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ORIGINAL ARTICLE

EXPLORING THE RELATIONSHIP BETWEEN VITAMIN D LEVELS AND OBSESSIVE-COMPULSIVE DISORDER: A COMPREHENSIVE META-ANALYSIS AND SYSTEMATIC REVIEW

ZAHIRUDDIN OTHMAN[1], WAN NUR AMALINA ZAKARIA[2], ADI WIJAYA[3]

Abstract:

Background: *A growing body of research has implicated lower levels of vitamin D in the pathogenesis of neurological and psychiatric disorders including obsessive-compulsive disorder (OCD). The main of this study was to investigate the relationship between vitamin D levels and OCD.* ***Methods:*** *This meta-analysis follows the PRISMA guidelines and utilizes PubMed, Scopus, Web of Science, and Lens databases without temporal constraints. Six pertinent studies were selected to ensure methodological consistency and robustness in our analysis. Data were pooled using a Random-Effects Model to estimate the standard mean difference (SMD) for evaluation of the strength of association analyses.* ***Results:*** *Our analysis revealed a noteworthy reduction in vitamin D levels among individuals with OCD compared to controls (SMD = -0.603, 95% CI = -0.8001 to -0.4053, p < 0.001, I2 = 50.86%; Q statistic p = 0.093).* ***Conclusion:*** *These findings underscore the significant impact of vitamin D in the pathogenesis of OCD, suggesting its potential role in both the prevention and treatment of this psychiatric disorder. However, despite the compelling evidence presented, further studies are warranted to refine our understanding and draw more precise conclusions regarding the intricate interplay between vitamin D levels and OCD.*

Keyword: *Vitamin D, obsessive-compulsive disorder, random-effects model, meta-analysis*

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Introduction:

Vitamin D, crucial for bone health, is primarily synthesized through sun exposure and found in certain foods like liver, tuna, and salmon. Its deficiency is associated with various health issues, including mortality, skin diseases, heart conditions, cancer, and mental disorders.[1-8] The extensive expression of vitamin D receptors in organ systems has been implicated in the widespread systemic effects of vitamin D.[1,9]

Lower serum vitamin D levels have been linked to mental disorders.[10,11] Mental disorders, encompassing elements like psychological distress and mood swings, are complex and often associated with depression, characterized by persistent sadness or lack of interest.[10,11] Research suggests a potential role of vitamin D in mental disorders, supported by the

1. Department of Psychiatry, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kota Bharu, Malaysia
2. Human Genome Centre, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kota Bharu, Malaysia
3. Department of Health Information Management, Universitas Indonesia Maju, Jakarta 12610, Indonesia

Address of Correspondence: Dr. Zahiruddin Othman, Department of Psychiatry, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kota Bharu, Malaysia, E-mail: zahirkb@usm.my

presence of vitamin D receptors in various brain areas linked to psychological illness.[9,12] While the pathogenesis of psychological distress involves diverse mechanisms, studies show conflicting associations between low vitamin D levels and psychological distress.[13-16] Additionally, research on vitamin D deficiency's impact on memory and cognitive decline presents varying results.[17-19]

The current body of literature investigating the link between vitamin D and Obsessive-Compulsive Disorder (OCD) encompasses a variety of study designs, including observational studies, case-control studies, and reviews.[20] Some studies propose a potential association between lower vitamin D levels and increased susceptibility to OCD, emphasizing the crucial role of vitamin D in the biosynthesis of dopamine and catecholamines as a cofactor.[21] The deficiency of vitamin D may exacerbate OCD symptoms by impairing neurotransmitter synthesis and escalating inflammatory and oxidative stress.[20] However, conflicting results exist in the literature, with certain studies failing to establish a significant association.[22,23] A prior meta-analysis of serum vitamins and homocysteine levels in individuals with OCD found no correlation between vitamin D and OCD.[24]

