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Original Article

Vitamin D +Docosahexaenoic acid supplementation: effects on serum markers and symptoms in ADHD children

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Abstract: Objective: To investigate the effect of vitamin D combined with Docosahexaenoic acid (DHA) supplementation on serum indicators, clinical symptoms and disease severity in children with attention deficit hyperactivity disorder (ADHD), and identify independent risk factors for treatment efficacy. Methods: A retrospective analysis was performed on 367 children with ADHD admitted from August 2020 to August 2024, divided into control group (routine behavioral education + atomoxetine hydrochloride, n=180) and nutritional intervention (NI) group (additional vitamin D + DHA, n=187). The sample was split into training set (n=256) and validation set (n=111) at a 7:3 ratio, with relevant indicators analyzed via logistic regression, nomogram and ROC curve. Results: After 3 months of treatment, the NI group had significantly lower ADHD Rating Scale IV (ADHD-RS-IV) and Clinical Global Impression Scale-Severity (CGI-S) scores, higher serum 25-hydroxyvitamin D [25(OH)D] and ferritin (SF) levels, higher total effective rate (94.49% vs 82.95%, P=0.004), and lower adverse reaction rate (4.72% vs 13.18%, P=0.018) than the control group (all P<0.05). Baseline ADHD-RS-IV≥26.5 points, CGI-S≥4.5 points, 25(OH)D<14.26 ng/mL and SF<19.61 ng/mL were independent risk factors for poor efficacy; their combined detection had an Area Under the Curve (AUC) of 0.901 in the validation set. Conclusion: Vitamin D combined with DHA can improve clinical symptoms, serum nutritional indicators, efficacy and safety of ADHD children. The 4 indicators are key factors affecting efficacy, and their combined detection has more accurate diagnostic efficiency.

Keywords: Vitamin D, docosahexaenoic acid, attention deficit hyperactivity disorder, 25-hydroxyvitamin D, serum ferritin

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders in school-aged children [1, 2]. Characterized by persistent inattention, hyperactivity, and impulsive behaviors, the disorder exerts long-term detrimental effects on children's academic performance, neurodevelopment, social function, and overall family quality of life [3, 4]. First-line clinical management for ADHD predominantly consists of behavioral intervention combined with pharmacotherapy, among which atomoxetine hydrochloride is widely used in clinical practice for its ability to ameliorate abnormal behavioral symptoms in children to a certain extent [5]. However, this agent is limited by unsatisfactory long-term therapeutic efficacy and a high incidence of adverse events [6]. Therefore, there is an urgent need to explore safe and effective adjuvant therapeutic strategies to optimize clinical outcomes in children with ADHD, beyond conventional pharmacotherapy and behavioral intervention.

In recent years, nutritional intervention has gained increasing recognition for its role in children's physical and mental health, and has been widely applied in the management of various mental and neurodevelopmental disorders [7]. This intervention modality not only alleviates clinical symptoms in affected children, but also enhances the efficacy of conventional

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pharmacotherapy by replenishing nutrients deficient in children's daily diet [8]. Previous evidence has indicated that children with ADHD commonly have a high-sugar, high-fat dietary pattern, accompanied by insufficient intake of multiple nutrients, including vitamin D and docosahexaenoic acid (DHA) [9]. Vitamin D exerts pleiotropic effects beyond its classic role in calcium metabolism, bone development, and hormone synthesis; it modulates central nervous system function by regulating neuronal differentiation, suppressing inflammatory responses, and optimizing neurotransmitter release [10]. As a core structural component of the cerebral cortex and retinal photoreceptor membranes, DHA not only facilitates synaptogenesis and regulates dopaminergic system function, but also exerts well-documented anti-inflammatory and antioxidant effects [11]. While existing studies have preliminarily verified the symptomatic improvement of single supplementation with either vitamin D or DHA in children with ADHD, most have focused solely on the intervention effect of a single nutrient, and large-scale clinical studies investigating the adjuvant efficacy of vitamin D combined with DHA in ADHD remain scarce. Furthermore, existing research has mostly focused on symptomatic improvement measured by rating scales, with few studies linking these changes to alterations in serum nutritional biomarkers such as ferritin, making it difficult to elucidate the underlying mechanisms of the intervention. In addition, no studies have systematically screened the independent risk factors affecting the efficacy of nutritional intervention for ADHD, which hinders the development of precise and individualized intervention strategies in clinical practice.

