Vitamin D Deficiency as a Risk Factor for Schizophrenia: A meta-analysis of Observational Studies

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Abstract

Background: Schizophrenia is a heterogeneous disorder in which there is interaction between genetic and environmental factors. Study have found that vitamin D deficiency is a risk factor for schizophrenia. We conducted a meta-analysis to investigate the relationship between schizophrenia and blood vitamin D level.

Methods: A systematic review and meta-analysis have been conducted. All published observational articles have been searched from PubMed, Web of Science, Scopus, Cochrane library and Embase until September 2019. The Newcastle-Ottawa scale was used to examine the quality of the included studies.

Results: A total of 38 articles have been included in this study. The lower level of vitamin D was found in people with schizophrenia compared with controls (WMD =-4.50, 95%CI [-6.69, -2.32]). Subgroup analyses based on study design, the patient's hospitalization status, quality of the study, outcomes, and the country explained part of between-study heterogeneity. No significant differences in publication bias were observed. The overall prevalence of vitamin D deficiency and insufficiency in schizophrenic patients were 66%, 95%CI [57%–76%] and 76%, 95%CI [69%, 83%], respectively. Subjects with schizophrenia were more likely to have vitamin D deficiency or vitamin D insufficiency compared to controls (2.03, 95%CI [1.49, 2.77]; 2.43, 95%CI [1.40, 4.23]).

Conclusion: The results of this systematic review show that low vitamin D levels might contribute to the development of schizophrenia. The prevalence of vitamin D deficient or insufficient in schizophrenia was higher than that in healthy controls or another psychotic disease .

Background

Vitamin D (Vit D) is an important hormone that is widely known for its essential role in calcium absorption and bone health [1]. Data support a role for Vit D within the central nervous system as a neuroprotective and dopamine modulating steroid [2]. However, Vit D deficiency is becoming a common problem in many countries. It is estimated that 1 billion people have Vit D deficiency or insufficiency worldwide [3]. Many studies have highlighted hypovitaminosis D as a potential environmental risk factor for various conditions such as multiple sclerosis, asthma, cardiovascular diseases, and, more recently, psychiatric disorders [4, 5]. A growing body of literature is related to vitamin D status and risk of brain disorders including schizophrenia or psychosis [6]. Patients with schizophrenia, in particular, are more likely to be deficient than individuals with other psychiatric disorders [7, 8]. Incidence of Vit D deficiency was found both increased in animal models (e.g., the litter of vitamin-D depleted pregnant female rats) and in humans with developing schizophrenia [9].

Schizophrenia is a chronic and complicated disorder characterized by multifaceted psychopathology of psychotic symptoms, negative symptoms and cognitive deficits [10]. Typical symptoms can be separated into positive symptoms (e.g., hallucinations, delusions, and thought disorder), negative symptoms (e.g., deficits in social interaction, emotional expression, and motivation), and cognitive dysfunction (e.g., impaired attention/information processing, problem-solving, processing speed, verbal and visual learning, and memory and working memory) [11]. Schizophrenia lifetime prevalence is about 1% of the general population, meaning millions of people worldwide suffer from the disease [12] which contributes to a substantial burden of disease globally (13.4 million years) [13].

Epidemiological data and data on different geographical regions suggest that schizophrenia is more common in those born in winter and spring [14, 15] and its prevalence also rises with increasing latitude [14, 16]. The prevalence is also higher in black than white [17]. For hypovitaminosis D is more prominent in winter, in high latitudes, and individuals with dark skin, there is an infer that vitamin D plays a vital role in schizophrenia. Besides, deficits in nutrients and vitamin D in long-term schizophrenia were observed from illness onset and were associated with worse symptomology [18]. Adults with schizophrenia also have been found to have lower serum 25-hydroxyvitamin D (25(OH)D) levels than the general population [8, 19].