The necessity for a meta-analysis arises to consolidate existing evidence and establish a more robust understanding of the relationship between vitamin D and OCD. Through the synthesis of data from diverse studies, a meta-analysis enhances statistical power, enabling the detection of subtle associations that might be obscured in individual investigations.[25] Additionally, it provides a means to identify sources of heterogeneity and explore potential moderating factors, contributing to a more nuanced interpretation of the overall evidence.[26] Conducting a meta-analysis is crucial for resolving conflicting findings, paving the way for a comprehensive and conclusive understanding of the interplay between vitamin D levels and OCD. This, in turn, holds the potential to inform clinical practices, guide future research endeavours, and facilitate the development of targeted interventions for individuals with OCD.

Methods:

Study design:

The methodology and outcomes were reported following the PRISMA framework.[27] A predefined protocol, registered under the International Prospective Register of Systematic Reviews (PROSPERO) database with the ID number CRD42024500226, guided the review. The protocol details can be found at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=500226.

Search for relevant literature:

A comprehensive online search was conducted across various databases, including PubMed, Scopus, Web of Science, and Lens encompassing all published research studies. The search queries employed to retrieve relevant information were as follows: (vitamin D OR vitamin D2 OR vitamin D3 OR ergocalciferol OR cholecalciferol OR 25-hydroxyvitamin D OR 3-epi-25-hydroxyvitamin D OR calcitriol OR dihydroxycholecalciferol) AND obsessive-compulsive OR OCD (last updated in January 2024). Studies addressing OCD and vitamin D were identified based on the examination of their titles and abstracts. Only publications meeting the predetermined eligibility criteria were selected for further scrutiny. Additionally, the references of the retrieved reports were examined to identify any additional relevant studies.

Criteria for inclusion and exclusion of studies:

The current meta-analysis adhered to the following criteria for the inclusion of published reports: (a) inclusion of only case-control studies examining the vitamin D level in OCD patients, (b) recruitment of clearly defined and confirmed OCD patients as well as OCD-free controls, (c) reporting vitamin D levels in both cases and controls, (d) articles in English language, and (e) utilization of statistically relevant data collection and analysis methods. Exclusion criteria were applied based on: (a) duplicate or overlapping reports, (b) casestudies or case series, (c) absence of reported vitamin D levels, and (d) inclusion of review or abstract data.

Data extraction:

Two investigators (W.N.A.Z. and Z.O.) independently evaluated the quality of the extracted data using a standardized protocol. A predetermined set of inclusion/exclusion criteria, along with sequential exclusion criteria outlined in the data-collection form, was rigorously followed to ensure the precision of the collected data. In cases of disagreement between the investigators regarding the data's quality, a consensus was sought initially, and any remaining discrepancies were resolved through open discussion with the arbitrator (A.W.). The information extracted from the retrieved publications included the first author's name, country of origin, year of publication, number and source of cases and controls, study type, vitamin D levels, and the association with OCD.

Quality assessment using Newcastle–Ottawa Scale:

Two investigators, namely W.N.A.Z. and Z.O., independently conducted the quality assessment of the chosen studies using the Newcastle–Ottawa Scale (NOS) for quality evaluation.[28] The NOS quality assessment criteria primarily included: (a) selection of subjects, with a scoring range of 0–4 points, (b) subject comparability, with a scoring range of 0–2 points, and (c) clinical outcome, with a scoring range of 0–3 points.[29]Case–control studies that obtained 5 or more stars in the NOS assessment were considered to have moderate to good quality.[28]In the event of any discrepancies on any criterion between the investigators mentioned above, a comprehensive discussion was initiated and resolved through detailed deliberation in the presence of a third investigator (A.W.), who acted as an adjudicator.