This retrospective study was conducted based on a large sample of school-aged children with ADHD. We compared the clinical efficacy and safety of conventional treatment versus conventional treatment combined with vitamin D and DHA supplementation, comprehensively evaluated the clinical value of the combined intervention by integrating symptomatic rating scales and serum biological markers, and constructed and validated an individualized prediction model for the therapeutic effect of nutritional intervention in ADHD. This study aims to provide clinical evidence for the development of personalized intervention strategies for children with ADHD.

Materials and methods

Patients' selection

A total of 452 children diagnosed with attention deficit hyperactivity disorder (ADHD) at Baoji Maternal and Child Health Hospital from August 2020 to August 2024 were retrospectively enrolled in this study. Inclusion criteria: A confirmed diagnosis of ADHD by specialists from the Department of Child Psychology/Child Health Care of our hospital; aged 8 to 12 years, regardless of gender; no prior history of standard pharmacotherapy, systematic behavioral intervention, or nutritional supplementation with vitamin D, DHA, iron supplements and other relevant agents for ADHD, to exclude confounding effects of previous interventions on study outcomes; completion of the full 3-month treatment course and the entire scheduled follow-up period; complete and intact clinical medical records; no concomitant use of other drugs or dietary supplements that might interfere with the study results during treatment. Exclusion criteria: Comorbidity with other severe mental disorders, organic neurological diseases, or serious somatic illnesses; a diagnosis of intellectual developmental disorder or global developmental delay; contraindications to the study medications or a documented history of hypersensitivity to the agents used in this study; administration of relevant nutritional supplements, glucocorticoids, immunosuppressants or other potentially interfering drugs within 3 months prior to enrollment; severe deficiency of clinical medical records; failure to complete the full 3-month treatment course or the entire follow-up period.

The flow of participant screening and enrollment is illustrated in **Figure 1**. A total of 367 eligible children were finally included in the study, who were then randomly assigned to a training set and a validation set at a ratio of 7:3. The training set comprised 256 cases, including 127 cases in the nutrition intervention (NI) group and 129 cases in the control group; the validation set included 111 cases, with 61 cases in the NI group and 50 cases in the control group. Baseline data of the study cohorts were well balanced after grouping, ensuring no statistically significant differences in demographic characteristics and clinical baseline indicators between the training set and the validation set ($P>0.05$). This study was approved

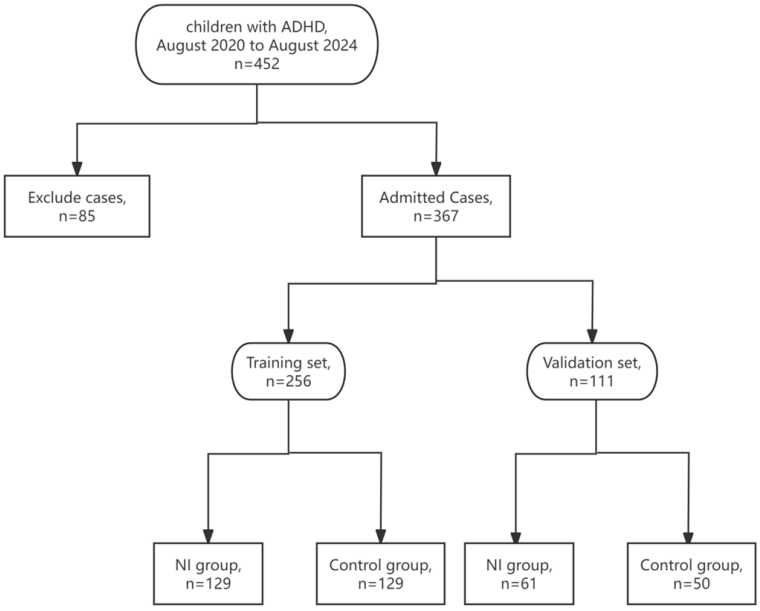

Figure 1. Flow diagram.