A study conducted Vit D status on neonatal and risk of schizophrenia demonstrated that low vitamin D concentrations had a significantly increased risk of schizophrenia (up to twofold) compared to neonates with concentrations ranging between 40.5 and 50.9 nmol/L. Interestingly, neonates with excessive concentrations of vitamin D also had an elevated risk for this disorder [20]. While most of the epidemiological data or systematic review only reported that hypovitaminosis D is associated with schizophrenia [9, 21, 22]. Another study in the neonatal population found that Vit D supplementation during the first year of life was associated with a reduced risk of schizophrenia in males but not in females [23]. Some even have failed to find a significant association between Vit D and schizophrenia [24]. Conclusion on the prevalence of schizophrenia between male and female was also inconsistent [25-27]. Although there was a mass of researches on the relationship of schizophrenia and Vit D deficiency, it is still worth exploring further. Therefore, we undertook a systematic review and meta-analysis to investigate whether Vit D deficiency is associated with schizophrenia.

Methods

Search strategy

A systematic research on all published articles was retrieved by searching PubMed, the Cochrane Library, Embase, ISI (Web of science) and Scopus databases using the following combination of descriptors: (schizophrenia OR psychotic disorders OR mental disorders OR psychiatric) AND (vitamin D OR 25-hydroxyvitamin D OR calcidiol OR cholecalciferol OR hydroxycholecalciferols OR ergocalciferols OR 25-hydroxyvitamin D2 OR dihydrotachysterol OR calcifediol OR dihydroxycholecalciferols OR calcitriol) from inception to April, 2019. The references list of retrieved articles was also manually reviewed to identify relevant studies missed by the search strategy.

Inclusion and Exclusion criteria

The eligible studies must meet the following inclusion criteria: (1) original studies to evaluate the association of Vit D status and risk of schizophrenia; (2) providing the blood Vit D level of schizophrenic patients and control or prevalence of Vit D deficiency or insufficiency (VDD or VDI) of subjects. The animal

experiment, review and studies focus on the effects of Vit D supplements on schizophrenia were excluded. No restrictions on study design, biomarkers of Vit D, race, disease stage or severity. We also did not include one study with the outcome of 1,25(OH) D_3 [28]. Two studies with the cutoff point of 10 [29] or 12 ng/mL [30] and seven studies had no cutoff point of VDD or lack of relevant data [8, 20, 31-35] was excluded from this meta-analysis. We also found two other abstracts that seemed to have overlapped sample sizes [36, 37]; therefore, we included only the one with a larger sample size [36]. One study compared the difference between highland and lowland of Vit D of patients who lived in Tanah Karo also excluded[38].

Data extraction and Outcomes

All published articles were observed studies with full text or abstract, data of schizophrenia or schizoaffective or other schizophrenia spectrum disorders were merged. We collect information from each identified study include the study ID (first author and year of publication), number of each group, average age, country, diagnosis tool of schizophrenia, measurement of Vit D and outcomes. The primary outcome for the study was the peripheral blood level of Vit D. For consistency, Vit D present in nmol/L were converted to ng/mL by using the conversion factor (1 ng/mL = 2.5 nmol/L). Some studies reported medians and the interquartile range of Vit D levels[39-41], we calculated the mean and SD using required formulas [42]. One study [43] reported mean and 95% CI instead of SD, or means and SD of two groups such as male and female [44], respectively, we converted them to mean and SD according to the Cochrane Handbook for Systematic Reviews of Interventions. The secondary outcomes were the number of samples positive or ORs for VDD or VDI and differences between sex of serum Vit D in schizophrenic patients. VDD was defined as a serum 25(OH)D, a stable marker of Vit D status, the concentration of ≤ 20 ng/mL, which has been widely used in relative studies as the cut-off point for VDD [45]. VDI was defined as a concentration of 25(OH)D ≤ 30 ng/mL based on most of the included studies.

Quality assessment of studies

In the current analysis, the Newcastle-Ottawa scale [46] was used to examine the quality of case-control studies and a maximum of nine scores can be awarded to each study included in this meta-analysis. The quality score of greater than 6 as high-quality studies and those with a score of 6 or fewer points were considered as low-quality studies.