Statistical analysis:

Data analyses were performed using Jamovi® 2.3 software.[30]Statistical significance was defined as $p < 0.05$. Heterogeneity was assessed using the I^2 statistic. The values between 25% and 50%, 50% and 75%, and greater than 75% indicate the presence of low, moderate, and high heterogeneity between studies.[31] The random-effects model was employed to facilitate the generalization of conclusions given the inclusion of more than five studies.[32] Publication bias was evaluated using funnel plots and tests by Fail-Safe N, Beggs and Eggers.[33,34]

Results:

Search results:

The diagram illustrating the process of the literature search is depicted in Figure 1.A total of 490 articles were initially identified in the electronic databases. After eliminating duplicate articles, 393 remained. Following a review of abstracts and titles, 383 articles unrelated to the subject were excluded. Of the remaining 10 articles, 3 were excluded after a detailed analysis of their full texts, categorized as follows: 2 were review articles, and 1 wasan animal study. Seven articles were considered for qualitative synthesis, and ultimately, a total of six research studies involving 573 patients and 578 controls were included in the quantitative synthesis.

Study quality:

Table 1 summarizes the selected studies (n=7), which underwent assessment for quality assessment using the NOS. Each of these studies received a score of 5

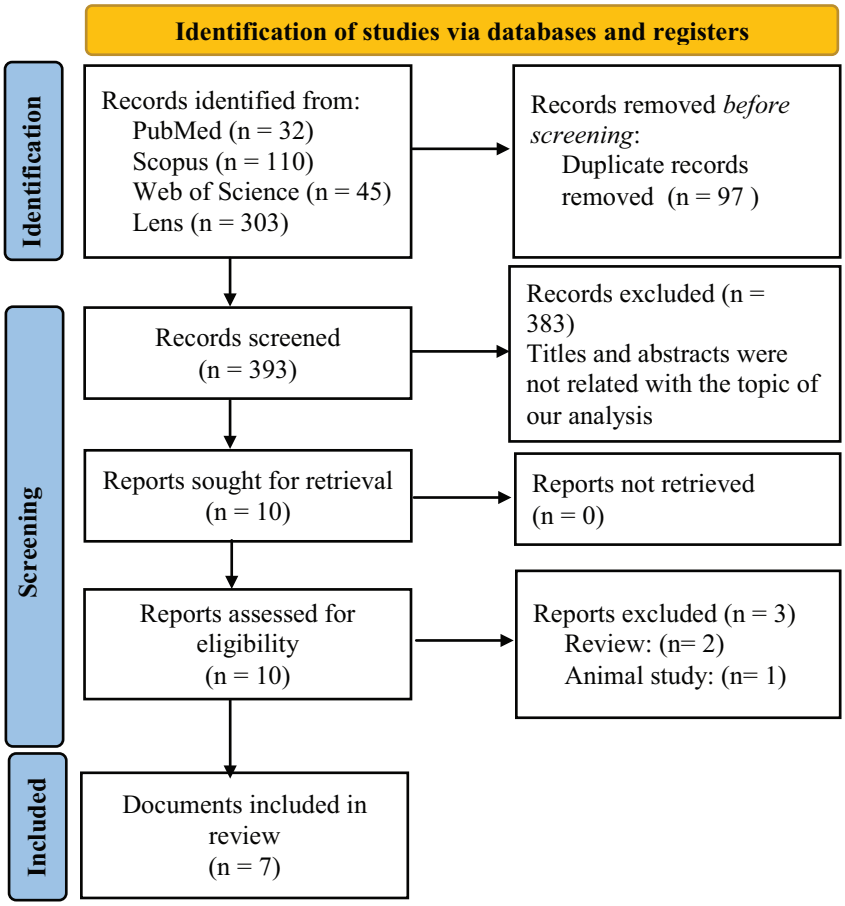

Figure 1: *Flow chart of database search.*[27]

Table-I

Characteristics of the included studies.