by the Medical Ethics Committee of Baoji Maternal and Child Health Hospital, and the entire research was conducted in strict accordance with the ethical principles of the Declaration of Helsinki. Given that this study only involved retrospective review of the children's existing clinical medical records, with no interference in clinical diagnosis and treatment practices nor any alterations to the children's established treatment regimens, a waiver of informed consent was granted by the ethics committee.

Data extraction

All clinical treatment regimens for the enrolled children in this study were formulated by associate chief physicians or above from the Department of Child Psychology and Child Health Care of our hospital, who had at least 5 years of specialized clinical experience in the management of attention deficit hyperactivity disorder (ADHD). Prior to the initiation of clinical treatment, the attending specialists had fully informed the children's legal guardians in detail of the clinical characteristics of ADHD, as well as the rationale, expected therapeutic effects, treatment course and potential adverse reactions of each available treatment regimen.

The control group received routine behavioral education and oral administration of Atomoxetine Hydrochloride Capsules (Jiangsu Zhengda Fenghai Pharmaceutical Co., Ltd., H20133346, 10 mg/capsule) at an initial dose of 0.5 mg/(kg.d). The dosage was adjusted according to the children's tolerance one week after medication, with the maximum dose not exceeding 1.2 mg/(kg.d). On the basis of the same routine behavioral education combined with atomoxetine hydrochloride treatment as the control group, the nutritional intervention group was additionally supplemented with vitamin D3 capsules (Qingdao Shuangjing Pharmaceutical Co., Ltd., H20113033, 400 IU/capsule, 2 capsules per day, total dose 800 IU) and DHA algal oil capsules (By-Health Co., Ltd., G2014-0213, 100 mg/capsule, 4 capsules per day, total dose 400 mg) daily for a continuous intervention of 3 months. Outcome assessor blinding was adopted in this study, where the assessors were blinded to the children's group allocation to reduce information bias during research data collection. All follow-up work for the children was conducted by professionally trained medical staff.

Outcome measures

Primary indicators: (1) Total effective rate: The total and markedly effective rates of the two groups were evaluated at 3 months post-treatment, based on changes in clinical symptoms and ADHD-RS-IV scores. The efficacy criteria were defined as follows: Markedly effective: nearly complete resolution of hyperactivity and inattention symptoms, with a ≥50% reduction in ADHD-RS-IV scores; Effective: a notable improvement in hyperactivity and inattention symptoms, with a 30% to 50% reduction in ADHD-RS-IV scores; Ineffective: no obvious improvement or even exacerbation of hyperactivity and inattention symptoms, with a <30% reduction in ADHD-RS-IV scores. The markedly effective rate was also calculated for both groups. Based on the above efficacy criteria, the children were categorized into a marked recovery group and a poor recovery group. The calculation formulas were as follows: Total

effective rate = (Number of markedly effective cases + Number of effective cases)/Total number of cases × 100%. Markedly effective rate = Number of markedly effective cases/Total number of cases × 100%.

(2) Adverse reactions: Adverse events were closely monitored and fully recorded for all children in both groups throughout the entire 3-month intervention period.

Secondary indicators: (1) ADHD Rating Scale IV (ADHD-RS-IV, Parent Version): ADHD-RS-IV scores were collected for all children before treatment and at 3 months post-treatment. The scale consists of 18 symptom items rated on a 4-point scale (1 to 4), completed by the children's parents or legal guardians based on the child's behavioral performance over the preceding 6 months. Higher scores indicated more severe ADHD clinical symptoms [12].

(2) Clinical Global Impression Scale-Severity (CGI-S) Score: CGI-S scores were collected for both groups before treatment and at 3 months post-treatment. This scale assesses the severity of children's clinical symptoms on a scale of 0 to 7, with scores ranging from 0 (no symptoms) to 7 (extremely severe symptoms). Higher scores represented greater disease severity [13].