For cross-section studies included in this meta-analysis, we used an 11-item checklist which was recommended by the Agency for Healthcare Research and Quality (AHRQ) [47]. An item would be scored "0" if it was answered "No" or "Unclear"; if it was answered "Yes", then the item scored '1'. Article quality was assessed as follows: low-quality = 0-3; moderate-quality = 4-7; high-quality = 8-11.

Statistical analysis

Stata, version 14.0 (Stata Corp) were applied to collect relevant data and analysis in this meta-analysis. For outcomes, we chose weighted mean difference (WMD) to assess continuous variables (i.e. periphery blood levels of vitamin D), while risk difference (RD) or odds ratio to evaluate dichotomous outcomes such as VDD or VDI. Each numerical outcome value was presented with a 95% confidence interval (95% CI) as well. The standard error (SE) of the incidence of VDD or VDI were calculated for meta-analysis of the prevalence of VDD and VDI. Of note, when the incidence of VDD obey normal distribution, and n^*P , $n^*(1-P)$ were both bigger than 5, RD was used for evaluating, otherwise we used odds ratio (OR) to assess the prevalence of VDD or VDI. Differences in the prevalence of VDD and VDI between schizophrenia and controls were assessed by odds ratio. Summary estimates with their corresponding SDs were derived by the method of Der Simonian and Laird by using a random-effects model, which incorporates between-study variability. Heterogeneity across studies was assessed using the Q-statistic. Meta-regression and subgroup analyses were performed to find the source of heterogeneity using a random-effects model. Publication bias was detected by Egger's test and Begg's test, $P < 0.05$ was considered a significant publication bias. In addition, the sensitivity analysis was conducted to test the stability of results by Stata 12.0 software.

Results

Study characteristics

The detailed steps of the literature search flow and screening process were depicted in Figure 1. A total of 16869 articles were identified via a primary search of the aforementioned literature databases, from which 2359 citations were removed because of duplication. Screening of article title and abstract by separate two researchers (JL Zhu and WW Luo), 14395 citations were removed due not to meet the inclusion criteria and 112 potential related articles were reminded approximately. Further assessment of full text and abstract, 36 articles did not match on the schizophrenic patients, 9 articles conducted on capable of Vit D supplementation to schizophrenia, 10 articles without full text or abstract, and 14 articles lack outcomes or relevant data. Ultimately, a total of 31 articles included 20 case-control (18 full-text articles and 2 abstracts) and 11 cross-section studies (10 full-text articles and one abstracts) were considered in this meta-analysis.

Studies characteristics were summarized in Table 1 and Table 2. Sample sizes of included studies ranged from 17 to 6241 persons, and in total 2848 participants. Age span is from 17 to 79. These papers were published between 1987 and 2018; most of the diagnosis tools of schizophrenia were DSM-IV and ICD-10. No matter measured 25(OH) D_2 or 25(OH) D_3 and their measurements. Sixteen of them were reported from European countries and 19 from non-European countries. Quality assessment of studies showed that 5 of case-control studies [48-52] were considered as low-quality and the rest [24, 39, 44, 53-64] were high-quality studies. The quality score of cross-section studies showed that 3 of 11 were high-quality [40, 65, 66], one study assessed as low-quality [36] and the rest of the studies [41, 43, 67-71] were moderate-quality.

Mean concentration of 25(OH)D and schizophrenia

Twenty-nine study populations from 33 studies [24, 39-41, 43, 44, 48, 50, 52-65, 67, 70-75] were included in the meta-analysis of the mean level of 25(OH)D. As shown in Figure 2, the results indicated that there were statistically significant differences in mean concentration of 25(OH)D between schizophrenia and control group in case-control studies (WMD=-5.91, 95% CI [-7.90, -2.48], $P<0.001$) and cross-section studies (WMD=-2.60, 95% CI [-4.20, -0.99], $P=0.022$). However, between study-heterogeneity was significant (Q test, $P<0.0001$, $I^2=96.1\%$). Between group-heterogeneity implied significant difference between study design subgroups ($P=0.11$, $I^2=61.7\%$). Of note, the control group in the case-control studies consisted of healthy subjects with no history of psychiatric disorders while in the cross-sectional studies, psychiatric patients but non-schizophrenic were considered to be the control group. Consequently, we were able to conclude that, compared with healthy subjects or other psychiatric patients, peripheral blood mean level of 25(OH)D achieved inferior in schizophrenia patients.