Author, Year	Country	Sample size (OCD/control)	Age, years (OCD/control)	25(OH)D level, nmol/L (OCD/control)
Celik et al., 2016	Turkey	33 (14F, 19M)/20 (4F, 16M)	9.50 ± 2.50/11.70 ± 5.20	17.39 ± 9.48/21.54 ± 10.23 (P=0.180)
Esnafoglu & Yaman, 2017	Turkey	52 (26F, 26M)/30 (16F, 14M)	14.70 ± 2.30/14.20 ± 2.60	16.1 ± 6.8/29.4 ± 12.1(P< 0.001)
Yacizi et al., 2017	Turkey	60 (24F, 36M)/59 (21F, 38M)	11.15 ± 2.77/10.89 ± 2.66	15.88 ± 6.96/18.21 ± 13.24 (P=0.234)
Stagi et al., 2018	Italy	179 (49F, 130M)/224 (50F, 174M)	8.45 ± 2.51/8.34 ± 2.46	20.4 ± 6.9/24.8 ± 7.3 (P<0.0001)
Mohamed et al., 2022	Egypt	25/25 (M)	28.68 ± 7.11/27.04 ± 3.91	16.08 ± 6.61/21.14 ± 8.78 (P=0.026)
Soyak & Karakukcu, 2022	Turkey	174 (88F, 86M)/170 (92F, 78M)	29.00 ± 1.27/28.00 ± 1.53	19.40 ± 8.69/27.80 ± 10.90 (P< 0.001)
Imre & Kocabas, 2023	Turkey	50 (12F, 38M)/50 (13F, 37M)	27.70 ± 8.10/27.70 ± 5.90	10.4 ± 4.57/13.6 ± 4.79 (P=0.001)

Table-II

The included case-control studies quality assessment according to the NOS.

STUDY	Selection (4)				Comparability (2)	Exposure (3)			Total
	Is the case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls based on the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non response rate	
Celik et al., 2016	*	*		*		*	*		5
Esnafoglu & Yaman, 2017	*	*		*		*	*		5
Yacizi et al, 2017	*	*	*	*	**	*	*		8
Stagi et al., 2018		*		*	**	*	*		6
Mohamed et al., 2022	*	*			*	*	*		5
Soyak & Karakukcu, 2022	*	*	*	*	**	*	*		8
Imre & Kocabas, 2023	*	*	*	*	**	*	*		8

stars or higher, indicating a moderate to good level of quality (Table 2).

Test of heterogeneity:

The initial assessment of heterogeneity across all seven included studies revealed a substantial I^2 of 74.15% and a significant Q statistic p-value of 0.004, indicating notable variation beyond chance (Table 3). Recognizing the need to uphold the assumptions of homogeneity, a meticulous examination was conducted, leading to the decision to exclude Esnafoglu and Yaman-2017 from the meta-analysis.[21] This exclusion was justified by the study's prominent impact on heterogeneity parameters, specifically its substantial absolute difference in means. Upon excluding Esnafoglu and Yaman-2017,[21] the I^2 decreased to 50.89%, reflecting a shift to moderate heterogeneity, and the Q statistic p-value increased to 0.093, surpassing the significance threshold. Consequently, the refined meta-analysis, now comprising six studies, ensures a more homogenous and robust framework for deriving meaningful conclusions.

Further analysis was carried out using the standardized mean difference as the outcome measure. A random-effects model was fitted to the data. The amount of heterogeneity (i.e., tau^2), was estimated using the restricted maximum-likelihood estimator.[39] In addition to the estimate of tau^2, the Q-test for heterogeneity and the I^2 statistic are reported.[40,41] In case any amount of heterogeneity is detected (i.e., $tau^2 > 0$, regardless of the results of the Q-test), a prediction interval for the true outcomes is also provided. Studentized residuals and Cook's distances are used to examine whether studies may be outliers and/or influential in the context of the model. Studies with a studentized residual larger than the 100 x (1 - 0.05/(2 X k))th percentile of a standard normal distribution are considered potential outliers (i.e., using a Bonferroni correction with two-sided alpha = 0.05 for k studies included in the meta-analysis). Studies with a Cook's distance larger than the median plus six times the interquartile range of the Cook's distances are considered to be influential. The rank correlation test and the regression test, using the standard error of the observed outcomes as predictors, are used to check for funnel plot asymmetry.