(3) Serum Biomarkers: Venous blood samples were collected from all children in both groups before treatment and at 3 months post-treatment to measure serum levels of 25-hydroxyvitamin D [25(OH)D] and serum ferritin (SF). Quantitative determination of these two biomarkers was performed via the immunoturbidimetric method.

Statistical analysis

All data were analyzed using the SPSS 20.0 statistical software (IBM Corp., Armonk, NY, USA). Quantitative data were expressed as ($\overline{x}$±sd) and compared using the independent-samples t-test. Categorical data were presented as n (%) and analyzed by χ^2 tests. A multivariate logistic regression model was constructed to identify independent factors affecting the treatment efficacy of children with ADHD. A nomogram model was further developed to evaluate its predictive value for treatment efficacy, and receiver operating characteristic (ROC) curves were plotted to verify the diagnostic performance of the model and related indicators. A two-tailed *P* value <0.05 was considered statistically significant.

Results

Baseline data of training set and validation set

No significant differences were observed in general demographic and clinical characteristics between the training set and the validation set (all P>0.05, **Table 1**).

Baseline data

The NI group and the control group exhibited no statistically significant differences in all baseline general characteristics (all P>0.05, **Table 2**).

ADHD-RS-IV scores and CGI-S scores

Prior to treatment, there were no significant differences in ADHD-RS-IV (**Figure 2A**) or CGI-S scores (**Figure 2B**) between the NI group and the control group (all P>0.05). After 3 months of intervention, both scores were significantly reduced in both groups; notably, the NI group had significantly lower ADHD-RS-IV and CGI-S scores than the control group (all P>0.05).

Serum factors

Serum 25(OH)D (**Figure 3A**) and SF (**Figure 3B**) levels showed no significant between-group differences before treatment (all P>0.05). Following 3 months of treatment, 25(OH)D and SF levels were elevated in both groups, and the NI group had a more prominent increase in these two biomarkers compared with the control group (all P>0.05).

Treatment outcomes

At 3 months post-treatment, the total effective rate of the NI group was 94.49% (120/127), which was significantly higher than that of the control group (87.78%, 158/180) (P<0.05, **Table 3**).

Incidence of adverse reactions

During the 3-month treatment course, the incidence of adverse reactions in the NI group was 3.33% (6/187), significantly lower than that in

Table 1. Baseline data of the training set and the validation set [n (%), $\bar{x}\pm sd$]

	Training set (n=256)	Validation set (n=111)	t/χ^2	*P*
Age (yr)	8.55±0.54	8.50±0.57	0.801	0.424
Gender			0.263	0.608
Male	132 (51.56)	54 (48.65)		
Female	124 (48.44)	57 (51.35)		
Course of the disease (yr)	2.50±0.51	2.45±0.53	0.852	0.395
IQ	118.56±6.29	118.05±6.78	0.697	0.487
BMI (kg/m^2)	22.50±1.03	22.41±1.10	0.753	0.452
Maternal education level			0.574	0.751
High school degree	28 (10.94)	10 (9.01)		
College degree	140 (54.69)	59 (53.15)		
Bachelor degree or above	88 (34.38)	42 (37.84)		
Paternal education level			0.582	0.811
High school degree	34 (13.28)	12 (13.95)		
College degree	144 (56.25)	62 (57.36)		
Bachelor degree or above	78 (30.47)	37 (28.68)		

PS: NI: nutritional intervention; IQ: Intelligence Quotient; BMI: Body Mass Index; yr: year.

