitamin D deficiency (n = 8); 3) a meta-analysis on odds ratios (n = 8).

Results: Findings from a meta-analysis on means revealed that the overall mean difference in serum 25(OH)D levels between schizophrenic patients and control participants was −5.91 ng/mL [95% confidence interval (CI) −10.68, −1.14]. Subgroup analyses based on study design, the patient's hospitalization status, study quality, and study location did not explain between-study heterogeneity; however, type of biomarker assessed [25-dihydroxyvitamin D_3 vs 25OH)D)] could account for some degree of heterogeneity. Results from the meta-analysis on the prevalence of vitamin D deficiency indicated that the overall prevalence of vitamin D deficiency in schizophrenic patients was 65.3% (95% CI 46.4%–84.2%). Findings from the meta-analysis on odds ratios indicated that vitamin D-deficient persons were 2.16 times (95% CI 1.32, 3.56) more likely to have schizophrenia than those with vitamin D sufficiency. No evidence of heterogeneity was detected.

Conclusion: We found a strong association between vitamin D deficiency and schizophrenia. However, randomized clinical trials are required to confirm our findings. (***J Clin Endocrinol Metab*** **99: 0000–0000, 2014)**

Schizophrenia is a group set of neuropsychiatric disorders characterized by symptoms like hallucinations, delusions, confused thinking, and disorganized speech (1) that could impose great costs to the health care system. In a systematic review on 188 studies from 46 countries, the median prevalence of schizophrenia ranged from 4 to 7 per 1000 persons, depending on the type of prevalence (1). Despite low prevalence of schizophrenia, it is one of the great contributors to global burden of disease (2).

Prevalence of schizophrenia is widely (>10-fold) different across geographic regions. It is highly prevalent in high latitudes and cold climates. The prevalence is also higher in black than Caucasian people (3). Moreover, schizophrenic persons tend to be born in the winter/spring

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Abbreviations: BMI, body mass index; CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; 25(OH)D_3, 25-dihydroxyvitamin D_3; OR, odds ratio; RR, relative risk.

seasons (4). Previous studies have shown that second-generation migrants compared with first-generation who migrate to colder climates are at higher risk of developing schizophrenia (5). These ecological findings might imply the role of vitamin D in the etiology of schizophrenia because cutaneous production of vitamin D from sun exposure is less efficient at high latitudes, during winter, and in dark-skinned persons (6).

Although the role of vitamin D in schizophrenia has been investigated in several epidemiological studies, data are conflicting. In a Finnish birth cohort, vitamin D supplementation during the first year of life was associated with a reduced risk of schizophrenia in male subjects (7). In the dried blood samples of a Danish neonatal biobank, low concentrations of 25-hydroxyvitamin D_3 in neonates was associated with a 2-fold increased risk of developing schizophrenia later in life (8). Findings from most case-control studies on the serum levels of vitamin D in schizophrenic persons, compared with healthy controls, have also revealed significant inverse association between vitamin D status and schizophrenia (9). However, some studies have failed to find a significant association (10), and some others have found that higher vitamin D concentrations are associated with increased risk of schizophrenia (8). In addition, data on the relationship between sunlight exposure and schizophrenia did not provide convincing support for the link (11).

Although in a most recent mini-meta-analysis, schizophrenic patients have been found to have lower serum levels of vitamin D than healthy controls (12); due to an incomplete literature search and a significant between-study heterogeneity in that study, we aimed to conduct a comprehensive systematic review and meta-analysis to summarize available data on the association between serum vitamin D levels and schizophrenia.

Materials and Methods

Search strategy

A systematic search on all published articles until October 2013 was conducted in PubMed, ISI (Web of science), SCOPUS, and Google Scholar by two separate investigators (G.V. and P.S.) using the following MeSH key words: schizophrenia or mental disorders or psychiatric disorders and vitamin D or 25-hydroxyvitamin D or calcidiol or cholecalciferol or 25-hydroxyvitamin D [25(OH)D] or hydroxycholecalciferols or ergocalciferols or 25-hydroxyvitamin D_2 or dihydrotachysterol or calcifediol or dihydroxycholecalciferols or calcitriol. No language or time restrictions were applied. We examined the reference lists of included studies and contacted researchers in the specialty to identify any additional studies. Two reviewers independently screened the output of the search to identify potentially eligible studies.

Inclusion and exclusion criteria

All published articles that were observational studies, had been conducted on humans, and had measured serum levels of vitamin D in schizophrenic patients were included in the systematic review. Neither restriction for study design nor the biomarker of vitamin D status was performed. After removing duplicate citations, 1265 articles remained. The citations were reviewed through titles and abstracts by two separate researchers (G.V. and P.S.). We excluded 1240 articles due to not meeting the inclusion criteria, and finally 25 potential related articles remained for further assessment. We also did not include one study on maternal vitamin D status and risk of schizophrenia in offspring (13). Moreover, one study on vitamin D supplementation during the first year of life and risk of schizophrenia in adulthood was excluded due to lacking serum vitamin D levels (7). Furthermore, two studies that were in the abstract format in the scientific conferences were excluded due to lack of reporting relevant data (14, 15). We also found two other abstracts that seemed to have overlapped sample sizes (16, 17); therefore, we included only the one with larger sample size (16). One study by Kishimoto et al (18) that had measured only 1,25 dihydroxyvitamin D_3 was excluded from the systematic review. After these exclusions, 19 studies were used in this systematic review (8–10, 16, 19, 20–33) (Supplemental Figure 1). Required information was extracted and, if needed, was requested from the authors through e-mails. We included these 19 studies in three meta-analyses. Thirteen studies had reported means of serum 25(OH)D (9, 10, 19–23, 25, 26, 28, 29, 31, 32), eight had a reported prevalence of vitamin D deficiency in schizophrenic patients (9, 10, 16, 21, 24, 27, 29, 30), and eight studies had reported odds ratios for schizophrenia in vitamin D-deficient persons (8–10, 21, 24, 29, 30, 33). Separate analyses for means, prevalence, and odds ratios were done.