A total of k=6 studies were included in the analysis (Table 4). The observed standardized mean differences ranged from -0.8514 to -0.2194, with most estimates being negative (100%). The estimated average standardized mean difference (SMD) based on the random-effects model was (SMD= -0.603, 95% CI: -0.8001 to -0.4053). Therefore, the average outcome differed significantly from zero ($z = -5.9849$, $p < 0.001$). Table 5 presents the Q-test for heterogeneity was not significant, but some heterogeneity may still be present in the true outcomes ($Q(5) = 9.4403$, $p = 0.0927$, $tau^2 = 0.0282$, $I^2 = 50.86\%$). A 95% prediction interval for the true outcomes is given by -0.9864 to -0.2190. Hence, even though there may be some heterogeneity, the true outcomes of the studies are generally in the same direction as the estimated average outcome. An examination of the studentized residuals revealed that none of the studies had a value larger than ± 2.6383 and hence there was no indication of outliers in the context of this model. According to Cook's distances, none of the studies could be considered to be overly influential. Neither the rank correlation nor the regression test indicated

Table-III

Test of heterogeneity.

Study	|m1 - m2|	|n1-n2|	If deleted	
			I^2	Q Stat. p-value
Celik et al., 2016[22]	4.15	13	78.68%	0.003
Esnafoglu & Yaman, 2017[21]	13.3	22	50.86%	0.093
Yacizi et al, 2017[23]	2.33	1	59.38%	0.041
Stagi et al., 2018[35]	4.4	45	74.89%	0.003
Mohamed et al., 2022[36]	5.06	0	80.29%	0.002
Soyak & Karakukcu, 2022[37]	8.4	4	73.96%	0.007
Imre & Kocabas, 2023[38]	3.2	0	80.11%	0.002
All studies			74.15%	0.004

Table-IV

Random-Effects Model (k = 6).

	Estimate	SE	Z	p	CI Lower Bound	CI Upper Bound
Intercept	-0.603	0.101	-5.98	<.001	-0.800	-0.405

Note. Tau^2 Estimator: Restricted Maximum-Likelihood

any funnel plot asymmetry (p = 1.0000 and p = 0.3974, respectively).

Table 5 presents heterogeneity statistics, providing key insights into the variability within the meta-analysis. The estimated Tau is 0.168, indicating the extent of between-study variance. Tau squared is reported as 0.0282, with a standard error (SE) of 0.0373. The I^2 statistic, denoting the percentage of total variation attributable to heterogeneity rather than chance, is 50.86%, suggesting moderate heterogeneity among the included studies. The H^2 statistic, representing the ratio of total variance to sampling variance, is 2.035. The R^2 value is not specified. The degree of freedom (df) associated with the Q statistic is 5.000, with a Q-value of 9.440 and a corresponding p-value of 0.093. These statistics collectively offer a comprehensive assessment of the heterogeneity within the meta-analysis, aiding in the interpretation of study variations and the reliability of the overall findings.

The meta-analysis results yield valuable insights into model fit statistics and information criteria, as delineated in Table 6. The Maximum-Likelihood estimation method demonstrates superior performance across multiple criteria, with higher log-likelihood (0.479), lower deviance (8.463), and more favorable information criteria, including AIC (3.042), BIC (2.626), and AICc (7.042), in comparison to the Restricted Maximum-Likelihood approach. These metrics collectively indicate the robustness and parsimony of the maximum likelihood model in capturing the underlying patterns in the observed data. This finding is consistent with established standards in model evaluation and underscores the efficacy of the maximum likelihood estimation method, as outlined in the referenced Table 6.

Figure 2 depicts a Forest plot elucidating the SMD in

Table-V

Heterogeneity Statistics.

