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REVIEW

Associations Between Vitamin D and Core Symptoms in ASD: An Umbrella Review

Yuwei Jiang[1,2,*], Wenjun Dang[3,*], Lirong Sui[1], Tianci Gao[1], Xiangying Kong[1], Jin Guo[1], Shuang Liu[1], Hong Nie[3], Zhimei Jiang[1,2]

[1]College of Rehabilitation Medicine, Jiamusi University, Jiamusi City, Hei longJiang Province, People's Republic of China; [2]Pediatric Cerebral Palsy Prevention and Treatment Center of Heilongjiang Province, Jiamusi City, Hei longJiang Province, People's Republic of China; [3]College of Jiamusi, HeiLongJiang University of Chinese Medicine, Jiamusi City, Hei longJiang Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhimei Jiang; Shuang Liu, Email 15704601990@163.com; 307692456@qq.com

Abstract: We conducted an umbrella evaluation to quantitatively synthesize previous systematic reviews and meta-analyses, thereby collating evidence on the association between vitamin D and core symptoms in people with autism in anticipation of informing clinical vitamin D supplementation. Based on the pre-established protocol, we ended up with 9 studies. Based on rigorous analysis, we found that vitamin D deficiency early in life is a risk factor for the development of ASD and that vitamin D supplementation improves the core symptoms of ASD. Our study concludes that vitamin D supplementation is beneficial for individuals with autism, that vitamin D deficiency early in embryonic life increases the risk of ASD, and that our study supports the idea that prevention begins with vitamin D supplementation early in life. At the same time, we must recognize that our current conclusions support the benefits of vitamin D supplementation for children with ASD, but we are unable to determine the causal relationship, ie, how vitamin D works in ASD, and we need more basic research to explore the mechanisms involved.

Keywords: autism spectrum disorders, vitamin D, core symptoms, 25(OH)D, umbrella review

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by challenges in social communication and interaction, entailing two defining features: repetitive behaviors and restricted interests.[1] Individuals with ASD frequently present with behavioral challenges such as aggression, resistance to changes in routine, and deficits in conventional conversational skills. They also often suffer from social anxiety, attentional deficits, hyperactivity, sleep disruptions, and gastrointestinal disturbances.[2,3] These complex challenges significantly impede their ability to attain educational achievements comparable to their peers and to develop the skills necessary for independent living.[4–6]

Current epidemiological data indicate a significant increase in ASD prevalence, now affecting roughly 1 in 59 children.[7–9] This escalation in ASD cases has been linked to a complex interplay of genetic and environmental factors.[10–12] Studies have found that individuals with ASD possess lower levels of vitamin D compared to their typically developing counterparts.[13–15] Although the precise etiology of ASD remains elusive, both environmental and genetic contributors are acknowledged to influence its development.[16–18] Research suggests that genetic variations associated with nutrition and metabolism, including mitochondrial dysfunction and oxidative stress, are common among those with ASD.[19] Consequently, vitamin and mineral supplementation has been proposed as a means to modulate these underlying physiological disruptions.[19,20]

Vitamin D, an essential fat-soluble nutrient, also serves as a hormone precursor.[21] It is produced in the skin following ultraviolet light exposure and associates with vitamin D-binding protein for transport in the bloodstream. In the liver, the nutrient undergoes enzymatic conversion to 25-hydroxyvitamin D (1,25(OH)2D) by the enzyme 25-hydroxylase. In the kidneys by 1α-hydroxylase generates the biologically active form, 1.25-dihydroxyvitamin D (1,25(OH)2D),[22] which can modulate a variety of target genes through interaction with the vitamin D receptor (VDR), affecting brain function.[23,24]

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While 25(OH)D is the predominant circulating form of vitamin D, both the VDR and 1α-hydroxylase are widely present in brain tissue.[25] Nevertheless, Vitamin D3 (VD3) is highly susceptible to environmental stressors, rendering it vulnerable to oxidation which diminishes its physiological advantages and functions.[26] It is characterized by limited water solubility and suboptimal oral bioavailability, the latter approximating 44.8%.[27] As a lipid-soluble compound, Vitamin D absorption primarily occurs in the small intestine, where its uptake is bolstered by both active and passive mechanisms associated with fatty acid and fat transport.[28] Given its affordability and favorable benefit-to-risk profile, Vitamin D supplementation has emerged as a particularly promising strategy for managing autism.

Vitamin D, recognized as a crucial neurosteroid hormone,[29,30] is essential for neurodevelopment and modulates critical functions in the nervous system, including neuronal growth, synaptic transmission, and oxidative stress regulation.[31,32] Numerous studies suggest an association between 25-hydroxyvitamin D (25(OH)D) levels and ASD.[33–36] Small-scale epidemiological studies indicate that children with ASD often have significantly lower 25(OH)D levels compared to neurotypical peers,[37–40] a finding supported by a retrospective review of 616 samples.[41] However, results from clinical controlled studies are mixed. A 2020 meta-analysis described that vitamin D supplementation may worsen hyperactivity symptoms in ASD,[42] while another meta-analysis from the same year found potential symptom improvements following vitamin D supplementation.[43–45] Additionally, early childhood vitamin D supplementation could reduce ASD risk in younger siblings.[46,47] Rodent studies suggest that high-dose vitamin D may have protective and therapeutic effects, particularly as a preventative measure.[48,49]

Research also indicates shorter outdoor activity durations among children with ASD compared to controls during their second year, potentially reducing ultraviolet light exposure and subsequent vitamin D synthesis.[50] Links between vitamin D metabolism, genetic variations in the vitamin D receptor, and ASD have been identified.[51,52] Despite ongoing debates over the specifics of the relationship between 25(OH)D levels and ASD, given the inconsistent research findings and the public health urgency to clarify the role of vitamin D supplementation in ASD management, rigorous evaluation of its actual benefits is paramount. This necessitates comprehensive methodologies, including umbrella reviews, meta-analyses, and systematic reviews targeting vitamin D use in individuals with ASD, to render a more precise determination of its clinical efficacy.

Materials and Methods

Additional searches were conducted within the identified articles' references. Titles and abstracts were independently screened by two reviewers (Yuwei Jiang and Wenjun Dang), who excluded irrelevant studies and thoroughly evaluated the remaining for eligibility. Disagreements were resolved by a consensus Discussion with a third reviewer (Hong Nie).

Protocol

This study follows the preferred reporting items recommended by the the Umbrella Review Methodology Working Group and considers systematic reviews and meta-analysis (PRISMA).

Criteria for Considering Reviews for the Overview

Literature Search

PubMed, the Cochrane Database of Systematic Reviews, EMBASE, Sinomed, CNKI, wanfang data, and VIP were searched electronically for studies published from inception until December 31, 2023. The reference lists of included papers were also reviewed to identify any further relevant reviews for inclusion. In addition, manual searches were also performed by tracking citations from the reference lists of all included reviews and relevant reviews in autism intervention, as well as by contacting authors of included reviews. The terms used for the search were "autism", "vitamin D", and "systematic review OR meta analysis" separated by the Boolean operator AND. In order to understand the linking role of vitamin D for autism, we insisted on selecting RCT studies in which the intervention was vitamin D only.

Review Selection

We chose systematic reviews with or without meta-analysis. The reason for this is that we searched the relevant literature databases and there have been many systematic evaluations and meta-analyses for summaries of autism and vitamin D. And while the research team of the project has published systematic evaluations of vitamin D and Omega-3 in the

previous phase of the project, its findings show that vitamin D supplementation has a positive effect on the behavior of people with ASD. We were eager to find out whether vitamin D had a significant effect on other major aspects of ASD patients. For the supplementation of vitamin D for autism, there is no umbrella evaluation in the existing research method, which can include more studies at one time, and we are more obsessed with finding out the differences between different systematic evaluations, and under the umbrella evaluation of direct evidence, we can better reflect the effect of vitamin D supplementation for autism, and make better guidance for the next research.

Our review encompassed English and Chinese meta-analyses/systematic reviews (MAs/SRs) that evaluated vitamin D supplementation's efficacy for individuals with Autism Spectrum Disorder (ASD).

Primary outcomes: vitamin D levels, 25(OH)D3 level.

Secondary outcomes: assessments from the Childhood Autism Rating Scale (CARS) scores, the Autism Behavior Checklist (ABC), Social Responsiveness Scale (SRS), Autism Treatment Evaluation Checklist (ATEC) et al.

Exclusion Criteria: Excluded from this review were: non-systematic reviews, case studies, animal studies, conference abstracts, articles without full-text access or valid data, duplicates, and non-English/Chinese publications.

Data Extraction and Management

We recorded complete information about citations, date of publication, study type, database, quality assessment, sample size, countries, over all study size, and measurement tool assessed.

In order to ensure consistency in the inclusion of study populations for late comparisons, included studies focused on children diagnosed with ASD according to the criteria specified by the DSM-IV or DSM-V of the American Psychiatric Association, or the ICD-10 of the World Health Organization. In the selected studies, participants in the treatment group received vitamin D supplementation, without restrictions on dosage or duration of treatment.

Methodological Quality Assessment of Included Reviews

Two independent reviewers (Yuwei Jiang and Wenjun Dang) extracted data, including details such as authorship, publication year, origin, design, sample size, participant ages, diagnostic criteria, interventions, outcomes, and quality indicators like PRISMA, AMSTAR2, and GRADE. Inconsistencies were reconciled by consulting a third reviewer (Hong Nie).The quality of included studies was independently assessed by two researchers (Yuwei Jiang and Wenjun Dang), with consensus validations conducted thereafter. Discrepancies were settled through discussion or third-party adjudication (Xiangying Kong).