Data extraction

Required items of information were extracted from the published papers (Tables 1 and 2). It should be noted that we combined data for schizophrenic patients with those with schizoaffective or other schizophrenia spectrum disorders and reported the combined number as the patients' sample size. We also converted all serum levels of vitamin D to nanograms per milliliter. If a study had reported an SE (19) or 95% confidence interval (CI) for means of serum 25(OH)D (31), we calculated the SD. In addition, for one study that reported medians and the interquartile range of serum 25(OH)D levels (26), mean and SD was also calculated using required formulas (34).

Quality assessment of studies

The quality of studies included in this meta-analysis was examined by the Newcastle-Ottawa scale (35). Based on this method, the maximum of nine score can be awarded to each study for selection of study groups (schizophrenic patients and control group), comparability of groups, and substantiation of exposure (vitamin D deficiency). For cross-sectional studies that were included in the analysis, we used the same method by considering patients other than schizophrenia as the control subjects. The quality score ranged from 5.0 to 8.0, with the median of 6.0. In the current analysis, we considered the quality scores of greater than 6 as high-quality studies and those with the score of 6 or fewer points were considered as low-quality studies.

Table 1. Summary of Cross-Sectional Studies on Serum Levels of Vitamin D and Schizophrenia

First Author	n			In-/ Outpatient	Age, y[a]	Country	Biomarker	VDD Definition	VDD Prevalence, %		Mean Levels of Vitamin D		Diagnosis Tool	Vitamin D Assessment Method
	T	F	SCZ						SCZ	Controls[b]	SCZ	Controls[b]		
Abdullah et al (21)	290	91	185	In	40.0	United States	25(OH)D	Low: <32 ng/mL	88.6	91.45	21.2	20.16	ICD-9 BPRS	ICMA
Berg et al (22)	133	42	108	Both	Range 18–65	Norway	25(OH)D				17.22	17.35	DSM-IV	RIA
Humble et al (26)	117	64	20	Out	43.7	Sweden	25(OH)D				14.02	19.28	ICD-10	RIA
Hummer et al (27)	75	18	75	Both	34.8	Austria	25(OH)D_3	ND	Females: 52.9 Males: 50.9			ICD-10	ND	
Menkes et al (29)	102	46	49	In	Range 18–65	New Zealand	25(OH)D_3	Mild deficiency: 10–20 ng/mL	59.18	50.94	14.56	19.41	DSM-IV	ECLIA
								Severe: <10 ng/mL	26.53	11.32				
Murie et al (30)	32	0	25	In	44.1	Scotland	25(OH)D	Insufficient: 10–20 ng/mL	36	28.57			ND	LC-MS/MS
								Deficient: <10 ng/mL	56	71.42				
Partti et al (31)	6241	3433	48	Out	52.0	Finland	25(OH)D				15.58	17.51	SCID	RIA
Agarwal ()	63	26	63	Out	ND	United States	25(OH)D	Mild deficiency: 21–30 ng/mL	22.22			ND	ND	
									Moderate: 11–20	34.92				
									Severe: <10	15.87				

Abbreviations: BPRS, Brief Psychiatric Rating Scale; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*; ECLIA, electrochemiluminescence immunoassay; F, females; ICD, international center of disease; ICMA, immunochemiluminometric assay; LC-MS/MS, liquid chromatography-tandem mass spectrometry; ND, not defined; SCID, Structured Clinical Interview; SCZ, patients with schizophrenia spectrum disorders (schizophrenia and schizoaffective disorder); T, total number of participants; VDD, vitamin D deficiency.

[a] All values are mean unless indicated.

[b] Control group in these studies consists of psychiatric patients other than schizophrenia (depression, bipolar disorder etc).

Statistical analysis

The mean difference and SD of serum vitamin D levels in schizophrenic patients and control group, the prevalence of vitamin D deficiency in schizophrenic patients and its SE, and odds ratios (ORs) and 95% CIs for risk of schizophrenia in vitamin D deficient persons were used for the meta-analysis. Summary estimates with their corresponding SDs were derived by the method of DerSimonian and Laird by using a random-effects model, which incorporates between-study variability. Metaregression and subgroup analyses were performed to find the source of heterogeneity. Between-subgroup heterogeneity was evaluated using a fixed-effect model. Statistical heterogeneity between the studies was evaluated with Cochran's Q test. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or group of studies. Publication bias was assessed by visual inspection of funnel plots. Formal statistical assessment of funnel plot asymmetry was done with Egger's regression asymmetry test. Statistical analyses were carried out by the use of Stata, version 11.2 (Stata Corp). Values of $P < .05$ were considered statistically significant.

Results

Study characteristics

Of the 1265 articles found in our initial research, 19 studies including eight cross-sectional studies (seven full text articles and one abstract) (16, 21, 22, 26, 27, 29–31), 10 case-control studies (eight full text and two abstracts) (9, 10, 19, 20, 23–25, 28, 32, 33), and one nested case-control study (8) were considered in the systematic review and meta-analyses. These studies are summarized in Tables 1 and 2. Sample sizes of the included studies ranged from 17 to 848 persons, and in total 2804 participants aged 18–65 years were included in the systematic review. These papers have been published between 1988 and 2013; 11 of them (8, 20, 22, 23, 25–27, 30–33) were reported from European countries and eight (9, 10, 16, 19, 21, 24, 28, 29) from non-European countries. Based on the above-mentioned scoring method, six studies (9, 10, 23, 25, 28, 32) were rated high-quality studies, and seven reports (19, 20–22, 26, 29, 31) were defined as low-quality studies.