To explore the source of heterogeneity, subgroup analysis (based on the quality evaluation, location, age, and hospitalized status among included observational studies) were conducted. As shown in Table 3, the results indicated that between study-heterogeneity in the age group, over 50 years old was insignificant ($I^2=0\%$) while the others were significant ($I^2>50\%$). Tests for subgroup difference manifested country, quality of study and hospitalization status showed no significant differences ($P>0.05$, $I^2<50\%$). Study design, age and outcome may be part of source of heterogeneity ($I^2>50\%$).

Besides, three studies had reported higher serum Vit D concentration for female subjects than male subjects[44, 59, 69], only Yazici, AB's study reported female had a lower levels compared with male[73]. At the same time, one research reported Caucasian subjects had significant higher 25(OH)D levels compared with African American subjects ($P<0.001$)[59].

Prevalence of VDD or VDI in schizophrenic patients

The definition of Vit D deficiency in schizophrenia patients was different among studies. For these differences, we did a subgroup analysis. Seventeen studies with the VDD defined as lower than 20 ng/mL[24, 35, 36, 39, 51, 61-67, 70, 72, 73, 76, 77] and nine studies with the VDI defined as lower than 30 ng/mL[24, 36, 39, 41, 49, 51, 59, 65, 73] were included in this meta-analysis. One study had considered the cutoff point of 32 ng/mL for VDD, and we summarized it into a group of VDI [41]. Of note, one citation has the result of all schizophrenic patients have the VDI (lower than 30 ng/mL), which could not include in the comparison [29]. Results implied that the overall prevalence of VDD and VDI in schizophrenic patients were 66% (95%CI [57%–76%]) and 76% (95%CI [69%, 83%]) (Figure 3), respectively. Heterogeneity between study was significant (Q test, $P<0.001$; $I^2=98\%$ and 88%) and heterogeneity between subgroup wasn't significant (Q test, $P=0.27$; $I^2=18.9\%$).

ORs

To further investigation the differences of prevalence of VDD or VDI between schizophrenia and controls, we calculated the OR of fifteen studies on VDD [24, 39, 49, 51, 61-68, 70, 72, 73] and ten studies on VDI [24, 41, 49, 56, 58, 62, 63, 65, 70, 73], respectively. The meta-analysis demonstrated that the odds ratio of VDD and VDI were 2.03, 95%CI [1.49, 2.77] and 2.43, 95%CI [1.40, 4.23], respectively (Figure 4 and 5). Heterogeneity was significant ($I^2=59\%$, $P=0.002$ or $I^2=64\%$, $P=0.003$). Subgroup analysis indicated that study design might explain part of the source of heterogeneity ($I^2=59.7\%$ and 55.7%).

Publication Bias

A funnel plot on publication bias for mean concentration of 25(OH)D was displayed in Figure 6, and the result of Egger's test ($t=0.65$, $P=0.521>0.10$), and Begg's test ($z=1.32$, $P=0.181>0.05$), indicated no evidence of significant publication bias, especially cross-section studies.

Sensitivity Analysis

For the mean concentration of 25(OH)D, a sensitivity analysis was carried out to verify the stability of the result, which was done by excluding studies seriatim at a time to resynthesize the data. As Figure 7 signified, sensitivity analyses revealed that no individual studies significantly affected the mean concentration of Vit D, which indicated statistically robust results.