Assessment Methodological quality was assessed utilizing the AMSTAR2 tool, comprising 16 discrete items. Notably, items 2, 4, 7, 9, 11, 13, and 15 were identified as critical for the quality appraisal.

The comprehensiveness of the reporting quality in included studies was gauged through a meticulous review of the PRISMA checklist, which encompasses 27 criteria. In the discipline of meta-analyses/systematic reviews, a fully reported criterion was awarded 1 point, a partially reported one received 0.5 points, and an unreported criterion scored 0 points, culminating in a total possible score of 27. A score of 15 or less signified considerable informational inadequacies in the report, a score between 15 and 21 pointed to some deficiencies, and a score between 21 and 27 suggested a high level of reporting completeness.

The quality of evidence from Meta-Analyses/Systematic Reviews (MAs/SRs) was appraised using the GRADE system, which considers study limitations, inconsistency, indirectness, imprecision, and publication bias. The evidence from randomized controlled trials (RCTs) was rated based on these criteria: absent downgrades across the five domains indicated high-quality evidence; a single downgrade in any domain signified moderate quality; two downgrades denoted low quality; and three or more downgrades in any domain qualified the evidence as very low quality.

Results

Literature Search and Selection

The search yielded 159 articles, of which 73 were duplicates and subsequently removed, resulting in 86 unique articles. During the preliminary screening, 60 articles were excluded due to reasons including animal studies, interventions not related to vitamin D, or studies of multiple disorders rather than solely ASD, leaving 26 articles for further review. Upon

full-text evaluation, 17 articles were eliminated because full texts were inaccessible or they did not qualify as meta-analyses/systematic reviews (MAs/SRs), ultimately including 9 articles that met the inclusion criteria for the umbrella evaluation. Figure 1 Study selection flowchart illustrates the systematic literature selection process.

Characteristics of the Included

Studies of the nine selected articles, six were in English and three in Chinese, published from 2011 to 2023. A surge in publications was observed post-2020, encompassing a range of 3–34 individual studies. The body of work included both experimental and observational designs, with six experimental studies totaling 4663 participants and three observational studies comprising 30,136 participants. Participant ages varied widely from 0 to 23 years. In terms of methodological assessment, four studies were evaluated using the Cochrane risk-of-bias tool, three via the Newcastle-Ottawa Scale (NOS), and one according to the STROBE guidelines. One study underwent a dual evaluation employing both the Cochrane tool and MINORS criteria. Detailed information can be found in Table 1.

Quality Assessment of Included Studies

Upon assessing the methodological quality of the six randomized controlled trials (RCTs) incorporated in this study, it was found that two RCTs exhibited low methodological quality, whereas four were categorized as very low. Key factors affecting these assessments included: (1) One study[53] was registered prior to commencement but lacked detailed reconciliation with the original protocol, and the remaining four had no registration records; (2) Certain studies[43,54,56] failed to articulate the rationale behind utilizing RCTs; (3) Some reports[43,53–55] omitted discussion on the impact of study-specific risk of bias on the collection or interpretation of meta-analytic evidence; (4) Several reports[53,54] did not address bias risk when interpreting individual study outcomes; (5) Some analyses[53,54] inadequately accounted for heterogeneity within study findings; (6) Multiple studies[43,53,54,56] neglected to evaluate how the risk of bias within included RCTs might bias the overall meta-analytic conclusions; (7) Some publications[54,56] lacked declarations on conflicts of interest or funding sources, raising concerns about potential selective publication bias. Detailed information can be found in Table 2.

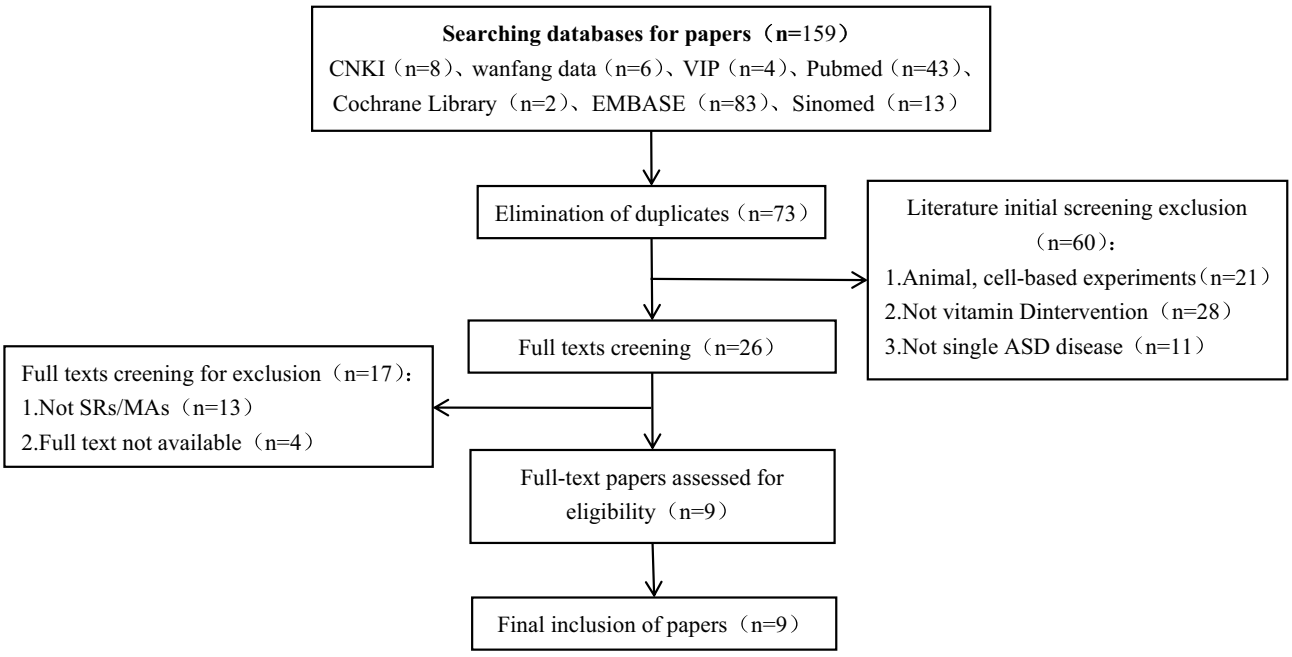

Figure 1 Study selection flowchart.

Table 1 Summary of Study Details

Literature	Study Type	Database	Population Setting	Quality Assessment	Sample Size	Countries	Measurement Tool	Conclusion
Zhang M et al 2023[53]	RCT	PubMed, Embase, Cochrane Library, WOS, CINAHL databases.Searched from inception to February 2022.	(1) the study was a randomized double-blind placebo-controlled clinical trial; (2) the studied subjects were children aged up to 18 years with an ASD diagnosis based on the established criteria; (3) the intervention Protocols were specified for vitamin D supple_x005f_x0002_mentation only in children with ASD and placebos were used in the control group; (4) the study used at least one outcome measurement scale.	Cochrane Risk Assessment Tool and the Cochrane bias test	6 studies, N=221 (VD=113; Placebo=108)	China	1. 25(OH)D3 level (MD: 16.81; 95% CI: 11.89, 21.72; p < 0.00001; I2 = 76%, p = 0.005) 2. SRS (MD: −8.74; 95% CI: −17.45, −0.03; p = 0.05; I2 = 0%) 3. ABC-lethargy (MD: −0.07; 95% CI: −1.70, 1.57; p = 0.93; I2 = 0%) 4. ABC-stereotypical behavior (MD: −0.05; 95% CI: −1.19, 1.10; p = 0.93, I2 = 33%) 5. ABC-inappropriate speech (MD: −0.04; 95% CI: −1.19, 1.10; p = 0.94, I2 = 57%) 6. ABC-irritability (MD: −1.79; 95% CI: −4.42, −0.85; p = 0.18, I2 = 61%, p = 0.08) 7. ABC-hyperactivity (MD: −1.35; 95% CI: −4.37, 1.67; p = 038, I2 = 48%, p = 0.14) 8. GARS-2— stereotypy (MD: −1.39; 95% CI: −2.7, −0.07; p = 0.04)	Vitamin D supplementation appears to improve stereotypical behaviors, but not other core symptoms and co-existing conditions.
Song L et al 2019[43]	RCT, NRCT	PubMed, EMBASE, Cochrane Library, WOS, Sino-Med, Wanfang Data, CNKI. Searched from inception to September 2019.	(1) studies on children with ASD diagnosed according to ICD-9 (ICD-10) and DSM-4 (DSM-5); (2) studies including children aged ≤ 18 years; (3) studies in which specific serum vitamin D levels were directly investigated; (4) studies reporting significant differences in vitamin D levels after intervention; (5) studies in which vitamin D supplementation was the intervention; (6) studies which were randomized controlled trials.	The Cochrane bias test	3 studies, N=1222 (VD=61; Placebo=61)	China	1.25(OH)D3 level (SMD = 0.3,95% CI =−0.06~0.65; p = 0.1; I2 = 0%)	Vitamin D supplementation can improve the typical symptoms of ASD.

(*Continued*)

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Table 1 (Continued).