Table 2. Baseline data of the two groups [n (%), $\bar{x}\pm sd$]

	NI Group (n=127)	Control group (n=129)	t/χ^2	*P*
Age (yr)	8.55±0.53	8.56±0.56	0.147	0.884
Gender			0.386	0.514
Male	63 (49.61)	69 (53.49)		
Female	64 (50.39)	60 (46.51)		
Course of the disease (yr)	2.49±0.52	2.51±0.50	0.314	0.754
IQ	118.80±6.16	118.32±6.42	0.610	0.542
BMI (kg/m^2)	22.53±1.01	22.46±1.06	0.541	0.589
Maternal education level			0.423	0.809
High school degree	14 (11.02)	14 (10.85)		
College degree	67 (52.76)	73 (73/129)		
Bachelor degree or above	46 (36.22)	42 (32.56)		
Paternal education level			0.418	0.811
High school degree	16 (12.61)	18 (13.95)		
College degree	70 (55.12)	74 (57.36)		
Bachelor degree or above	41 (32.28)	37 (28.68)		

PS: NI: nutritional intervention; IQ: Intelligence Quotient; BMI: Body Mass Index; yr: year.

the control group (12.09%, 17/180) (P<0.05, **Table 4**).

Univariate analysis

No significant differences were found between the poor recovery group and the significant recovery group in terms of age, gender, disease duration, IQ, BMI, maternal education level, and paternal education level (all P>0.05). In contrast, the poor recovery group had significantly higher baseline ADHD-RS-IV and CGI-S scores, as well as significantly lower serum 25(OH)D and SF levels, compared with the significant recovery group (all P<0.05, **Table 5**).

Multivariate analysis

Variables with significant differences identified in the univariate analysis were selected for further multivariate analysis and assigned binary values based on the optimal cut-off values of ADHD-RS-IV, CGI-S, 25(OH)D, and SF (**Table 6**). Multivariate logistic regression analysis revealed that baseline ADHD-RS-IV ≥26.5 points, CGI-S ≥4.5 points, serum 25(OH)D <14.26 ng/mL, and SF <19.61 ng/mL were independent risk factors for poor treatment efficacy in children with ADHD (**Table 7**).

Construction of the nomogram model and evaluation of diagnostic performance

Nomogram analysis showed that serum 25(OH)D was a strongly correlated indicator, contributing most significantly to the prediction of poor treatment efficacy; SF was the second most significant indicator, while ADHD-RS-IV and CGI-S scores had relatively weak contributions to the risk prediction (**Figure 4A**). The calibration curve demonstrated good predictive performance of the constructed nomogram model (χ^2=5.872, P=0.663, **Figure 4B**).

ROC curve

ROC curve analysis of the training set revealed that ADHD-RS-IV [Area Under the Curve (AUC):

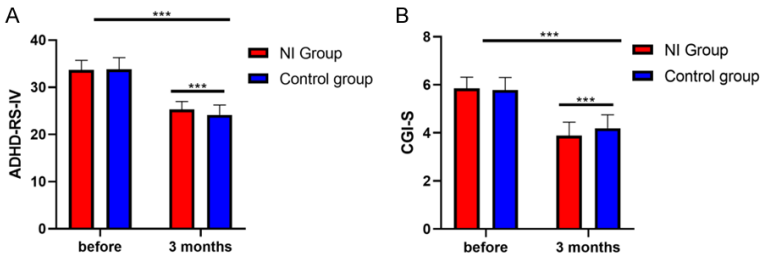

Figure 2. ADHD-RS-IV scores and CGI-S scores: (A) ADHD-RS-IV scores before and after treatment in both groups of children; (B) CGI-S scores before and after treatment in both groups of children. PS: ***: P<0.001. NI: nutritional intervention; ADHD: attention deficit hyperactivity disorder; ADHD-RS-IV: ADHD Rating Scale IV; CGI-SI: Clinical Global Impression Scale-Severity; 25(OH)D: 25-hydroxyvitamin D; SF: serum ferritin.