Discussion

In the present meta-analysis, we identified 24 case-control studies and 14 cross-section studies investigating the association between schizophrenia and Vit D deficiency, but no randomized control trail. Even though there were 27 studies considered high-quality, substantial heterogeneity still be observed between study estimates for schizophrenia. No matter type of schizophrenia and stage of schizophrenia, mean concentration of Vit D in individuals unveiled that significant reductions in Vit D among people with schizophrenia than healthy controls or other psychiatric patients (WMD= -4.50, 95%CI [-6.69, -2.32], $P<0.0001$). Prevalence of deficiency (<20 ng/ml) and insufficiency (<30 ng/ml) both indicated that hypovitaminosis D was quite common in schizophrenia (69%, 95%CI [62%, 76%]). Odds ratio showed that subjects with schizophrenia were increased risk of VDD 2.03 times and 2.43 times of VDI compared to controls. Four studies included in this meta-analysis discussed the sex difference of Vit D between schizophrenia and healthy subjects. Three of them reported female have higher serum Vit D concentration than male[44, 59, 69], only one was the opposite[73]. Evidence have provided a sex difference in the risk of developing schizophrenia[25, 26], while Saha's meta-analysis found no significant difference between female and male[27].

This evidence synthesis suggests that schizophrenic patients have lower Vit D level compare with healthy adults and other psychiatric patients. However, Vit D level is often low even among healthy adults, with the prevalence of Vit D deficiency decreased from 30% to 20% of healthy Iranian adults aged 35 years and older approximately in 2001 to 2013 [78]. As we know, the vitamin D endocrine system plays a primary role in the maintenance of extracellular fluid calcium concentration. Vitamin D deficiency was associated with bone disease and many other conditions such as cardiovascular disease, respiratory disease, gastrointestinal disease, neurological disease and so on [79]. The relationship between vitamin D and schizophrenia has aroused great concern between

human being. Epidemiological studies observed that in individuals born in winter or spring, an area in high latitude has a slight but significant increased risk for schizophrenia [16, 80, 81]. Due to exposure to sunlight and the serum level of vitamin D play an essential role in it.

In observational studies, one of the primary sources of bias is confounding. In this study, confounders possibly due to differences in sample sizes, a tool of diagnosis, severity or stage of the disease, matching between cases and controls and causal environmental factors, and so on. Analysis of subgroup on country, quality of study and hospitalization status demonstrated there were no significant differences between subgroups. Study design, age and outcome might be part of the source of heterogeneity. Three studies even have a opposite conclusion compared with the others[39, 41, 74].

Schizophrenia is a heterogeneous disorder in which there is interaction between genetic and environmental factors. The environmental factors include the date of birth, place of birth and seasonal effects, infectious diseases, complications during pregnancy and delivery, substance abuse, stress and nutritional deficiencies (e.g., famine, folic acid, iron, vitamin D) [82-84]. Previous literature[85, 86] has described older age and dark skin as potential risk factors associated with vitamin D deficiency. Because of these factors, different concentration of Vit D between studies might be the source of heterogeneity.

In the database, our results of meta-analysis were similar to a previous paper in this regard excepted we did a relationship of gender and included some new studies [22]. For sex differences in the risk of a particular disorder can yield important clues regarding its pathogenesis and evidence for a sex difference in the risk of schizophrenia is inconclusive. Compared to this article, we have a more stringent inclusion strategy and data was unified with a standard algorithm.

At the same time, the limitations of our study should be considered. Firstly, all of the studies were observational study, and the quality of literature is relatively general. Secondly, all of the studies included in the literature and published by the database had some publication bias. Size of the sample and the results of studies could affect the publication bias. Finally, due to the lack of sufficient information about patients' sex and age, we were unable to conduct subgroup analysis according to these included studies. Therefore, it is uncertain whether these discrepancies may influence the result to a certain extent and the results should be interpreted with caution.

Abbreviations

Vit D: vitamin D; 25(OH)D: 25-hydroxyvitamin D; VDD: vitamin D deficiency; VDI: vitamin D insufficiency; AHRQ: Agency for Healthcare Research and Quality; MD: mean difference; RD: risk difference; 95%CI: 95% confidence interval; SE: standard error; OR: odds ratio; WMD: weighted mean difference; SZ, schizophrenia; C, control; VD, Vitamin D; VDD, Vitamin D deficient; VDI, Vitamin D insufficient; IA, Immunoassay; RIA, Radioimmunoassay; CLIA, Chemiluminescence immunoassay; RLM, Routine laboratory methods; EI, Electroluminescence; LC-MS/MS, Liquid chromatography-tandem mass spectrometry; NM, not mentioned; ELFA, Enzyme-linked fluorescent immunoassay; T, total; SZ, schizophrenia; CLIA, Chemiluminescence immunoassay; ECLIA: electrochemiluminescence immunoassay; RIA, Radioimmunoassay; RDM: the Roche Diagnostic method

Declarations

Acknowledgments

Not applicable.