Tau	Tau^2	I^2	H^2	R^2	df	Q	p
0.168	0.0282 (SE=0.0373)	50.86%	2.035	.	5.000	9.440	0.093

Table-VI

Model Fit Statistics and Information Criteria.

	log-likelihood	Deviance	AIC	BIC	AICc
Maximum-Likelihood	0.479	8.463	3.042	2.626	7.042
Restricted Maximum-Likelihood	-0.002	0.004	4.004	3.222	10.004

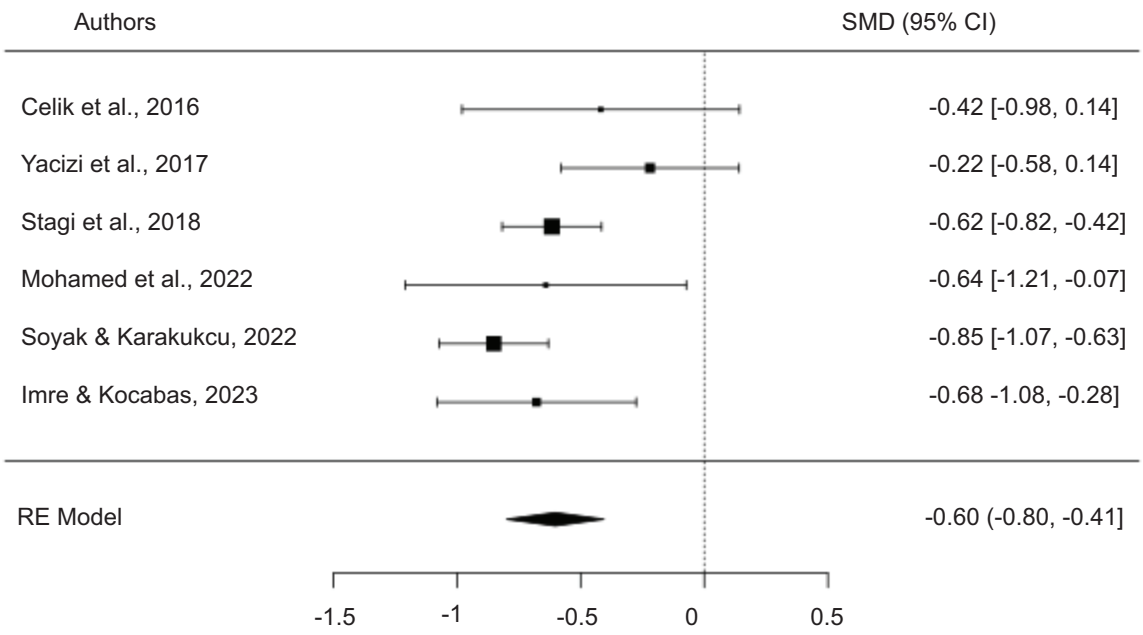

Figure 2: *Forest plot of the standardised mean difference (SMD) in vitamin D levels between OCD patients and healthy controls.*

vitamin D levels between individuals diagnosed with OCD and their healthy counterparts. The diagram presents individual study estimations through horizontal lines, accompanied by their corresponding 95% confidence intervals (CI). The overarching summary estimate, derived via a Random Effects (RE) model, signifies a standardized mean difference of -0.60, with a 95% CI ranging from -0.80 to -0.41. This collective statistic implies a substantial and negative correlation between OCD and vitamin D levels, indicating that, on average, individuals with OCD exhibit lower vitamin D levels compared to their healthy counterparts. The breadth of the confidence interval reflects the precision of the estimate, with a narrower interval denoting heightened precision. The Forest plot visually communicates the heterogeneity intrinsic to individual study outcomes, underscoring the robustness of the discerned relationship between OCD and vitamin D levels.