Literature	Study Type	Database	Population Setting	Quality Assessment	Sample Size	Countries	Measurement Tool	Conclusion
Shuang cheng et al 2021[54]	RCT, NRCT	PubMed, Cochrane Library, WOS, Embase, CNKI, VIP, SinoMed, WanFang Data. Searched from inception to November 5,2021.	(1)study types included RCTs and NRCTs, and NRCTs included single-arm studies with their own and two-arm studies with a control group; (2)children with a clear diagnosis of ASD diagnosed according to DSM-5 and ICD-10; (3)The vitamin D group was treated with vitamin D at any dose and for any length of time; (4)Main outcome indicators CARS, ABC, SRS, ATEC, incidence of adverse drug reactions.	The Cochrane bias test, MINORS (methodological index for non_x005f_x0002_randomized studies)	10 studies, N=982 (T=564; C=418)	China	1.SRS (MD = –3.75, 95% CI(–5.22, –2.28), P<0.01, I2 = 0%); 2.CARS total (MD= –5.19, 95% CI(–7.14, –3.23), P< 0.01, I2 = 96%); 3.ABC-lethargy (MD = –3.85, 95% CI(–6.18, –1.52), P<0.01, I2 = 96%); 4.ABC-stereotypical behavior (MD = –3.12, 95% CI(–4.11, –2.12), P<0.01, I2 = 57%); 5.ABC-inappropriate speech (MD = –2.15, 95% CI(–3.90, –0.39), P=0.02, I2 = 94%); 6.ABC-irritability (MD = –5.59, 95% CI(–7.21, –3.97), P<0.01, I2 = 82%); 7.ABC-hyperactivity (MD = –3.46, 95% CI(–4.27, –2.64), P<0.01, I2 = 66%); 8.ATEC total (MD = –17.19, 95% CI(–31.71, –2.68), P= 0.02, I2 = 76%).	Vitamin D Treatment Improves Core Symptoms in Children with ASD
Wang T et al 2015[55]	RCT	MEDLINE, EMBASE, PsycINFO, Web of Knowledge, Scopus. Searched from January 1980 to May 2015	(1) ASD diagnose according to criteria established in DSM IV(TR); (2) participants aged between 2 and 16 years; (3) measurement of 25-(OH) D concentration in peripheral blood; (4) studies which reported 25-(OH) D concentrations using a mean and standard deviation, with sample size and P value; (5) full text articles that were pub_x005f_x0002_lished in English.	Newcastle-Ottawa Scale (NOS)	11 studies, N=1652 (ASD=870; C=782)	China	1.25(OH)D level (WMD = −8.63; 95% CI (−13.17, −4.09), P = 0.0002)	Decreased levels of vitamin D may be a risk factor for ASD.

Caiwei Li et al 2011[56]	RCT	CNKI, WanFang Data, CBM, VIP, ChiCTR, PubMed, Embase, WOS, Clinical Trials, Cochrane library. Searched from inception to February 1, 2022.	(1)RCT; (2)case group: children aged < 18 years with a definite diagnosis of ASD according to DSM-IV and DSM-V diagnostic criteria. control group: healthy children matching the region, age and gender of the affected children. (3)exposure factor: Vitamin D supplementation or vitamin D in combination with other treatments in any dose, form, or duration. (4)outcomes:25(OH)D3 level, ABC, CARS, ATEC, SRS, SSGARS-2.	The Cochrane bias test	15 studies, N=818	China	1.25(OH)D3 level (SMD=0.83, 95% CI: (0.56, 1.09), P<0.00001); 2.ABC-lethargy (MD = –1.31, 95% CI(–3.56, 0.94), P=0.25, I2 = 0%) 3.ABC-stereotypical behavior (MD = 0.09, 95% CI(–1.38, 1.57), P=0.90, I2 = 69%) 4.ABC-inappropriate speech (MD = 0.79, 95% CI(–0.26, 1.84), P=0.14, I2 = 0%) 5.ABC-irritability (MD =−2.91, 95% CI(–5.37, −0.44), P=0.02, I2 = 0%) 6.ABC-hyperactivity (MD:-3.19, 95% CI: [−5.54, −0.85], P= 0.008, I2 = 0%) 7.CARS (MD=−2.66, 95% CI:(−6.51, 1.19), P=0.18, I2 = 0%) 8.ATEC (MD=−2.64, 95% CI:(−14.29, 9.00), P=0.66,) 9.SRS (MD=−6.68, 95% CI:(−15.11, 1.75), P=0.12, I2 = 0%); 10.SSGARS-2 (MD:-0.70, 95% CI:(−3.13, 1.74), P=0.57).	Reduced serum 25(OH)D levels may be a risk factor for the development of ASD, and vitamin D treatment may improve irritability in children with ASD.
Bingbing Li et al 2022[42]	RCT	PubMed, PsychINFO, Cochrane library, WOS. Searched from inception to March 20, 2019.	(1) the design was an RCT; (2) the population was children aged <18 years whose primary diagnosis was ASD based on established criteria, (3) the protocols were specified for vitamin D supplementation only or vitamin D combined with other vitamins in children with ASD and placebo or no supplementation in the control group, and (4) there was at least one outcome measure, including core symptoms of ASD such as social interaction, communication, and RRB or symptoms or behaviors associated with ASD, including hyperactivity, irritability, and sensory issues.	The Cochrane Risk Assessment Tool	3 studies, N=108 (VD=56; Placebo=52)	China	1.ABC-Social interaction (pooled MD: −1.54; 95% CI: [−4.09, 1.01]; p =0.24, I2 = 0%); 2.ABC-Communication ((pooled MD: −0.05; 95% CI: [−1.79, 1.69]; p = 0.96, I2 = 60%); 3.ABC-Repetitive and restricted behaviors and interest (pooled MD: 0.85; 95% CI: [−0.33, 2.02]; p =0.16, I2 = 0%); 4.ABC-Hyperactivity (pooled MD: −3.20; 95% CI:[−6.06, −0.34]; p = 0.03, I2 = 10%); 5.ABC-Irritability (pooled MD: −2.31; 95% CI: [−6.08,1.46]; p = 0.23, I2 = 64%);	Vitamin D supplementation is not beneficial for core symptoms or other co-existing behaviors and conditions.

(*Continued*)

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Table 1 (Continued).

Literature	Study Type	Database	Population Setting	Quality Assessment	Sample Size	Countries	Measurement Tool	Conclusion
Zuqun Wang et al 2020[18]	Case-control study	PubMed, EMBASE, WOS, Cochrane Library. Searched from inception to 27 November 2019.	(1)Participants: children or adolescents aged less than 18, pregnant women, and neonates. (2)Intervention/exposure: insufficient or deficient vitamin D level in peripheral blood. (3)Comparison: sufficient vitamin D level in peripheral blood. (4)Outcome: autism spectrum disorder. (5)Study design: case–control, cohort, and nested case–control studies.	The Newcastle–Ottawa Scale (NOS)	34 studies, N=20340 (ASD=5074; control=15266)	China	1.vitamin D levels (24 case control studies) (MD= −7.46, 95% CI:(−10.26, −4.66), P<0.01, I2 = 98%); 2.vitamin D levels (10 case control studies) (MD= 5.23, 95% CI:(3.13, 8.73), P<0.01, I2 = 78%); 3.vitamin D levels (15 case control studies) (MD= −6.20, 95% CI:(−9.62, −2.78), P<0.01, I2 = 97%); 4.vitamin D levels (7 meta-analysis studies) (MD= −3.15, 95% CI:(−6.57, 0.26), P<0.01, I2 = 99%); 5.vitamin D levels (9 prospective studies) (MD= 1.54, 95% CI:(1.12, 2.10), P<0.01, I2 = 81%);	Vitamin D deficiency early in life is associated with a slightly increased risk of ASD.
Maria Carmen Gallardo Carrasco et al 2022[57]	Observational study	Medline, Cochrane, Pubmed, PsycINFO, WOS. Searched from inception to January 10, 2021.	(1) studies should compare blood levels of vitamin D and/or fatty acids and/or folate in children diagnosed with ASD with the values in children without this disorder; (2) the par_x005f_x0002_ticipants' age was between 0 and 18 years; (3) studies should have been published between 2014 and 2020; (4) ASD was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, ffth edition DSM-V (APA, 2014); (5) the age of the control group must range from 0 to 18 years and they should not have any neurodevelopmental pathology.	STROBE initiative statement	20 studies, N=5888 (ASD=2827; control=3061)	Spain	1.vitamin D levels(SMD, 95% CI=−0.83 [−1.15, −0.50], χ2=153.35, p=0.0001; I2=92%;) subgroup 1 (8 studies, N = 1726; SG = 900, CG = 826): SMD, 95% CI = − 0.43 [− 0.59, − 0.27], χ2 = 14.80, p = 0.04; I2 = 53%; subgroup 2 (4 studies, N=246; SG =122; CG =124): SMD, 95% CI = − 2.03 [− 2.53, − 1.52], χ2 = 7.29, p = 0.06; I2 = 53%;	Vitamin D may improve the course of the disease and may also reduce the risk of autism developing.