Findings from systematic review

Overall, 13 studies reported mean and SD for vitamin D (9, 10, 19, 20–23, 25, 26, 28, 29, 31, 32). The minimum and maximum difference between mean levels of vitamin D in schizophrenic patients and control group was 0.13 and 19.35 ng/mL, respectively. Moreover, most studies (9, 19, 23, 25, 26, 28, 29) had reported lower serum vitamin D concentrations in schizophrenic patients compared with the control group; however, some reports had failed to reach a significant difference (10, 20–22, 31, 32). Eight studies had reported the prevalence of vitamin D deficiency in schizophrenic patients (9, 10, 16, 21, 24, 27, 29,

Table 2. Summary of Case-Control Studies on Serum Levels of Vitamin D and Schizophrenia

First Author	n				In-/ Outpatient	Age, y		Country	Biomarker
	SCZ	F	Control	F		SCZ	Control		
Wyszogrodzka-Kucharska et al ()	60		38		Out	31.1	31.7	Poland	$25(OH)D_3$
Cha et al (24)	14		32		Out	ND	ND	South Korea	25(OH)D
Bergemann et al (23)	72	72	71	71	Out	33.8	33.7	Germany	25(OH)D
Doknic et al (25)	26	14	35	24	Out	31.3	32.2	Serbia	25(OH)D
Higuchi et al (19)	12	7	5	0	In	35.9	33.8	Japan	$25(OH)D_3$
Itzhaky et al (9)	50	16	50	37	In	40.2	39.7	Israel	25(OH)D
Jamilian et al (28)	100	32	100	50	Out	35.67	35.26	Iran	25(OH)D
Norelli et al (10)	40	8	20	9	In	42.8	44.2	New York	25(OH)D
Rey-Sánchez et al (32)	73	25	73	25	In	59.84	60.37	Spain	$25(OH)D_3$
Schneider et al (20)	34	15	31	12	In	61.89 38.9	61.24 38.8	Germany	$25(OH)D_3$
McGrath et al ()	424		424		ND	ND	ND	Denmark	$25(OH)D_3$

Abbreviations: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*; ECLIA, electrochemiluminescence immunoassay; F, females; ICD, international center of disease; LC-MS/MS, liquid chromatography-tandem mass spectrometry; ND, not defined; PANSS, Positive and Negative Syndrome Scale; PLC, protein liquid chromatography; SCZ, schizophrenic patients; VDD, vitamin D deficiency.

[a] All values are parentage of vitamin D deficiency unless indicated.

30). The prevalence of vitamin D deficiency was in the range of 14.3%–98%. Furthermore, one study (8) had reported a relative risk (RR) for the risk of developing schizophrenia in vitamin D-deficient participants, and for seven studies (9, 10, 21, 24, 29, 30, 33), ORs were calculated. The ORs of these eight studies ranged from 0.63 to 13.59.

Findings from meta-analysis on means

All eligible studies for the systematic review were included in the meta-analysis. Thirteen studies with 14 effect sizes were included in the meta-analysis of means (9, 10, 19, 20–23, 25, 26, 28, 29, 31, 32). Finding from the meta-analysis on these studies revealed that the overall mean difference in serum 25(OH)D levels between schizophrenic patients and control participants was −5.91 ng/mL (95% CI −10.68, −1.14) (Figure 1). However, between-study heterogeneity was significant (Q test, $P < .001$; $I^2 = 97.6\%$). To investigate the source of heterogeneity, subgroup analyses (based on study design, study location, type of biomarker assessed, hospitalization status, and quality score) were conducted (Table 3). The control group in the case-control studies consisted of healthy subjects with no history of psychiatric disorders, but in the cross-sectional studies, psychiatric patients, other than schizophrenia, had been considered as the control group. Therefore, the subgroup analysis based on study design (case control or cross-sectional) and the status of control participants (healthy or unhealthy) had the same results (Figure 1).

We found that a mean difference of serum levels of vitamin D between schizophrenic patients and the control group was significant in case-control studies, European and non-European countries, and studies that included inpatients. The overall mean difference of serum levels of

Table 2. Continued

VDD Definition	VDD Prevalence, %[a]		Mean Levels of Vitamin D		Matching Factors	Diagnosis Tool	Vitamin D Assessment Method
	SZC	Control	SCZ	Control			
ND	16	0			ND	DSM-IV	ND
Insufficient: 20–30 ng/mL	35.7	4.3			ND	DSM-IV	RIA
Deficient: <20 ng/mL	14.3	0					
			16.3	24.6	Age, sex	DSM-IV (ICD)-10	RIA
			9.45	28.8	Age, sex, BMI, education	DSM-IV PANSS	ECLIA
			12.6	22.3	ND	ND	PLC
Insufficient: 15–30 ng/mL	40.8	63.3	15.0	20.2	Age	PANSS	Immunoassay
Deficient: <15 ng/mL	57.1	24.5					
			18.82	21.34	Age	DSM-4-TR	ND
Normal: >30 ng/mL	17.5	20	19.5	22.7	Age, gender, race or ethnicity, BMI	DSM-IV	ND
Severe deficiency: <20 ng/mL	58	45					
Females			20.42	33.12	Age, sex, weight, height, gonadal status	DSM-IV CIE-10 (ICD-10)	RIA
Males			15.12	18.13			
			35.1	45.9	ND	DSM-III-R ICD-10	Immunoassay
Summarized RR for less than 16.22 ng/mL	RR 2.06 (95% CI 1.57–2.71)			Sex, exact date of birth, birth in Denmark, being alive	ICD-10	LC-MS/MS	