Authors' contributions

Conceptualization: WXP, JLZ. Data curation: JLZ, WWL, XC, YL. Formal analysis: JLZ, WWL. Investigation: QZZ, XC, YL, JLZ. Methodology: QZZ, WXP. Project administration: WXP. Software: JLZ, XC, YL. Writing-original draft: JLZ, WWL. Writing-review and editing: WXP, QZZ. All authors have read and approved the manuscript.

Author's information

All researchers in the study were trained regarding the protocol and Good Clinical Practice guidelines.

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Availability of data and materials

Data are available from the first and the corresponding authors.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Baseline Characteristics for Case-control Studies included in Meta-analysis

Study ID	Number of Cases (%male)		Age (mean or range)	in/out patient	Diagnosis tool	Ethnicity or Country	Outcomes	Measurement of VD	Categories of VDD and VDI (ng/ml)	VDD or VDI		Mean level of VD (ng, nmol)	
	SZ	C								SZ	C	SZ	C
Higuchi-1987	12(42%)	5(100%)	18-57	in		Japan	25(OH)D3	HPLC				12.6±2.2	22.3±1.1
Schneider-2000	34(56%)	31(61%)	21-81	in	DSM-III-R	Germany	25(OH)D3	IA				35.1±26.1	45.9±11.1
Bergemann-2008	72(0%)	71(0%)	20-46	in	DSM-IV ICD-10	Germany	25(OH)D					16.3±7.9	24.6±10.1
Rey-Sánchez-2009	73(66%)	73(66%)	61	in	DSM-IV CIE-10	Spain	25(OH)D3	RIA	deficient:<15	F:19 M:33		F:20.42±26.05 M:15.12±11.96	F:33.12 M:18.13
Norelli-2010	40	20	18-65	in	DSM-IV	White Black	25(OH)D		deficient:<20 insufficient:<30	23 33	9 16	19.5±9.3	22.7±10.1
Cha-2011	14	32			DSM-IV	South Korea	25(OH)D	RIA	deficient:<20 insufficient:<30	2 5	0 1		
Doknic-2011	26(46%)	35(31%)	32	out	DSM-IV	Serbia	25(OH)D	CLIA				9.22±1.12	28.76±1.12
Jamilian-2013	100(68%)	100(50%)	35.5	in	DSM-4-TR	Iran	25(OH)D	RLM				18.8±4.56	21.32±1.12
Clelland-2014	64(48%)	90(49%)	18-65	in	DSM IV	African-American Caucasian Hispanic	25(OH)D	CLIA	insufficient:<30	44	42	31.63 ± 22.64	37.06 ± 11.12