Yue wang et al 2021[58]	Case–control study	Medline, EMBase, PubMed, Scopus, Cochrane Library, EBSCO, WOS, CBMdisc, CNKI, WanFang Data, VIP. Searched from inception to January 10, 2021.	(1) The type of study was limited to a case-control study; (2) The age of the participants was 0–18 years old; (3) The children included in the study were diagnosed with ASD according to the Diagnostic Statistical Manual of Mental Disorders, Fourth or Fifth Edition (DSM-IV or DSM-V); (4) Healthy children were used as a control group; (5) The relationship between vitamin D and ASD has been explored in the literature, and the means and standard deviations, sample sizes, and P-values of serum 25-(OH)D levels in the experimental and control groups have been clearly reported. Serum 25-(OH)D levels were measured by liquid chromatography-tandem mass spectrometry, enzyme-linked immunosorbent assay, chemiluminescence, and so on. (6) For multiple literature reports by the same author, only the literature published at a later date was selected.	The Newcastle–Ottawa Scale (NOS)	14 studies, N=2402 (ASD=1135; control=1267)	China	1.vitamin D levels WMD = –8. 91, 95% CI: –12. 45~ –5. 37, P<0. 01, I2 = 97%; Subgroup 1: China subgroup WMD = –10.81, 95% CI: –16.80~ –4.82, P<0. 01, I2 = 97%; Subgroup 2: The Middle East subgroup WMD = –9.35, 95% CI: –18.09~ –0.60, P=0. 04, I2 = 98%; Subgroup 3: Europe and the United States (excluding Middle Eastern countries) subgroup WMD = –6.22, 95% CI: –12.87~ 0.44, P=0. 07, I2 = 97%;	Vitamin D deficiency may be a risk factor for autism spectrum disorders in children with ASD.

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Table 2 AMSTAR 2 Quality Assessment Scale

Number	Zhang M, et al[53]	Song L, et al[43]	Shuang cheng, et al[54]	Wang T, et al[55]	Caiwei Li, et al[56]	Bingbing Li, et al[42]
①	Y	Y	Y	Y	Y	Y
②	Y	N	N	N	N	N
③	Y	N	N	Y	N	Y
④	Y	Y	Y	Y	Y	Y
⑤	Y	Y	Y	Y	Y	Y
⑥	Y	Y	Y	Y	Y	Y
⑦	Y	Y	Y	Y	Y	Y
⑧	Y	Y	Y	Y	Y	Y
⑨	Y	Y	Y	Y	Y	Y
⑩	Y	Y	Y	Y	Y	Y
⑪	Y	Y	Y	Y	Y	Y
⑫	N	N	N	N	Y	Y
⑬	N	Y	N	Y	Y	Y
⑭	N	Y	N	Y	Y	Y
⑮	N	N	N	PY	N	PY
⑯	Y	Y	N	Y	N	Y
Quality Assessment	Very low	Very low	Very low	Low	Very low	Low

Assessment of Reporting Quality

Reporting quality was evaluated using the PRISMA checklist. Scores of the studies analyzed spanned from 21 to 23, with two studies each obtaining scores of 21, 22, and 23, respectively. Deficiencies identified included: (1) An absence of described methods for countering bias due to data omission in the synthesis process, potentially contributing to reporting bias; (2) A lack of detailed risk of bias due to missing results for each combined outcome, increasing the possibility of reporting bias; (3) The majority of studies failed to couch their results within the broader evidence context in the evidence summary, which complicates comparisons with similar MAs/SRs and may lead to imprecise result interpretation and reporting bias; (4) Omissions in the detailing of study protocol registrations, which impedes readers' ability to discern between pre-planned and reported information, heightening the risk of reporting bias.Detailed information can be found in Table 3.

GRADE Assessment of Evidence Quality

In this analysis, 35 outcome measures were evaluated using the GRADE framework. For RCT-derived evidence, assessed outcomes included levels of 25-hydroxyvitamin D (25(OH)D), Social Responsiveness Scale (SRS) scores, and subscales and total scores from the Autism Behavior Checklist (ABC), Gilliam Autism Rating Scale (GARS), Childhood Autism Rating Scale (CARS), and Autism Treatment Evaluation Checklist (ATEC). Observational studies solely addressed the

Table 3 PRISMA 2020 Checklist

	Item	Checklist Item	Complete Report		Partial Report+no Report	
			Numbers	Percentage (%)	Numbers	Percentage (%)
Title	1	Title	6	100		
Abstract	2	Abstracts checklist	6	100		
INTRODUCTION	3 4	Rationale Objectives	6 6	100 100		

(*Continued*)

Table 3 (Continued).

	Item	Checklist Item	Complete Report		Partial Report+no Report	
			Numbers	Percentage (%)	Numbers	Percentage (%)
METHODS	5	Eligibility criteria	6	100		
	6	Information sources	6	100		
	7	Search strategy	6	100		
	8	Selection process	6	100		
	9	Data collection process	6	100		
	10	Data items	2	33.33	4	66.67
	11	Study risk of bias assessment	2	33.33	4	66.67
	12	Effect measures	6	100		
	13	Synthesis methods	6	100		
	14	Reporting bias assessment			6	100
	15	Certainty assessment	5	83.33	1	16.67
RESULTS	16	Study selection	6	100		
	17	Study characteristics	6	100		
	18	Risk of bias in studies	2	33.33	4	66.67
	19	Results of individual studies	6	100		
	20	Results of syntheses	6	100		
	21	Reporting biases			6	100
	22	Certainty of evidence	5	83.33	1	16.67
DISCUSSION	23	Discussion	6	100		
OTHER INFORMATION	24	Registration and protocol	6	100		
	25	Support	6	100		
	26	Competing interests	5	83.33	1	16.67
	27	Availability of data, code and other materials			6	100

association between vitamin D and ASD. GRADE's quality classification yielded 20 outcomes as low quality and 15 as very low quality, attributable to: (1) Limitations in study methodologies, notably due to the moderate to low quality of primary RCTs, with many neglecting to delineate blinding, randomization, and allocation concealment processes; (2) Inconsistency, exemplified by moderate to high heterogeneity in data synthesis, possibly related to the inclusion of many low-quality studies and disparate confidence intervals leading to significant I2 values upon result amalgamation; (3) A lack of precision in original literature, often due to small sample sizes and wide confidence intervals in study findings. Detailed information can be found in Table 4.

Discussion

Factors Influencing the Effectiveness of Vitamin D Supplementation on ASD Incidence

The efficacy of vitamin D supplementation in managing ASD can be affected by numerous factors, such as dosage, treatment duration, timing of measurement, and achieved serum 25(OH)D concentrations.[59] Referring to related studies, for vitamin D supplementation studies, factors such as malabsorption, liver disease, and kidney disease are excluded before enrollment in normal children, because diseases in these populations can affect vitamin D absorption, distribution, and metabolism. However, in the RCT studies of autism, disease factors affecting vitamin D were not actually excluded. This exclusion criterion is the same in the criteria of the review of the relationship between vitamin D dose and serum levels.[60] The type of vitamin D supplementation is also an influencing factor on serum effects, but this one distinction is not reflected in many studies. Types of vitamin D include vitamin D2 and vitamin D3, but vitamin D2 and vitamin D3 do

Table 4 GRADE Evidence Quality Rating Results

	Outcome Indicator	1.Study Limitations	2. Inconsistency of Results	3. Indirectness of Evidence	4. Imprecision	5. Reporting Bias	Quality of Evidence
Zhang M, et al[53]	25 (OH) D level	0	−1	0	−1	0	low
	SRS	0	0	0	−2	0	low
	ABC-lethargy	0	0	0	−2	0	low
	ABC-stereotypical behavior	0	0	0	−2	0	low
	ABC-inappropriate speech	0	−1	0	−2	0	very low
	ABC-irritability	0	−1	0	−2	0	very low
	ABC-hyperactivity	0	0	0	−2	0	low
	GARS-2— stereotypy	0	0	0	−2	0	low
Song L, et al[43]	25 (OH) D level	0	0	0	−2	0	low
Shuang cheng, et al[54]	SRS	−1	0	0	−2	0	very low
	CARS total	−1	−2	0	−1	0	very low
	ABC-lethargy	−1	−2	0	−1	0	very low
	ABC-stereotypical behavior	−1	−2	0	−1	0	very low
	ABC-inappropriate speech	−1	−2	0	−1	0	very low
	ABC-irritability	−1	−2	0	−1	0	very low
	ABC-hyperactivity	−1	−2	0	−1	0	very low
	ATEC total	−1	−2	0	−2	0	very low
Wang T, et al[55]	25 (OH) D level	0	−2	0	−1	−1	very low
Caiwei Li, et al[56]	25 (OH) D level	0	−2	0	−2	0	very low
	SRS	0	0	0	−2	0	low
	ABC-lethargy	0	0	0	−2	0	low
	ABC-stereotypical behavior	0	0	0	−2	0	low
	ABC-inappropriate speech	0	−1	0	−2	0	very low
	ABC-irritability	0	0	0	−2	0	low
	ABC-hyperactivity	0	0	0	−2	0	low
	CARS total	0	−2	0	−2	0	very low
	ATEC total	0	0	0	−2	0	low
	SSGARS-2	0	0	0	−2	0	low
Bingbing Li, et al[42]	ABC-Social interaction	0	0	0	−2	0	low
	ABC-Communication	0	−1	0	−2	0	very low
	ABC-Repetitive and restricted behaviors and interest	0	0	0	−2	0	low
	ABC-Hyperactivity	0	0	0	−2	0	low
	ABC-Irritability	0	−1	0	−2	0	very low
Zuqun Wang, et al[18]	Vitamin D and ASD relationship	0	−2	0	−1	0	very low
Maria Carmen Gallardo Carrasco, et al[57]	Vitamin D and ASD relationship	0	−2	0	−1	0	very low
Yue wang, et al[58]	Vitamin D and ASD relationship	0	−2	0	−1	−1	very low

not have the same molecular structure, and thus are converted to 25(OH)D at different rates of breakdown. However, a query of relevant studies did not reveal a difference between vitamin D2 and vitamin D3 supplementation in autistic patients, which could be a next step in research. A search of the literature found that for normal children, a single large dose of supplementation to improve the effect of serum 25(OH)D in patients, vitamin D3 is significantly better than vitamin D2.