vitamin D between schizophrenic patients and the control group was not significant in cross-sectional studies and those that included outpatients. The subgroup analysis based on type of biomarker [25-dihydroxyvitamin D_3 ($25[OH]D_3$) vs 25(OH)D] revealed that the mean levels of serum vitamin D were significantly different between schizophrenic patients and controls in studies that assessed the vitamin D status through the measurement of 25-dihydroxyvitamin D_3 [$25(OH)D_3$] but was not significant for studies that considered 25(OH)D as a biomarker. When we examined the association based on study quality, we found a significant difference in mean levels of vitamin D between schizophrenic and control participants in both high- (quality score > 6) and low-quality (quality score ≤ 6) studies. After subgroup analysis, we found that the between-study heterogeneity could not be explained by study design, study location, hospitalization status, and quality of studies. However, type of biomarker assessed could account for some degree of heterogeneity such that for studies that assessed $25(OH)D_3$, the between-study heterogeneity was not significant (Q test, $P = .24$; $I^2 = 26.2\%$). A metaregression on 10 of 13 (9, 10, 19, 20, 23, 25, 26, 28, 31, 32) studies that had provided the mean age of schizophrenic patients and controls revealed that age could not explain the between-study heterogeneity ($\beta = .17$, $P = .27$, I^2 residual = 97.3%). Findings from the sensitivity analysis revealed that none of the studies significantly influenced the overall effect. Although a slight asymmetry was found in Begg's funnel plot, results from Egger's test showed no significant publication bias ($P = .34$).

Finding from meta-analysis on prevalence of vitamin D deficiency

Eight studies, with nine effect sizes (9, 10, 16, 21, 24, 27, 29, 30), that had data on vitamin D deficiency in

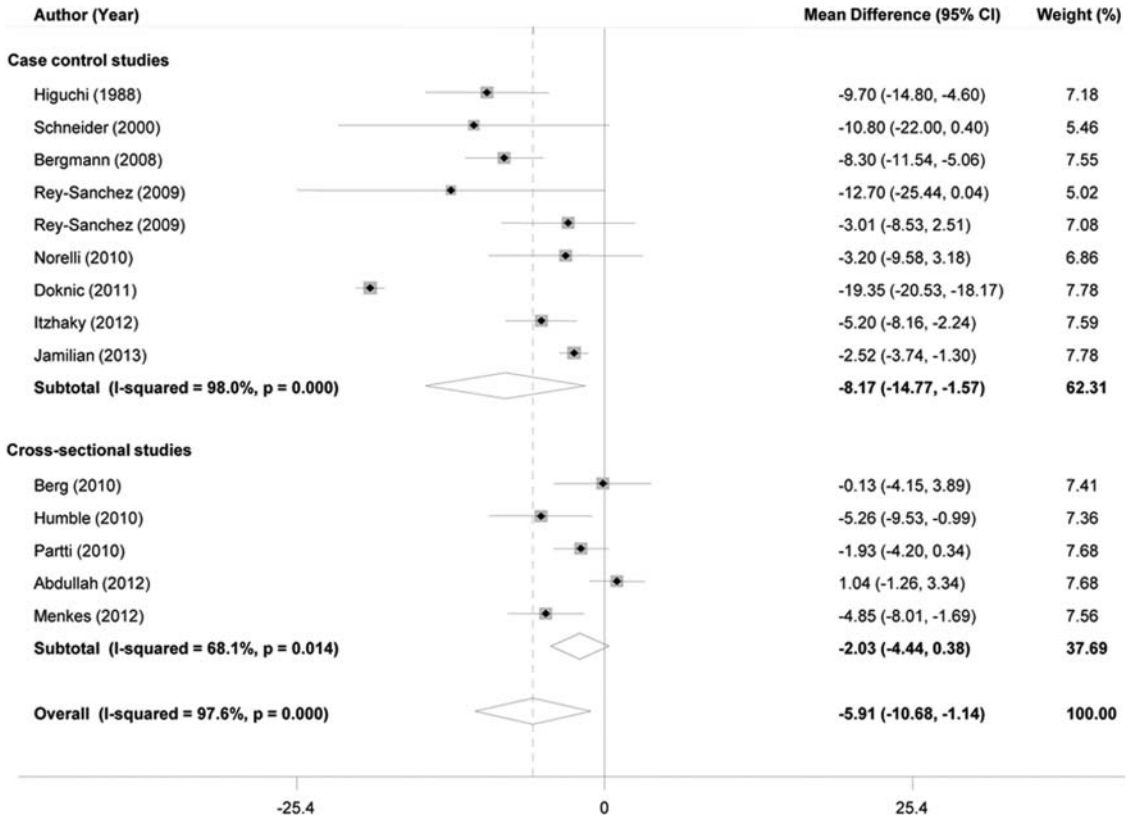

Figure 1. Forest plot of observational studies that assessed the mean difference of serum levels of vitamin D in schizophrenic patients vs control participants.