Table 7 serves as a comprehensive evaluation of potential publication bias utilizing various statistical tests. The Fail-Safe N test reveals a substantial value of 169.000, coupled with a p-value below 0.001, indicative of potential susceptibility to publication bias, as evidenced by the considerable number of non-significant studies needed to nullify the observed effect. The Begg and Mazumdar Rank Correlation test yields a correlation value of 0.067 with a p-value of 1.000, denoting a lack of significant rank correlation and providing no discernible evidence supporting publication bias.Egger's Regression test produces a value of 0.846 with a p-value of 0.397 and the Begg funnel plot (Figure 3)suggests an absence of significant asymmetry. These findings provide no evidence of publication bias. Additionally, the Trim and Fill Number of Studies report a value of 0.000, signifying potential asymmetry but without an associated p-value for conclusive determination. Collectively, these outcomes cumulatively suggest a lack of compelling evidence supporting publication bias within the examined studies. Consequently, these findings affirm the reliability of the meta-analysis results, underscoring their suitability for use in subsequent analyses and interpretations.

Table-VII

Publication Bias Assessment.

Test Name	value	p
Fail-Safe N	169.000	<.001
Begg and Mazumdar Rank Correlation	0.067	1.000
Egger's Regression	0.846	0.397
Trim and Fill Number of Studies	0.000	.

Note. Fail-safe N Calculation Using the Rosenthal Approach

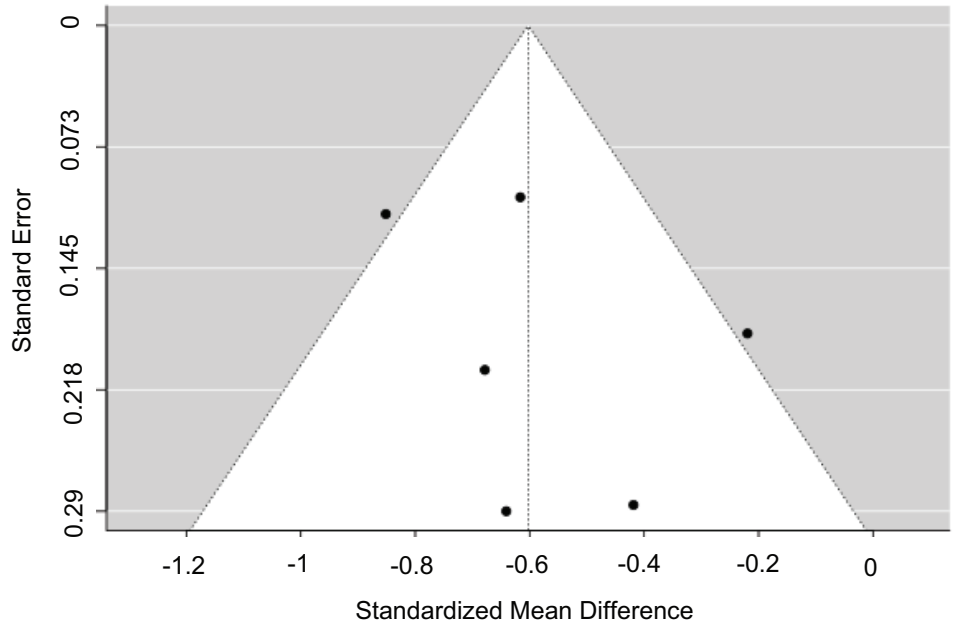

Figure 3.*Funnel plot of the SMD in vitamin D levels between OCD patients and healthy controls.*

Discussion:

Our study investigated vitamin D levels in individuals with OCD compared to controls, revealing intriguing findings across different age groups. Notably, prior studies by Turkish authors observed a reduction, though not statistically significant, in vitamin D levels among children and adolescents with OCD in studies conducted by Celik and Yacizi.[22,23] Conversely, a separate investigation focusing on children and adolescents with OCD reported a significant decline in vitamin D levels compared to controls. In contrast, all studies involving adults with OCD consistently demonstrated a statistically significant reduction in vitamin D levels when compared to control groups.[36-38] This disparity in findings among age groups underscores the potential complexity of the relationship between OCD and vitamin D levels, suggesting that age-related factors and the presence of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) may influence the observed associations. Further investigation is warranted to explore the nuanced dynamics of vitamin D levels in different age cohorts with OCD, considering potential contributing factors and implications for understanding the disorder.