Age is also an important factor, although the studies included in this review were all conducted on children under the age of 18 to better understand the benefits of vitamin D supplementation on neurodevelopment. However, many studies did not conduct detailed age analyses. Referring to the included literature for further analysis, children under the age of 18 were divided into several different time periods, with only Kerley et al[61] studies stratifying by age (<6 and 6 years), and the treatment effects of vitamin D also showed that those <3 years of age had a more significant improvement. Therefore, it is suggested that vitamin D supplementation should be given during infancy or pregnancy. Based on this result, this review also hypothesizes that there may be a window of opportunity during the early stages of life in which vitamin D supplementation would be more beneficial for establishing neural connections, and we hope that future experimental studies can explore the optimal supplementation period.

In RCTs two adjusted the vitamin D dosage according to patient weight,[62] while another applied a uniform high dose of 50,000 IU weekly.[63] The American Endocrine Society recommends maintaining serum 25(OH)D levels between 100–150 nmol/L (40–60 ng/mL),[64,65] yet specific dosing guidelines for children with ASD are still to be established. It is postulated that higher doses may be required to reach desired serum 25(OH)D levels in ASD cases. Kerley et al[66] observed that 11.11% of their subjects experienced no serum 25(OH)D increase post-supplementation, suggesting that ASD subtypes with concurrent gastrointestinal issues could impede vitamin D absorption and highlighting the necessity for tailored research in determining efficacious dosing. Additionally, for ASD patients with significant vitamin D absorption or metabolism difficulties, calcitriol could serve as an alternative treatment. Rigorous monitoring of serum 25(OH)D levels before, during, and post-intervention is essential to optimize dosage regimens. Unfortunately, many prospective studies are limited by a solitary measurement of vitamin D levels, inadequately portraying the overall vitamin D status across different developmental phases. Moreover, substantial variability within observational studies may arise from a range of demographic characteristics.

Furthermore, it can be seen from the included RCT literature, as shown in Tables 5–8, the supplementation doses vary. We strive to find a dose that is suitable for more geographical populations, where Saad et al study[67] is a RCT conducted in Egypt, which clearly indicates that 300 IU vitamin D3/kg/day of vitamin D is generally well tolerated by the ASD children. After supplementation for 4 months, the symptoms of ASD improved significantly, proving the effectiveness and tolerability of high-dose vitamin D for ASD children. We also need to consider that Saad et al study[67] was conducted in the Egyptian region, where different levels of sunlight can affect the children's vitamin D content. In RCT studies, more rigorous involvement needs to take into account factors such as sunlight, latitude and longitude, and season. Among them, the most rigorous study is Mazahery et al,[45] which considered different seasons' serum 25(OH)D concentrations in different regions when conducting the study. At the same time, Mazahery et al[45] study considering the different nutritional deficiencies of ASD patients before the study, conducted a preliminary management strategy, including vitamin D, iron, and vitamin B12. This is also something that can be further referenced in future RCT studies. Fernell et al study[68] included individuals with autism spectrum disorder (ASD) and their siblings, compared to which, the common linkage factors and genetic factors of ASD are closer, which is conducive to obtaining better research results.

The Relationship Between Vitamin D and ASD

Vitamin D and Brain Development

Vitamin D is vital to early brain development,[102] particularly in synaptic formation, potentially leading to neurochemical alterations and changes in neuronal function.[103] Research indicates that vitamin D underpins various aspects of brain homeostasis and neurodevelopment, such as neuronal migration and growth, excitatory and inhibitory neurotransmission, production of neurotrophic factors, and cytokine regulation.[104–107] Dysregulation in any of these domains can directly affect brain development. Specifically, vitamin D's role in neurotrophic factor expression is instrumental in modulating

Table 5 Detailed Information of Literatures Included in Systematic Reviews (RCT Studies)

Study	Country	Study Design	Sample Size	Age	Sex (M/F)	Dose	Duration	Baseline 25 (OH)D Levels	Final 25(OH)D Levels	Autism criteria	Outcome measure	Included literature	Key findings
Nan lv 2021[69]	China	RCT	68 (ASD 34 / control 34)	3.47±1.18 (ASD) 3.45±1.21 (control)	29/5(ASD) 30/4(control)	700 IU/d	3 months	ASD:16.85 ± 1.26 Control: 16.84 ± 1.28	ASD:27.76 ± 1.82 Control: 15.68 ± 1.82	DSM-IV	GARS, ABC, 25-(OH)D	[56]	Vitamins A and D may promote cognitive, language, and behavioral improvements in children with ASD.
Jing Huang et al 2020[70]	China	RCT	135(VD) 135(placebo)	3.26±0.85 (VD) 3.58±0.63 (placebo)	–	150000IU/d vitamin D3	3 months	25.79±2.14(VD) 25.57±1.96 (placebo)		DSM-IV	ABC, ATEC, Gesell, C–PEP	[54,56]	VitD3 combined with ESDM intervention for children with ASD can help to improve the symptoms of ASD, and has a significant effect on the improvement of language, cognitive and social skills.
Javadfar et al 2020[44]	Iran	RCT	22(VD) 21(placebo)	8.88(VD) 8.95(placebo)	20/2(VD) 16/5(placebo)	300IU/kg, maximum of 6000 IU/d (unclear vitamin D3 or D2)	15 weeks	8.19(ng/mL, VD) 10.84(ng/mL, placebo)	39.10(ng/mL, VD) 8.94(ng/mL, placebo)	DSM-IV	CARS, ABC-C, ATEC, BMI, Serum 25(OH) D3, IL-6, serotonin	[53,54,56]	Vitamin D supplementation can improve ASD symptoms.
Shulan Huang et al 2020[71]	China	RCT	150(VD) 150(placebo)	1.6±0.8(VD) 1.7±0.6 (placebo)	–	150000IU/d vitamin D3	3 months				GARS, ABC	[54]	Compared with ESDM alone, the use of vitamin D3 in combination with the ESDM model in young children with ASD effectively reduces the children's total CARS score and total ABC score, which is effective and worthy of promotion.

Ansari et al 2020b[63]	Iran	RCT	10(VD) 10(placebo)	10.30±2.90 (VD) 10.00±2.90 (placebo)	10/0(VD) 10/0(placebo)	50000 IU/ week or 50000IU/2 week(vitamin D3)	10 weeks	11.12(ng/mL, VD) 10.30(ng/mL, placebo)	31.60(ng/mL, VD) 10.20(ng/mL, placebo)	DSM-IV	GARS-2	[53,56]	Vitamin D supplements all significantly improved serum cytokine levels and behavioral problems in children with ASD.
Mazahery et al 2019[45]	New Zealand	RCT	19(VD) 16(placebo)	5.3±1.5(VD) 5.7±1.0 (placebo)	16/3(VD) 13/3(placebo)	2000IU/d (vitamin D3)	12 months	68.00(nmol/L, VD) 55.00(nmol/L, placebo)	95.00(nmol/L, VD) (nmol/L, placebo)		ABC	[42,43,53,54,56]	Vitamin D and omega- 3 LCPUFA reduced irritability symptoms in children with autism. Vitamin D also reduced ADHD symptoms in these children.
Mazahery et al 2019[45]	New Zealand	RCT	19(VD) 16(placebo)	2.5–8	NA	2000IU/d (vitamin D3)	12 months	63.00(nmol/L, VD) 56.00(nmol/L, placebo)	NA	DSM-IV	SRS, SPM	[42,53,54,56]	Both Omega-3 LCPUFA with or without vitamin D in combination may improve some of the core symptoms of ASD, but no definitive conclusions can be drawn at this time.

(*Continued*)

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Table 5 (Continued).

Study	Country	Study Design	Sample Size	Age	Sex (M/F)	Dose	Duration	Baseline 25 (OH)D Levels	Final 25(OH)D Levels	Autism criteria	Outcome measure	Included literature	Key findings
Junyan Feng et al 2019[72]	China	RCT	35(VD) 30(placebo)	28.0±1.6(VD) 29.0±0.9 (placebo)	–	150000IU/d vitamin D3	3 months	27.0±2.7(VD) 25.5±2.3 (placebo)	54.2±3.5(VD)	DSM-IV	GARS, ABC	[54]	ESDM treatment can effectively improve the clinical symptoms of young children with ASD, especially in the area of socialization, compared with conventional rehabilitation; ESDM combined with VitD3 treatment is better for the improvement of socialization ability of young children with ASD, which may be one of the best solutions to improve the clinical symptoms of young children with ASD at present.
Moradi et al 2018[62]	Iran	RCT	25(VD) 25(placebo)	0.97±8.04 (VD) 1.25±7.20 (placebo)	25/0(VD) 25/0(placebo)	300IU/kg, maximum of 5000 IU/d (vitamin D3)	3 months	4.61±12.60(ng/mL, VD) 4.87±11.52(ng/mL, placebo)	6.48±24.36(ng/mL, VD) 3.95±11.08(ng/mL, placebo)	DSM-IV vitamin D serum level less than 30 ng/mL	GARS-2	[53,56]	Combining perceptual-motor exercise and vitamin d3 supplementation for children with autism significantly reduces their stereotypical behaviors.