schizophrenic patients were included in this meta-analysis. The definition of vitamin D varied among studies. In some publications, the deficiency was defined as serum vitamin D levels of lower than 30 ng/mL, but some others had defined it as serum vitamin D levels of lower than 20 ng/mL or 10 ng/mL. The cutoff point of 20 ng/mL was frequently used in most studies (six of eight studies) (9, 10, 16, 24, 29, 30). One study had considered the cutoff point of 32 ng/mL for vitamin D deficiency (21), and the other one had not specified the cutoff point of vitamin D deficiency (27). Because we included these eight studies (with nine effect sizes) in the meta-analysis on the prevalence of vitamin D deficiency in schizophrenia, for the first six studies, the cut point of 20 ng/mL was used, and for the remaining two studies, we did not consider a new cutoff point and included them as was. We found that the overall prevalence of vitamin D deficiency in schizophrenic patients was 65.3% (95% CI 46.4%–84.2%) (Figure 2);

Table 3. Subgroup Analysis on Mean Serum Levels of Vitamin D and Schizophrenia

Subgroup	Number of Effect Sizes	Participants, n	I^2	Q Test	ES (95% CI)	*P* Value Between
Study design	14	1575	97.6	<0.001	−5.91 (−10.68, −1.14)	<.001
Case control	9	792	98.0	<0.001	−8.17 (−14.77, −1.57)	
Cross-sectional	5	783	68.1	0.014	−2.03 (−4.44, 0.38)	
Study location						<.001
European	8	806	97.5	<0.001	−7.48 (−14.82, −0.14)	
Non-European	6	769	77.2	0.007	−3.61 (−6.07, −1.15)	
Biomarker						.076
25(OH)D	9	1245	98.5	<0.001	−5.03 (−11.18, 1.12)	
$25(OH)D_3$	5	330	26.2	0.247	−6.45 (−9.49, −3.40)	
Quality score						<.001
High score (>6)	7	710	98.5	<0.001	−7.65 (−15.27, −0.03)	
Low score (≤6)	7	865	74.9	0.001	−3.45 (−6.21, −0.69)	
Hospitalization status	13	1442	97.8	<0.001	−6.38 (−11.37, −1.39)	<.001
In-patient	8	780	73.0	0.001	−4.76 (−7.91, −1.62)	
Outpatient	5	662	99.1	<0.001	−7.50 (−16.29, 1.29)	

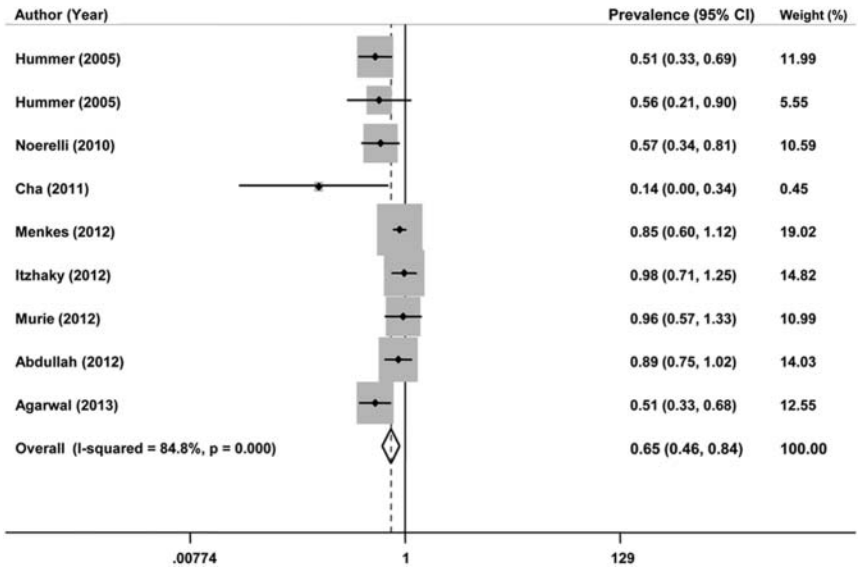

Figure 2. Forest plot of observational studies that assessed the prevalence of vitamin D deficiency in schizophrenic patients.

however, between-study heterogeneity was significant (Q test, $P < .001$; $I^2 = 84.84$). Subgroup analysis based on vitamin D deficiency cutoff points (<20 ng/mL vs <32 ng/mL and undefined jointly), study design (case-control or cross-sectional), type of biomarker used for defining deficiency [25(OH)D or $25(OH)D_3$], and study location (European or non-European) did not explain heterogeneity. In addition, the metaregression based on latitude did not provide a reason for the heterogeneity ($\beta = .014$, $P < .001$). A sensitivity analysis showed that none of the single studies had a significant effect on overall effect size. Although a slight asymmetry was seen in Begg's funnel plot, no proof of significant publication bias was found by Egger's test ($P = .47$).

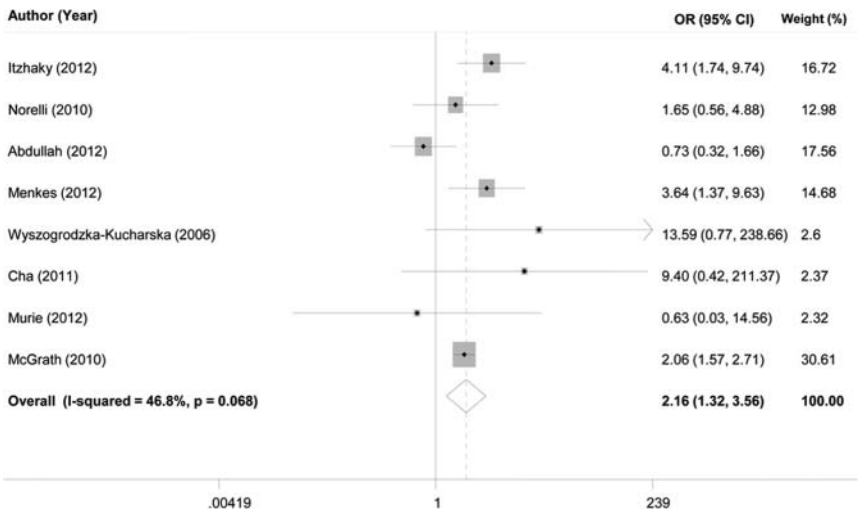

Figure 3. Forest plot of observational studies for the association of vitamin D deficiency and risk of schizophrenia (ORs).