Vitamin D, recognized for its non-skeletal functions, including modulating innate and adaptive immunity, is associated with an increased susceptibility to infectious and autoimmune diseases.[42] Insufficient levels of vitamin D may alter immune responses and pose a risk factor in conditions like PANDAS, especially in children and adolescents.[22,35] Additionally, vitamin D plays a vital role in increasing the intestinal absorption of calcium, magnesium, and phosphate, with reports suggesting various other biological benefits. However, a prevalent global insufficiency of vitamin D among the elderly, children, and adults raises concerns about its potential impact on health.[43]

The complex aetiology of OCD involves a combination of neurochemical, genetic, structural, immunological, and neuropsychological factors.[44] Neurochemical studies implicate neurotransmitters like dopamine, serotonin, and glutamate in the underlying mechanisms of OCD.[45-47] Treatment approaches involving SSRIs, antipsychotic agents, and glutamatergic agents align with these findings.[48-50] Importantly, vitamin D regulates tyrosine hydroxylase, a key enzyme in neurotransmitter synthesis, and its deficiency may contribute to an imbalance in neurotransmitters, potentially influencing emotional and behavioural issues, including OCD.[51,52] It has also been postulated recently that vitamin D may influence the gut microbiota and regulate the synthesis of serotonin.[53]

Furthermore, oxidative stress and neuroprotective mechanisms are implicated in OCD development. Vitamin D deficiency may compromise antioxidant defence systems, making neurons vulnerable to oxidative damage.[54-56]The inhibition of inducible nitric oxide synthase (iNOS) by vitamin D protects against neurotoxicity, and altered neurotrophin levels in OCD patients suggest a potential reduction in neuroprotectivity due to vitamin D deficiency.[57-60]

The cortico-striatal-thalamic-cortical circuits implicated in OCD, involving basal ganglia, cortical, and thalamic structures, are associated with basal ganglion-related disorders. Notably, a higher incidence of OCD is observed in disorders like Sydenham's chorea, Huntington's chorea, and Tourette syndrome, all related to the basal ganglia.[61] Eyles et al. reported that brain regions with the highest density of vitamin D receptors and 1-alpha hydroxylase, essential for vitamin D synthesis, include the hypothalamus and dopaminergic neurons in the substantia nigra.[12]Additionally, vitamin D regulates the nigrostriatal pathway and exhibits a protective effect on dopaminergic neurons against toxins.

Moreover, numerous studies have also indicated a correlation between low vitamin D levels at birth and later development of mental and neurological conditions such as OCD, attention deficit hyperactivity disorder (ADHD), cognitive issues, and dementia. However, this correlation is weak and does not establish causation. Several small randomized controlled trials have shown improvements in individuals with psychiatric disorders after taking vitamin supplements.[24]

Conclusion:

Our meta-analysis study sheds light on the intricate interplay between OCD and vitamin D levels, revealing distinct patterns across different age groups. While prior research indicates a significant reduction in vitamin D levels among adults with OCD, the findings among children and adolescents are less consistent, potentially influenced by age-related factors and conditions like PANDAS. The role of vitamin D in modulating immune responses and neurotransmitter synthesis underscores its relevance in OCD pathophysiology. Moreover, the implications of vitamin D deficiency on oxidative stress, neuroprotective mechanisms, and basal ganglia-related circuits further emphasize its potential impact on OCD development. However, the correlation between low vitamin D levels and psychiatric disorders necessitates further exploration through rigorous investigations. Overall, our study contributes to the evolving understanding

of the multifaceted relationships between OCD, vitamin D, and various contributing factors, paving the way for future research and potential therapeutic interventions in OCD management.

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Data availability:
Data will be made available on request.

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