Fang et al 2018b[62]	China	RCT	12(VD) 12(OM) 12(VD+OM) 12(PL)	10±2(VD) 10±2(OM) 10±3(VD+OM) 10±3(PL)	67(VD) 50(OM) 58(VD+OM) 58(PL)	VD:800 U of vitamin D3/day OM:900 mg of omega-3/day VD+OM:800 U of vitamin D3/day and 900 mg of omega-3/day PL: placebo	12 months	VD:32±10 OM:29±12 VD+OM:30±10 PL:28±10(ng/mL)		DSM-5	GARS	[43,56]	Vitamin D supplementation or vitamin D combined with omega-3 fatty acids using the TEACCH intervention improves symptoms in children with ASD. Vitamin D + omega-3 fatty acids are effective adjunctive therapies for treating children with ASD
Saad et al 2018[67]	Egypt	RCT	55(VD) 54(placebo)	5.3±1.9(VD) 5.6±2.7 (placebo)	43/12(VD) 42/12 (placebo)	300IU/d vitamin D3, maximum of 5000 IU/d	4 months	26.3±12.7(VD) 27.1±15.1 (placebo)	45.9±17.2(VD) 28.2±13.8 (placebo)	DSM-IV	25(OH)D3, CARS, ABC, SRS, ATEC, Biomarkers: vitamin D levels, calcium, phosphorous, magnesium, glucose, potassium, alkaline phosphate, lead, blood urea nitrogen (BUN), serum creatinine, AST, ALT	[54]	The study is the first double-blind randomized controlled trial to demonstrate the efficacy of vitamin d3 in patients with ASD. Based on the parameters measured in the study, oral vitamin D supplementation can safely improve signs and symptoms of ASD and can be recommended for children with ASD.
Feng et al (2017)[73]	China	RCT	500(ASD:215 / Controls:285)	ASD:4.76 ±0.95 y Controls:5.12 ±1.15 y	ASD:173/42 Controls:225/60	150 000 IU every month and orally administered at a dosage of 400 IU every day	3 months			DSM-IV	ABC, CARS, 25 (OH) D levels	[18]	Vitamin D Supplementation may directly improve core symptoms of Autism, possibly even in younger autistic children.

(*Continued*)

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Table 5 (Continued).

Study	Country	Study Design	Sample Size	Age	Sex (M/F)	Dose	Duration	Baseline 25 (OH)D Levels	Final 25(OH)D Levels	Autism criteria	Outcome measure	Included literature	Key findings
Kerley et al 2017[61]	Ireland	RCT	18(VD) 20(placebo)	7.9±23.4(VD) 6.9±3.8 (placebo)	15/3(VD) 18/2(placebo)	2000IU/d (vitamin D3)	20 weeks	58.60(nmol/L, VD) 51.70(nmol/L, placebo)	86.10(nmol/L, VD) 50.60(nmol/L, placebo)	Autism Diagnostic Observation Schedule, Diagnostic and Statistical Manual of Mental Disorders or Diagnostic Instrument for Social and Communication Disorders)	ABC, SRS, DD-CGAS, Biochemistry: CRP; Neutrophil: lymphocyte; Ca2+;25(OH)D	[42,43,53,56]	Vitamin D supplementation had no effect on primary outcomes in children with ASD, but the effects were limited and inconsistent.
Xiaoyan Duan et al 2015[74]	China	RCT	36(VD)	3.69±1.67 (VD) 5.12±1.15 (placebo)	–	150000IU/d vitamin D3	3 months				GARS, ABC	[54]	The serum 25(OH) D levels of children with ASD were significantly lower than those of healthy controls, and serum 25(OH) D levels were negatively correlated with the degree of behavioral abnormalities in children with ASD; the behavioral abnormalities of children with ASD improved after the administration of vitamin D supplementation, and early vitamin D treatment was more effective than late treatment.
Hanan et al 2014[75]	Egypt	RCT	10(VD) 11(placebo)	2.7±1.9(VD) 5.8±2.9 (placebo)	–	2000IU/d vitamin D3	6 months	47±20 nmol/L			GARS, VABS, ATEC	[54]	Oral vitamin D supplementation has been shown to improve 25-hydroxyvitamin D status in children with autism.

Table 6 Detailed Information of Literatures Included in Systematic Reviews (Case-Control Studies)

Study	Country	Study Design	Sample Size	Age	Sex (M/F)	Baseline 25(OH)D Levels	Autism Criteria	Outcome Measure	Included Literature	Key Findings
Schmidt et al (2019)[15]	USA	Case-control	ASD:357 Controls:234	43.6±9.6(ASD) 42.3±9.8(control)	ASD:310/47 Controls:191/43	ASD:32.04±14.96 Controls:33.08±15.72	ADOS, ADI-R		[18]	Suggests that neonatal vitamin D may be associated with ASD in females and developmental delay in non-Hispanic white children.
Windham et al (2019)[76]	USA	Case-control	ASD:563 Controls:436	–	ASD:461/101 Controls:360/76	ASD:34.04±14.1 Controls:33.72±11.85	DSM-IV-TR		[18]	Lower 25(OH)D did not correlate with higher risk of ASD.
Lee et al (2019)[77]	USA	Nested case-control	ASD:449 Controls:574	–	–	ASD:10.28±5.96 Controls:10.64±6.31	ICD-9, ICD-10, and DSM-IV		[18]	Vitamin D concentrations early in life may be associated with an increased risk of neurodevelopmental disorders, including ASD.
Bičíková et al (2019)[78]	Czech Republic	Case-control	85 (ASD:45 / Controls:40)	ASD:4–7 y Controls:5–9 y	–	ASD:26.03±10.38 Controls:28.14±8.29			[18]	No statistically significant differences in vitamin D were observed between children with autism and healthy controls. The results of our study suggest that the supply of vitamin D in the young population is inadequate. We found that more than 60% of the young population had suboptimal levels of vitamin D.
Meguid et al 2010[13]	Egypt	Case-control	112 (ASD 70 / control 42)	5.3±2.8(ASD) 6.1±1.8(control)	–	ASD: 28. 50±16. 40 Control: 40. 10±11. 80	DSM-IV		[18,55,58]	Circulating vitamin D levels (25 (OH)D and 1.25(OH)2D) were significantly lower in children with autism than in healthy controls.
Yan Ma. 2019[79]	China	Case-control	193 (ASD 93 / control 100)	6.02 ± 1.02(ASD) 5.78±1.10(control)	ASD:53/40 Controls:60/40	ASD: 65.62 ± 10.02 Control: 89.29 ± 12.23	DSM-IV	CRAS	[58]	Serum 25(OH) D and folate levels were significantly lower in children with autism spectrum disorders, and changes in their levels were closely related to the extent of the children's condition.

(*Continued*)

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Table 6 (Continued).

Study	Country	Study Design	Sample Size	Age	Sex (M/F)	Baseline 25(OH)D Levels	Autism Criteria	Outcome Measure	Included Literature	Key Findings
Altun et al (2018)[38]	Turkey	Case-control	105(ASD:60 / Controls:45)	ASD:5.8±2.7 y Controls:6.7±2.5 y	ASD:52/8 Controls:36/9	ASD:13.79±1.03 Controls:16.58±1.06	DSM-IV-TR	CRAS	[18]	Low serum vitamin D and VDR levels, high homocysteine and low vitamins B6, B12 and folate may play an important role in the pathogenesis of ASD.
Basheer et al (2017)[80]	India	Case-control	70(ASD:40 / Controls:30)	ASD:3–12 y control:3–12 y		ASD:13.5±4.7 Controls:12.7±4.7	DSM-V ADI-R	CRAS, ADI-R, SS and SCG	[18]	
Bener et al (2017)[41]	Turkey	Case-control	616(ASD:308 / Controls:308)	ASD:5.39±1.66 y Controls:5.62±1.81 y	ASD:153/155 Controls:137/171	ASD:18.79±8.35 Controls:22.18±9.00	DSM-IV ADOS		[18]	Children with autism had higher rates of iron and vitamin D deficiency and anemia compared to controls.
Cieślińska et al (2017)[81]	Poland	Case-control	304(ASD:108 / Controls:196	ASD:6.8(3–11) y control:8.5(4–18) y	ASD:91/17 Controls:98/98	ASD:49.4±4.23 Controls:41.5±3.39	ICD-10, ICD-F84.0		[18]	Genetic polymorphisms in two SNPs in the VDR may be associated with the development of ASD symptoms by affecting the function of vitamin D3 metabolism, whereas vitamin D3 levels were not significantly different between ASD and non-ASD children.
Desoky et al (2017)[82]	Egypt	Case-control	100(ASD:60 / Controls:40)	ASD:7.03±2.34 y Controls:7.91±3.21y	ASD:55/5 Controls:20/20	ASD:18.63±10.8 Controls:45.9±8.85		CRAS	[18]	CD5 was significantly negatively correlated with FT3, FT4, and 25(OH)D, indicating that the higher the CD5, the lower the FT3, FT4, and 25(OH)D, the higher the CARS score, and the higher the severity of autism.
Chen et al (2016)[83]		Case-control	ASD:68 Control:68	–	–	–	DSM-V		[18]	