Findings from meta-analysis on odds ratios

To further investigate the association, we did the meta-analysis on ORs. Totally, eight studies were included in this analysis. Seven of eight studies had not reported ORs, and we calculated the estimate using number of persons with schizophrenia in vitamin D sufficient (>20 ng/mL) and deficient individuals (<20 ng/mL) (9, 10, 21, 24, 29, 30, 33). One study had directly reported relative risks for developing schizophrenic in vitamin D-deficient individuals (8). Results from this meta-analysis are shown in Figure 3. We found that vitamin D-deficient persons were 2.16 times (95% CI 1.32, 3.56) more likely to have schizophrenia than those with vitamin D sufficiency. No evidence of heterogeneity was found ($I^2 = 46.8\%$, $P = .06$). No particular study had a significant impact on overall effect size based on the sensitivity analysis. Again, we did not find any significant publication bias using Egger's test ($P = .46$).

Discussion

Based on the findings of this meta-analysis, we found a strong association between vitamin D deficiency and schizophrenia. Mean serum vitamin D levels were significantly lower in schizophrenic patients compared with controls. The prevalence of vitamin D deficiency was also high in schizophrenic patients. Furthermore, vitamin D-deficient individuals were at greater odds of having schizophrenia. To our knowledge, this is the first comprehensive meta-analysis that examined the association of vitamin D deficiency with schizophrenia.

The results of our meta-analysis were in the same direction with other narrative or systematic reviews that reported an association between vitamin D deficiency and schizophrenia (36–38). Our findings on mean serum vitamin D levels were similar to a recently published mini-meta-analysis in this regard (12). However, that study had not included six relevant studies (10, 19, 20, 21, 23, 26) in the analysis. In addition,

Murri et al (12) have reported their final effect size as Hedges' (grams), which is very hard to interpret. But we were able to reach the exact mean difference of serum vitamin D levels between schizophrenic patients and controls that had not been derived in the previous study, and such findings might help other investigators for conducting future studies especially controlled clinical trials. Moreover, they found a significant between study heterogeneity, even after subgroup analysis, which further highlights their incomplete literature search. We conducted several subgroup analyses to find the source of heterogeneity. Finally, they have restricted their analysis to the studies that had reported mean levels of serum vitamin D and have not included the studies that had reported their effect size as prevalence of vitamin D deficiency or ORs.

In our subgroup analysis based on study design, schizophrenic patients had significantly lower levels of vitamin D than healthy controls in case-control studies. Only three of eight case-control studies (10, 20, 32) failed to find such a difference, which might be due to small sample sizes or the existence of vitamin D deficiency in controls. Some investigators have attributed this lack of a significant difference to the high body mass index (BMI) in control participants, which in turn is associated with lower levels of vitamin D (10). In the current study, we did not find a significant difference in mean serum vitamin D levels between schizophrenic patients and controls in cross-sectional studies. Considering psychiatric patients other than schizophrenia as the control (or comparison) group might explain this finding. Earlier studies have shown lower levels of vitamin D in these patients than a general healthy population (12, 39). Only two of five cross-sectional studies (26, 29) had reported significantly lower levels of vitamin D in schizophrenic patients than controls, which were patients with depression and bipolar disorders.

In this study, we conducted the meta-analysis on the prevalence of vitamin D deficiency in schizophrenic patients. We found a high prevalence of vitamin D deficiency in these patients. Although vitamin D deficiency is currently highly prevalent in all groups, such a high prevalence of vitamin D deficiency (65.3%) in schizophrenic patients, compared with the highest prevalence of 50% in healthy individuals around the world (40), highlights its possible role in brain function. However, further studies from different geographic areas are required to confirm this finding.

Our findings on ORs revealed that vitamin D-deficient individuals had 2.16 times greater odds of having schizophrenia compared with vitamin D-sufficient persons. However, except for a nested case-control study (8) that had reported RRs for developing schizophrenia in adulthood based on neonatal vitamin D deficiency, the ORs for other studies included in this meta-analysis were calculated using the prevalence of schizophrenia in vitamin D-sufficient and deficient persons. Therefore, causality cannot be inferred from this finding because in most studies the exposure and the outcome coexisted. It should be noted that in the study by McGrath et al (8), the fourth quintile (with serum vitamin D levels of 16.22–20.39 ng/mL) was considered as the reference. To include this study in the meta-analysis, first we obtained a summarized OR for first, second, and third quintiles and then used this summarized OR in the final meta-analysis. Therefore, for this single study, the cutoff point of vitamin D deficiency was less than 16.22 ng/mL, whereas for other studies in the meta-analysis, the cutoff point of vitamin D levels was less than 20 ng/mL. Our findings from this meta-analysis was in contrast to the increased risk of schizophrenia with serum vitamin D levels of 20.4 ng/mL in the study by McGrath et al (8). However, McGrath et al (9) have attributed this unexpected result to the deficiency of an active form of vitamin D due to the gene polymorphism.