Bogers-2016	80	29	42	both		Caucasian non-Caucasian	25(OH)D3		deficient:<20	63	17		
Itzhaky-2012	50(68%)	50(26%)	19-65	in	PANSS	Israel	25(OH)D	CLIA	deficient:<15 insufficient:<30	28 20	12 31	15.0±7.3	20.2±1.12
Yuksel-2014	81(58%)	40(48%)	18-65	out in	DSM-IV-TR	Turkish Kurdish Other	25(OH)D	EI	deficient:<10 insufficient:<20	35 40	12 22	7.92±2.89 14.99±4.89	14.94±1.12
Grados-2015	13	17		In	NM	Spain	25(OH)D	CLIA	deficient:<20 insufficient:<30			12.87±17.2	21.45±1.12
Graham-2015	20(60%)	20(60%)	17-33	Out	SCID	Caucasian African-American	25(OH)D	CLIA	deficient:<30	11		28.2±12.6	29.9±1.12
Zhu-2015	93(44%)	93(56%)	18-65	out	DSM-IV	Yellow	25(OH)D	RIA				10.55±5.32	17.48±1.12
Bulut-2016	80(53%)	74(53%)	18-55	out	DSM-IV TR	Turkey	25(OH)D	EI	deficient:<10 insufficient:<20	20 11	6 21	23.46±13.98	23.69±1.12
Endres-2016	60(58%)	3917(44%)	18-79	in	ICD-10	Germany	25(OH)D	CLIA	deficient:<20 insufficient:<30	48 9 3	2244 815 858	15.0±9.8	18±1.12
Akinlade-2017	60	30	19-55	in	DSM-IV ICD-10	Ibadan	25(OH)D	ELISA	sufficient:>30 deficient:<20 insufficient:<30	35 24	2 17	19.75±5.19	28.06±1.12
Kulaksizoglu-2017	64(56%)	54(57%)	18-65	out	DSM-IV-TR	Turkey	25(OH)D	CLIA				10.06±2.64	10.86±1.12
Salavert-2017	22(73%)	22(27%)	18-65	in	DSM-IV	European	25(OH)D	CLIA	deficient:<20	19	8	13.14 ± 5.96	22.63 ± 1.12
Ikonen-2019	40(55%)	4659(50%)	31	both	ICD-10	Finland	25(OH)D	HPLC-MS	deficient:<12 insufficient:<20 sufficient:>20	1 11 28	149 1172 3338	26.2±4.44	27.3±1.12
Yazici, AB-2019	189	109	41.4	in	DSM-IV	Turkey	25(OH)D	ELFA	deficient:<20 insufficient:<30 sufficient:>30	126 41 22	56 38 15	F:15.44±8.8 M:19.41±10.04 17.52±9.65	F:17.78 M:23.97 21.26±1.12
Yazici, E-2019	in:30 Out:30	28	19-65	both	DSM-IV DSM-IV	Turkey	25(OH)D	ELISA				in:16.20±17.93 out:11.37±4.58	13.69±1.12
Malik-2019	80	40	39.4	both	DSM-IV-TR	Pakistan	25(OH)D		deficient:<10 insufficient:<20 sufficient:>20	35 29 6	12 20 8		