Saad et al 2016[84]	Egypt	Case-control	122(ASD) 100(case control)	5.09±1.42(ASD) 4.88±1.30(case control)	–	ASD:18.02±8.75 Controls:42.51±9.48	DSM-IV	GARS, ABC, SRS	[18,54,55,58]	Vitamin D may have beneficial effects in patients with ASD, especially when final serum levels exceed 40 ng/mL.
Coşkun et al (2016)[85]	Turkey	Case-control	167 (ASD:85 / Controls:82)	ASD:43.4±25.3 m Controls:47.1±14.2 m	ASD:72/13 Controls:54/28	ASD:79.5±25.9 Controls:65.1±23.9	DSM-V		[18]	25(OH)D is involved in autism pathophysiology and serum 25 (OH)D levels may be affected by FokI polymorphisms in children with ASD.
Guler et al (2016)[86]	Turkey	Case-control	120(ASD:60 / Controls:60)	ASD:7.10±1.50 y Controls:6.93±1.59 y	ASD:44/16 Controls:39/21	ASD:25.58±10.31 Controls:25.35±9.92	DSM-V		[18]	No correlation between serum 25(OH)D levels and total CSHQ was found in this study in the ASD and control groups. The correlation between serum 25 (OH)D levels and night waking/ daytime sleepiness scores was particularly significant. This significant improvement was observed after treatment by total CSHQ levels in the ASD and control groups. The results suggest that 25(OH)D replacement therapy can be used in patients with ASD and healthy individuals with sleep disorders.
Moharreri et al (2015)[87]	Iran	Case-control	27 (ASD:13 / Controls:14)	ASD:5.7±2.24 y Controls:5.7±2.24 y	ASD: M:F 11/2 Controls: M:F 12/2	ASD:13.00±9.9 Controls:12.00±8.3	DSM-IV		[18]	According to the results of the study, there was no significant difference in serum levels of vitamin D between children with and without autism, and there was no significant relationship between the levels of this vitamin and the severity of autism.
DU et al 2015[88]	China	Case-control	226 (ASD 117 / control 109)	4.1±2.2(ASD) 3.9±2.0(control)	–	ASD: 19.00 ± 9.00 Control: 36.00 ± 13.00	DSM-IV		[18,55,58]	Lower 25(OH) D in ASD group

(*Continued*)

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Table 6 (Continued).

Study	Country	Study Design	Sample Size	Age	Sex (M/F)	Baseline 25(OH)D Levels	Autism Criteria	Outcome Measure	Included Literature	Key Findings
Fernell et al 2015[68]	Sweden	Case-control	116 (ASD 58 / control 58)	14–32 months	ASD:52/6 Controls:23/34	ASD: 24.00 ± 19.60 Control: 31.90 ± 27.70			[18,55,57,58]	The role of vitamin D in the development of ASD is pointed out by the results of three different independent studies: (1) the increased risk of ASD in the offspring of immigrants, especially from countries with dark-skinned populations and cultures in which women use coveralls; (2) low levels of (OH)D in neonatal cohorts who later develop ASD, as well as in child and adult cohorts; and (3) the association between season of birth and ASD, which in our study did not extend to high-risk immigrant groups in our study, suggesting that these groups are exposed to suboptimal vitamin D levels throughout the year. Although low levels of vitamin D may have a genetic cause and therefore be associated with ASD, our study for the first time excludes lifestyle mechanisms associated with ASD as an explanation for low 25(OH)D levels.
Ugur et al 2014[89]	Turkey	Case-control	108 (ASD 54 / control 54)	ASD:59.6±15.0 m Controls:55.7±13.8 m	–	ASD: 25.12 ± 11.28 Control: 21.11 ± 9.65	DSM-IV	ABC, the Aberrant Behaviour Checklist (AbBC), CARS	[18,55,57,58]	The findings do not support the idea that serum levels of vitamin D and folate may be lower in children with autism. However, vitamin D and folate deficiencies may play a role in the development of early or prenatal ASD.

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Gong et al 2014[90]	China	Case-control	96 (ASD 48 / control 48)	ASD:3.67±1.21 y Controls:3.67±1.21 y	ASD: 40/8 Controls: 40/8	ASD: 19.90 ± 3.80 Control: 22.60 ± 4.50	DSM-IV	CRAS	[18,55,57,58]	Lower 25(OH)D levels may be independently associated with the severity of ASD in Chinese patients, and lower serum 25 (OH)D its levels can be considered an independent risk factor for ASD.
Bener et al 2014[41]	Qatar	Case-control	508 (ASD 254 / control 254)	ASD:5.51±1.58 Controls:5.76±1.56	ASD:165/89 Controls:144/110	ASD: 18.39 ± 8.2 Control: 21.59 ± 8.4	ADOS		[55,57,58]	Vitamin D deficiency is higher in children with autism than in healthy children, and vitamin D supplementation may be a safe and more effective strategy to reduce the risk of autism.
Neumeyer et al 2013[39]	USA	Case-control	37 (ASD 18 / control 19)	ASD:10.6±0.4 y Controls:11.2±0.3 y	–	ASD: 26.70 ± 1.90 Control: 31.70 ± 1.60	DSM-IV		[18,55]	BMD in ASD lower than control group. 25(OH) D lower in ASD than control group
Tostes et al 2012[40]	Brazil	Case-control	48 (ASD 24 / control 24)	7.4±2.7(ASD) 7.2±1.8(control)	ASD:18/6 Controls:18/6	ASD: 26.48 ± 3.48 Control: 40.52 ± 3.13	DSM-IV	25-OHD levels	[18,55,58]	Vitamin D deficiency evidenced by serum levels of 25-OHD in children with autism.
Mostafa et al 2012[37]	Saudi Arabia	case-control	80 (ASD 50 / control 30)	ASD:8.24±2.37 y Controls:8.63±2.65 y	–	ASD: 18.50 ± 14.00 Control: 33.00 ± 11.00	DSM-IV		[18,55]	Lower 25(OH) D in ASD, significant negatively correlated with CARS scores. anti-MAG significant negative correlations with serum 25(OH) D
Adams et al 2011[91]	USA	Case-control	99 (ASD 55 / control 44)	ASD:10±3.1 y Controls:11±3.1 y	ASD:49/6 Controls:39/5	ASD: 29.90 ± 8.40 Control: 28.60 ± 8.40	LC-MS/MS		[18,55,58]	Significant associations were found between biomarkers and all three autism severity scales, including vitamins, minerals, and plasma amino acids.

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Table 7 Detailed Information of Literatures Included in Systematic Reviews (Cohort Studies)

Study	Country	Study Design	Sample size	Age	Sex (M/F)	Autism criteria	Included Literature	Key Findings
Ali et al (2019)[92]	Australia	Cohort study	ASD:26 Controls:2500	–	–	ADOS/DSM-IV/ DSM-5	[18]	
Vinkhuyzen et al (2017)[93]	Australia	Cohort study	ASD:46 Controls:2870	–	–	A specialised multidisciplinary team	[18]	
Wu et al (2017)[94]	China	Cohort study	ASD:310 Controls:1240	ASD:11.3 Controls:8.1	ASD:240/70 Controls:960/280	DSM-V, ADI-R	[18]	Neonatal vitamin D status was significantly associated with the risk of ASDs and ID. The nature of those relationships was nonlinear.

hippocampal development and cognition, as evidenced by the significant influence of the vitamin D receptor (VDR) and 1-alpha hydroxylase in the hippocampus.[108]

Experimental models have demonstrated that vitamin D deficiency during gestation may result in pronounced brain structural abnormalities and altered neurodevelopmental markers postnatally,[109] potentially impairing memory and cognitive function in children.[110–113] Consequently, low vitamin D levels during pregnancy have been linked with an increased risk of ASD,[93] corroborated by the findings of multiple meta-analyses. Additional research underscores a positive association between maternal hypovitaminosis D and reduced head circumference in neonates,[114] a common characteristic in autism. Moreover, genetic variations in the VDR gene have been closely associated with ASD.[85] Study by Schmidt et al[115] highlighted a significant connection between the GC AA genotype/A allele of the VDR gene and ASD prevalence through comparative analysis between children with ASD and typically developing peers.

Immune Response

There exists a complex interplay between the immune and nervous systems, with significant implications for brain development and functionality.[116] Immune activation is increasingly recognized as a potential risk factor forASD, and vitamin D deficiency might perturb the immune responses in individuals with ASD.[117,118] There is potential for vitamin D supplementation to mitigate ASD-related behavioral disturbances stemming from such immune activation. Vitamin D3 plays a multifaceted role in immune function, including the activation and regulation of T cells, B cells, and synaptic cells;[119] it also promotes upregulation of dendritic cells and an increase in interleukin-10 levels.[120] Notably, altered T cell activity may affect the adaptive immune responses in children with ASD.[121] Elevated levels of autoimmune markers—specifically, interferon-gamma, interleukin-1 beta, interleukin-6, and interleukin-12[122,123]—have been observed in ASD patients, with studies establishing a strong positive association between these cytokine levels and ASD symptom severity.[55] Furthermore, animal models suggest that sustained vitamin D insufficiency can activate microglia and provoke an inflammatory response.[124] Corroborating these findings, clinical research indicates that vitamin D supplementation can enhance social and communicative abilities in patients with ASD and exert an anti-inflammatory effect.[125]

Oxidative Stress

Reactive oxygen species (ROS) play a pivotal role in the etiology and progression of ASD, as well as in the manifestation of its severity.[126,127] A hallmark of ASD could be oxidative stress, with heightened levels in the brain causing developmental damage and resulting in ASD-related symptoms.[128] Vitamin D is notable for its antioxidant capabilities, which include suppressing nitric oxide synthase synthesis, elevating glutathione levels—an intrinsic neuroprotectant—and attenuating neuroglial activation and subsequent neuroinflammation.[128] The antioxidant glutathione is vital for the survival of neurons in early development, and vitamin D's ability to boost intracellular glutathione is crucial for the brain's detoxification mechanisms.[129] Moreover, vitamin D influences the expression of glial cell line-derived neurotrophic factor (GDNF), essential for dopaminergic neuron viability, and a deficiency in vitamin D may disrupt dopaminergic signaling.[130] Clinical observations have revealed that lymphocytes and granulocytes in ASD patients