The mechanisms through which vitamin D deficiency might be associated with schizophrenia are still unclear. These patients tend to spend less time on outdoor activities that might be the reason for decreased levels of vitamin D (38). Almost half of the studies included in our analysis had recruited inpatients. This could be a possible reason for reduced cutaneous synthesis of vitamin D in the skin. However, Norelli et al (10) showed no significant difference in serum levels of vitamin D between acute care patients with less than 60 days of hospitalization and long-stay patients (more than 6 months) in the hospital. Moreover, findings from in vitro studies suggest that consumption of antipsychotic drugs in schizophrenia might interact by vitamin D production in the skin (41). Some investigators believe that the relationship between vitamin D and schizophrenia might be linked with earlier stages of life. They have proposed that developmental vitamin D deficiency could be a risk factor for schizophrenia (8, 13, 36). Findings from animal models have shown that developmental vitamin D deficiency in the gestational period affect dopamine metabolism and alters dopamine system in developing brain of rats (42), and the dopamine hypothesis of schizophrenia seems to be the acceptable pathway in the pathology of schizophrenia (43).

Although we were able to include a considerable number of studies in our meta-analysis, we were unable to access the full text of some studies. Therefore, we either used the abstracts that contained part of data we needed (16, 24, 33) or excluded the studies that lacked the required data (14, 15). In addition, it must be kept in mind that in cross-sectional studies, psychiatric patients other

than schizophrenia were considered as the control group, and these patients have been shown to have lower levels of serum vitamin D compared with healthy subjects. Another limitation that must be taken into account is that schizophrenic patients tend to gain a significant amount of weight after being on antipsychotic medications (44). Therefore it is difficult to ascertain, based on the data presented in this study, whether the 25-vitamin D deficiency is the result of the treatment of the disease or potentially a causal factor. Our previous meta-analysis revealed an inverse relationship between serum vitamin D levels and BMI (45). Also, a number of antiseizure medications are also associated with significant 25-vitamin D deficiency (25, 27), and we were unable to consider antipsychotic drugs in our meta-analyses. In addition, data on other possible comorbidities that might be associated with vitamin D deficiency, especially for inpatient individuals, were not considered in our meta-analysis.

In conclusion, we found a strong association between vitamin D deficiency and schizophrenia. However, well-designed controlled clinical trials are needed to confirm our findings.

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References

1. **Saha S, Chant D, Welham J, McGrath J.** A systematic review of the prevalence of schizophrenia. *PLoS Med*. 2005;2(5):e141.
2. **Whiteford HA, Degenhardt L, Rehm J, et al.** Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013; 382(9904):1575–1586.
3. **Kinney DK, Teixeira P, Hsu D, et al.** Relation of schizophrenia prevalence to latitude, climate, fish consumption, infant mortality, and skin color: a role for prenatal vitamin d deficiency and infections? *Schizophr Bull*. 2009;35(3):582–595.
4. **Davies G, Welham J, Chant D, Torrey EF, McGrath J.** A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. *Schizophr Bull*. 2003;29(3):587–593.
5. **Cantor-Graae E, Selten J-P.** Schizophrenia and migration: a meta-analysis and review. *Am J Psych*. 2005;162(1):12–24.
6. **Holick MF.** Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr*. 1995;61(3):638S–645S.
7. **McGrath J, Saari K, Hakko H, et al.** Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. *Schizophr Res*. 2004;67(2–3):237–245.
8. **McGrath JJ, Eyles DW, Pedersen CB, et al.** Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. *Arch Gen Psychiatry*. 2010;67(9):889–894.
9. **Itzhaky D, Amital D, Gorden K, Bogomolni A, Arnson Y, Amital H.** Low serum vitamin D concentrations in patients with schizophrenia. *Isr Med Assoc J*. 2012;14(2):88–92.
10. **Norelli LJ, Coates AD, Kovasznay BM.** A comparison of 25-hydroxyvitamin D serum levels in acute and long-stay psychiatric inpatients: a preliminary investigation. *e-SPEN*. 2010;5(4):e187–e189.
11. **Kendell RE, Adams W.** Exposure to sunlight, vitamin D and schizophrenia. *Schizophr Res*. 2002;54(3):193–198.
12. **Murri MB, Respino M, Masotti M, et al.** Vitamin D and psychosis: mini meta-analysis. *Schizophr Res*. 2013;150(1):235–239.
13. **McGrath J, Eyles D, Mowry B, Yolken R, Buka S.** Low maternal vitamin D as a risk factor for schizophrenia: a pilot study using banked sera. *Schizophr Res*. 2003;63(1–2):73–78.
14. **Boerman R, Cohen D, Schulte P.** Do vitamin D levels in bipolar and schizophrenia outpatients differ? Outcome of a Dutch cross-sectional study. *Eur Psychiatry*. 2013;28:1.
15. **Wyszogrodzka-Kucharska A, Rabe-Jabłońska J.** Calcium balance and regulation in schizophrenic patients treated with second generation antipsychotics. *Psychiatr Pol*. 2005;39(6):1157–1171.
16. **Agarwal S.** High incidence of vitamin D deficiency in patients with schizophrenia. *Eur Psychiatry*. 2013;28:1.
17. **Agarwal S.** Hypovitaminosis D and hypotestosteronemia in schizophrenia patients. *Eur Psychiatry*. 2013;28:1.
18. **Kishimoto T, Watanabe K, Shimada N, Makita K, Yagi G, Kashima H.** Antipsychotic-induced hyperprolactinemia inhibits the hypothalamo-pituitary-gonadal axis and reduces bone mineral density in male patients with schizophrenia. *J Clin Psychiatry*. 2008;69(3): 385–391.
19. **Higuchi T, Komoda T, Sugishita M, et al.** Certain neuroleptics reduce bone mineralization in schizophrenic patients. *Neuropsychobiology*. 1988;18(4):185–188.
20. **Schneider B, Weber B, Frensch A, Stein J, Fritz J.** Vitamin D in schizophrenia, major depression and alcoholism. *J Neural Transm*. 2000;107(7):839–842.
21. **Abdullah AK, Khan S, Mustafa SF, Qutubuddin AA, Davis CM.** Vitamin D status and cardiometabolic risk factors in long-term psychiatric inpatients. *Prim Care Companion J Clin Psychiatry*. 2012; 14(1).
22. **Berg AO, Psychol C, Melle I, et al.** A cross-sectional study of vitamin D deficiency among immigrants and Norwegians with psychosis compared to the general population. *J Clin Psychiatry*. 2010;71(12): 1598–1604.
23. **Bergemann N, Parzer P, Mundt C, Auler B.** High bone turnover but normal bone mineral density in women suffering from schizophrenia. *Psychol Med*. 2008;38(8):1195–1201.
24. **Cha B, Shin YM, Kim YS, et al.** Vitamin D deficiency in schizophrenia, bipolar disorder and major depressive disorder compared to healthy controls. *Eur Neuropsychopharmacol*. 2011;21:S429–S430.
25. **Doknic M, Maric NP, Britvic D, et al.** Bone remodeling, bone mass and weight gain in patients with stabilized schizophrenia in real-life conditions treated with long-acting injectable risperidone. *Neuroendocrinology*. 2011;94(3):246–254.
26. **Humble MB, Gustafsson S, Bejerot S.** Low serum levels of 25-hydroxyvitamin D (25-OHD) among psychiatric out-patients in Swe-