Ⓜage; Ⓜgender; Ⓜethnicity; ⓂBMI; Ⓜeducation served; Ⓜgonadal status; Ⓜseason of recruitment

SZ, schizophrenia; C, control; VD, Vitamin D; VDD, Vitamin D deficient; VDI, Vitamin D insufficient; IA, Immunoassay; RIA, Radioimmunoassay; CLIA, Chemiluminescence immunoassay; RLM, Routine laboratory methods; EI, Electroluminescence; LC-MS/MS, Liquid chromatography-tandem mass spectrometry; NM, not mentioned; ELFA, Enzyme-linked fluorescent immunoassay

Table 2 Baseline Characteristics for Cross-section studies included in Meta-analysis

First Author	Number of Cases (%male)		Age (mean or range)	in/outpatient	Diagnosis tool	Country	Outcomes	Measurement of VD	Categories of VDD and VDI (ng/ml)	Number of VDD or VDI		Mean level of VD (ng/ml)	
	C	SZ								C	SZ	C	SZ
Humber-2010	97(54%)	20(40%)	43.7	out	ICD-10	USA	25(OH)D	RIA				19.7±5.9	14.6±5.1
Partti-2010	6193(45%)	48(42%)	52.0	out	SCID	Finland	25(OH)D	RIA				17.5±13.2	15.6±12.4
Abdullah-2012	105	185	40	in	ICD-9 codes 295	Whites Non-whites African-Americans Hispanics Asians	25(OH)D	CLIA	low:<32	97	164	20.2±11.0	21.2±9.4
Menkes-2012	53	49	18-65	in		New Zealand	25(OH)D3	ECLIA	deficient:<10 insufficient:<20	6 27	13 29	23.8±11.1	14.6±5.8
Murie-2012	8	25	19-69	in		Chinese	25(OH)D	LC-MS/MS	deficient:<10 insufficient:<20	5 3	14 9		
Agarwal-2013 a		63		out		USA	25(OH)D		deficient:<10 insufficient:<20 sufficient:<30		10 22 14		
Cieslak-2014		22(59%)		both		USA	25(OH)D		insufficient:<30		20		17.3 ± 8.9
Bazzano-2016	52	61	18-65	in		USA	25(OH)D		deficient:<20 insufficient:<30	32 28	19 13	23.5±10.2	21.8±11.9
Boerman-2016	118	202		out	DSM-IV	Holland	25(OH)D	CLIA	deficient:<12 insufficient:<20 sufficient:<30 optimum:>30	27 37 30 24	70 65 45 22	21.18±11.3	17.8±11.0
Lally-2016	96	324(60%)	43.8	out	ICD-10	Black White Asian Mixed	25(OH)D	CLIA	deficient:<10 insufficient:<20			14.3±8.1	11.5±6.7
Bruins-2018	309	1531	45	out		Caucasian African European Other	25(OH)D	LC-MS RDM	insufficient:<20	182	972		
Patel-2018	61	18	40.6 (18-79)	in	ICD-10	Black White Asian Mixed	25(OH)D	CLIA	deficient:<12 insufficient:<20 sufficient:>20			13.0±13.4	11.8±10.3
Yoo-2018		302 (56%)	40.7 (18-82)	in		Korea	25(OH)D		insufficient:<20 sufficient:>20		236 66		15.5±6.4
Zoghbi-2019		196 (60%)			DSM-IV	Lebanon	25(OH)D	CLIA	deficient:<10 insufficient:<20 sufficient:>20		22 89 85		

T, total; SZ, schizophrenia; CLIA, Chemiluminescence immunoassay; ECLIA: electrochemiluminescence immunoassay; RIA, Radioimmunoassay; RDM: the Roche Diagnostic method

Table 3 Subgroup analysis on mean serum level of vitamin D and schizophrenia

Subgroup	Number of Studies	Participants, n	Heterogeneity (I^2)	P value of significance test	Subtotal [95% CI]	Subgroup difference
Study design	33	12333	96.1%	$P<0.01$	-4.50 [-6.69, -2.32]	$P=0.11$, $I^2=61.7\%$
case-control	25	10857	96.9%	$P<0.01$	-5.91 [-7.90, -2.48]	
cross-section	8	1476	57.3%	$P=0.022$	-2.60 [-4.20, -0.99]	
Country						$P=0.23$, $I^2=31.7\%$
European	14	10205	97.6%	$P=0.006$	-6.37 [-10.88, -1.86]	
Non-European	19	2131	87.3%	$P<0.01$	-3.41 [-5.03, -1.78]	
Quality of study						$P=0.95$, $I^2=0\%$
High	29	12089	96.2%	$P<0.01$	-4.48 [-6.90, -2.06]	
Low	4	244	95.8%	$P<0.01$	-4.71 [-11.12, 1.70]	
Hospitalization status						$P=0.73$, $I^2=0\%$
Out	7	757	98.2%	$P<0.01$	-5.55 [-12.39, 1.28]	
In	23	6716	83.5%	$P<0.01$	-4.20 [-5.71, -2.68]	
both	3	4860	94.2%	$P<0.01$	-2.70 [-6.86, 1.46]	
Outcome						$P=0.15$, $I^2=50.7\%$
25(OH)D	28	12003	97.1%	$P<0.01$	-4.71 [-7.60, -1.83]	
25(OH)D3	5	330	64.9%	$P=0.022$	-7.18 [-10.74, -3.61]	
Age						$P=0.11$, $I^2=61.8\%$
<50	24	7663	97.1%	$P<0.01$	-5.14 [-7.79, -2.48]	
>50	9	4674	0.0%	$P=0.52$	-2.71 [-3.97, -1.45]	

Figures

Figure 1

Flow chart of literature searching

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

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