Table 8 Detailed Information of Literatures Included in Systematic Reviews (Cross Sectional Studies)

Study	Country	Study Design	Sample Size	Age	Sex (M/F)	Baseline 25(OH)D Levels	Autism Criteria	Included Literature	Key Findings
Chtourou et al (2019)[95]	Tunisia	Cross sectional study	83 (ASD:40 Controls:43)	ASD:4.78±0.93 y Controls:4.76±1.08 y	–	ASD:17.13±9.65 Controls:21.34±8.1	DSM-V	[18]	Vitamin D deficiency is higher in children with ASD than in healthy children. Vitamin D supplementation may be an effective strategy to reduce the risk of autism.
Arastoo A A et al 2018[14]	Iran	Cross sectional study	62 (ASD 31 / control 31)	ASD:9.17±2.11 y Controls:9.31±2.09 y	ASD:26/5 Controls:28/3	ASD: 9.03 ± 4.14 Control: 15.25 ± 7.89	DSM-IV, ADI-R	[18,58]	There was a significant difference in serum 25-hydroxyvitamin D levels between the two groups, and different studies have confirmed that there was also no significant difference in sunlight exposure time between the two groups. Therefore, vitamin D supplements are recommended for children with asd under medical care.
El-Ansary et al (2018)[96]	Saudi Arabia	Cross sectional study	55 (ASD:28 / Controls:27)	ASD:7.0±2.34 y Controls:7.2±2.14 y	ASD:28/0 Controls:27/0	ASD:95.63±26.63 Controls:140.43 ±17.68	DSM-IV-TR	[18]	Saudi children with ASD have low levels of vitamin D. There is a significant negative correlation between vitamin D deficiency and impaired cognitive development as measured on CARS, and 25(OH)D3 and hs-CRP are abnormal in ASD.
Alzghoul et al (2018)[97]	Jordan	Cross sectional study	189 (ASD:83 Controls:106)	ASD:5.08 y Controls:5.02 y	ASD:83/0 Controls:106/0	ASD:23.4 Controls:37.5	DSM-V	[18]	Among Jordanian boys, low vitamin D levels were significantly associated with ASD. In addition, the number of gastrointestinal disorders was significantly higher in children with ASD and vitamin D disorders compared to children with ASD.

(*Continued*)

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Table 8 (Continued).

Study	Country	Study Design	Sample Size	Age	Sex (M/F)	Baseline 25(OH)D Levels	Autism Criteria	Included Literature	Key Findings
Yuhan Dong 2017[98]	China	cross sectional study	388 (ASD 87 / control 301)	4.7±0.7(ASD) 4.8±0.8(control)	10/6(ASD) 13/15(control)	ASD: 21.00 ± 8.00 Control: 36.00 ± 16.00	DSM-IV	[58]	Serum vitamin D levels were significantly lower in children with ASD than in healthy children, and there was a significant correlation between this and multiple core symptoms of ASD.
Garipardic et al (2017)[99]	Turkey	Cross sectional study	43(ASD:18 / Controls:25)	8.11±5.20(ASD) 9.90±4.13(control)	ASD:11/7 Controls:12/13	ASD:14.3±7.25 Controls:29.42±9.07	DSM-IV	[18]	Both ADHD and ASD may be accompanied by an increased risk of cardiovascular disease due to vitamin B12 and D deficiencies and their own characteristics. Therefore, these diseases should be followed closely.
Fahmy et al (2016)[100]	Egypt	Cross sectional study	82 (ASD 42 / control 40)	7.1±2.3(ASD) 7.6±3.1(control)	34/8(ASD) 19/21(control)	ASD:164.7 ± 71.5 Control: 177.9 ± 75.9	DSM-IV	[18,57]	Vitamin D deficiency is present in children with autism, which may be related to the pathogenesis of the disorder. There is a need to raise awareness of the importance of vitamin D in children's diets.
Bala er al.2016[101]	Turkey	Cross sectional study	43 (ASD 16 / control 27)	7.88±5.18(ASD) 9.80±4.01(control)	75/12(ASD) 249/52 (control)	ASD: 15.11±7.47 Control: 28.73±9.04	DSM-IV	[57]	The importance of vitamin B12 and D supplementation in patients with ASD and ADHD.

express mitochondrial H2O2 at significantly higher levels than those in healthy children,[131] suggesting increased vulnerability to oxidative stress in the brains of individuals with ASD.[132]

The Javadfar et al study[44] will statistically analyze the levels of serum IL-6 and vitamin D supplementation, but the study shows that supplementation with vitamin D did not result in a statistically significant decrease in the serum IL-6 levels of children with ASD. IL-6 is an important indicator of chronic inflammation and an independent predictor of ASD risk. The anti-inflammatory effects of vitamin D may include reducing active oxygen (ROS) levels by increasing cell glutathione, lowering ROS, monocyte chemotactic protein-1, and IL-8 secretion.

Serotonin

Serotonin (5-HT), synthesized from tryptophan via hydroxylation by tryptophan hydroxylase (TPH) and subsequent decarboxylation, is a critical neurotransmitter that emerges early in embryonic development and significantly shapes brain structure and neurotransmitter system development, including that of dopamine. The release of 5-HT and its receptors at synapses mediates numerous physiological functions and modulates neural transmission.[133]

Vitamin D upregulates the expression of enzymes such as tyrosine hydroxylase (TH)—involved in dopamine synthesis—and tryptophan hydroxylase 2 (TPH2), thereby enhancing 5-HTP production in the brain. Serotonin's function extends to the regulation of emotions and social decision-making processes. Additionally, vitamin D suppresses the transcription of TPH1 in peripheral tissues, which may result in elevated central and reduced peripheral serotonin levels. Serotonin is a recognized biomarker of ASD, characterized by lower cerebral levels and elevated peripheral concentrations in affected individuals,[134,135] with potential correlations to clinical severity in children with ASD.[136] Most of the body's serotonin is produced in the enterochromaffin cells of the intestines, while a small fraction is neuronally synthesized within the gut. Studies have identified dysregulation of the serotonergic system in ASD patients,[137,138] with markedly lower cerebral serotonin levels compared to the general population.[139] Animal studies have revealed that diminished serotonin during critical periods of brain development can lead to structural anomalies,[140] such as reduced synaptic density, whereas high perinatal serotonin consumption can precipitate ASD-like behaviors.[141] This evidence indicates that abnormal serotonin levels may disrupt normal brain development and are intimately linked to the pathogenesis of ASD.

Studies have speculated that adequate vitamin D may be necessary for the activation of the serotonin-synthesizing gene tryptophan hydroxylase 2 (TPH2). Vitamin D-mediated serotonin production is essential for generating serotonergic signaling during neurodevelopment, which shapes the developing brain, and throughout adulthood, it plays a key role in regulating multiple brain functions, including social behavior. In addition, adequate vitamin D hormone levels inhibit the expression of tryptophan hydroxylase 1 (TPH1), which is important for reducing gastrointestinal inflammation, increasing bone density, and maintaining autoimmunity.

Conclusion

This study analyzes a spectrum of research, the aggregated data suggest that vitamin D deficiency during early life may contribute to the risk of developing ASD, while experimental findings reveal that vitamin D supplementation might improve core ASD symptoms. Further research should explore whether high-dose vitamin D supplementation in early pregnancy could serve as a preventative measure against ASD.In essence, this investigation represents a foundational comprehensive review of vitamin D supplementation's efficacy in individuals with ASD. Focusing on the fact that we comprehensively reviewed and systematically collated the included studies for systematic evaluation, the collated results support the conclusions of this study. We also found a definite recommendation regarding the amount of vitamin D supplementation for children with ASD, but we also suggest the feasibility of taking into account informed consent, potential risks associated with supplementation, and individualized therapeutic approaches in RCT studies, given the limitations of RCT studies, focusing on the characteristics of different morbidity populations and geographic regions.The meta-analysis supports the notion that vitamin D supplementation can be beneficial in ASD management and that a deficiency in early life could augment the risk of ASD. These findings support the proactive initiation of vitamin D supplementation as a potential preventative intervention for ASD. At the same time, we should also realize that vitamin D supplementation is only one part of the therapeutic management of children with ASD, and that more research is needed to

explore all aspects of life that can help children with ASD. We come from the front lines of clinical practice, and we look forward to more ways to help children with ASD.

Study Limitations

While the reviewed studies converge on the theme of vitamin D supplementation in ASD, they diverge in aspects such as additional treatments, dosage levels, and treatment durations, complicating the consistency of the findings. Additionally, the long-term effects of vitamin D therapy on ASD are yet to be determined, Clinical trials are needed to validate the findings. Moreover, the umbrella evaluation approach used in this study was characterized by heterogeneity in study design, potential sources of bias, and generalization of findings to different populations. Although we have made efforts to search for the original literature in order to explore more studies to avoid heterogeneity, we found that the original literature included different types of studies, which on the one hand, broadened the richness of the study, and at the same time, allowed us to learn that The original paper first itself does have more heterogeneity.

Data Sharing Statement

The datasets supporting the conclusions of this article are included within the article.

Ethics Approval and Consent to Participate

Institutional Review Board Statement: Ethical review and approval were not required for this systematic review.

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Thank you for the countless nights spent trying to learn to fight for yourself. And we can plough deeper into the field of autism, we hope we can help more autistic children with our little efforts.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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