den: relations with season, age, ethnic origin and psychiatric diagnosis. *J Steroid Biochem Mol*. 2010;121(1–2):467–470.
27. **Hummer M, Malik P, Gasser RW, et al.** Osteoporosis in patients with schizophrenia. *Am J Psych*. 2005;162(1):162–167.
28. **Jamilian H, Bagherzadeh K, Nazeri Z, Hassanijirdehi M.** Vitamin D, parathyroid hormone, serum calcium and phosphorus in patients with schizophrenia and major depression. *Int J Psychiatry Clin Pract*. 2013;17(1):30–34.
29. **Menkes DB, Lancaster K, Grant M, Marsh RW, Dean P, du Toit SA.** Vitamin D status of psychiatric inpatients in New Zealand's Waikato region. *BMC Psychiatry*. 2012;12:68.
30. **Murie J, Messow CM, Fitzpatrick B.** Feasibility of screening for and treating vitamin D deficiency in forensic psychiatric inpatients. *J Forensic Leg Med*. 2012;19(8):457–464.
31. **Partti K, Heliovaara M, Impivaara O, Perala J, Saarni SI, Lonnqvist J, Suvisaari JM.** Skeletal status in psychotic disorders: a population-based study. *Psychosom. Med*. 2010;72(9):933–940.
32. **Rey-Sánchez P, Lavado-García JM, Canal-Macías ML, Gómez-Zubeldia M, Roncero-Martín R, Pedrera-Zamorano JD.** Ultrasound bone mass in schizophrenic patients on antipsychotic therapy. *Hum Psychopharmacol*. 2009;24(1):49–54.
33. **Wyszogrodzka-Kucharska A, Rabe-Jablonska J.** Vitamin D deficiency and impaired parathormone metabolism as a risk factor of low bone mineral density in patients with diagnosis of schizophrenia treated with second generation antipsychotics. *Eur Neuropsychopharmacol*. 2006;16:S373–S374.
34. **Hozo SP, Djulbegovic B, Hozo I.** Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5(1):13.
35. **Wells G, Shea B, O'Connell D, et al.** The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
36. **Kesby JP, Eyles DW, Burne TH, McGrath JJ.** The effects of vitamin D on brain development and adult brain function. *Mol Cell Endocrinol*. 2011;347(1–2):121–127.
37. **Kiraly SJ, Kiraly MA, Hawe RD, Makhani N.** Vitamin D as a neuroactive substance: Review. *ScientificWorldJournal*. 2006;6:125–139.
38. **McGrath JJ, Burne TH, Feron F, Mackay-Sim A, Eyles DW.** Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. *Schizophr Bull*. 2010;36(6):1073–1078.
39. **Anglin RE, Samaan Z, Walter SD, McDonald SD.** Vitamin D deficiency and depression in adults: systematic review and meta-analysis. *Br J Psychiatry*. 2013;202:100–107.
40. **Holick MF, Chen TC.** Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*. 2008;87(4):1080S–1086S.
41. **Lauth M, Rohnalter V, Bergström Å, Kooshesh M, Svenningsson P, Toftgård R.** Antipsychotic drugs regulate hedgehog signaling by modulation of 7-dehydrocholesterol reductase levels. *Mol Pharmacol*. 2010;78(3):486–496.
42. **Kesby JP, Cui X, Burne TH, Eyles DW.** Altered dopamine ontogeny in the developmentally vitamin D deficient rat and its relevance to schizophrenia. *Front Cell Neurosci*. 2013;7:111.
43. **Howes OD, Kapur S.** The dopamine hypothesis of schizophrenia: version iii—the final common pathway. *Schizophr Bull*. 2009;35(3):549–562.
44. **Allison DB, Casey DE.** Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry*. 2001;62(suppl 7):22–31.
45. **Saneei P, Salehi-Abargouei A, Esmaillzadeh A.** Serum 25-hydroxy vitamin D levels in relation to body mass index: a systematic review and meta-analysis. *Obes Rev*. 2013;14(5):393–404.