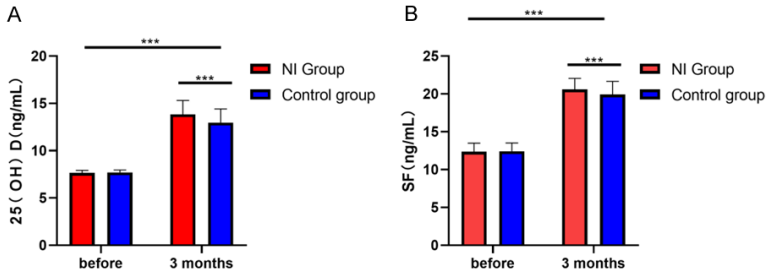

Figure 3. Serum factors: (A) 25(OH)D levels before and after treatment in both groups of pediatric patients; (B) SF levels before and after treatment in both groups of pediatric patients. PS: ***: P<0.001. 25(OH)D: 25-hydroxyvitamin D; SF: serum ferritin.

0.610, 95% CI: 0.538-0.681], CGI-S (AUC: 0.621, 95% CI: 0.552-0.690), serum 25(OH)D (AUC: 0.682, 95% CI: 0.617-0.746), and SF (AUC: 0.729, 95% CI: 0.667-0.790) all exhibited acceptable diagnostic efficacy for predicting treatment outcomes. The combined assessment of the four indicators had significantly better diagnostic efficacy (AUC: 0.895, 95% CI: 0.824-0.966) than any single indicator (**Figure 5A**). ROC curve analysis of the validation set yielded consistent results: ADHD-RS-IV (AUC: 0.776, 95% CI: 0.689-0.864), CGI-S (AUC: 0.624, 95% CI: 0.519-0.729), serum 25(OH)D (AUC: 0.703, 95% CI: 0.608-0.799), and SF (AUC: 0.837, 95% CI: 0.668-0.853) all had favorable diagnostic value, and the combined detection of the four indicators still showed the best diagnostic efficacy (AUC: 0.901, 95% CI: 0.844-0.959) (**Figure 5B**).

Discussion

ADHD exerts a profound impact on children's learning processes, social interactions, and even compromises their quality of life [14, 15]. Currently, clinical management primarily relies on pharmacotherapy combined with behavioral modification; however, this approach exhibits considerable inter-individual variability in efficacy and is prone to inducing multiple adverse reactions [16]. Thus, the development of safe, effective, and comprehensive intervention strategies has emerged as a key focus in clinical research within this field.

The results of this study demonstrated that the addition of vitamin D and DHA to conventional treatment significantly reduced children's ADHD-RS-IV and CGI-S scores, while effectively improving both the total effective rate and markedly effective rate. This finding is consistent with the observations reported by Hunter et al. [17] and Patrick et al. [18]. The underlying mechanisms may be as follows: The active form of vitamin D is 25(OH)D, which can penetrate the central nervous system, bind to specific receptors in regions such as the hippocampus and prefrontal cortex, regulate neuronal cell proliferation and differentiation, and enhance neurotransmitter release efficiency, thereby alleviating inattention and related impairments in children [19, 20]. As a critical structural component of the cerebral cortex and synaptic membranes, DHA can increase dopamine concentrations in the prefrontal cortex by enhancing synaptic transmission efficiency and dopamine transporter activity, thereby mitigating hyperactive and impulsive behaviors in children [21]. Furthermore, vitamin D can suppress inflammatory responses by modulating the NF-κB signaling pathway, whereas DHA can be converted into anti-inflammatory mediators to attenuate central nervous system inflammation. The synergistic effect of these two nutrients compensates for the limitations of conventional drug monotherapy in terms of neuroprotection and collectively optimizes the neural microenviron-

Table 3. Total effective rate in the two groups of pediatric patients [n (%)]

Groups	n	Significantly effective	Effective	Ineffective	Total effective rate	Significantly effective rate
NI Group	127	80 (62.99)	40 (31.50)	7 (5.51)	120 (94.49)	80 (62.99)
Control group	129	62 (48.06)	45 (34.88)	22 (17.05)	107 (82.95)	62 (48.06)
χ^2					8.488	5.775
P					0.004	0.016

PS: NI: nutritional intervention.

Table 4. Incidence of adverse reactions in both groups of children [n (%)]

Groups	n	Nausea and Vomiting	Headache	Drowsiness	Loss of Appetite	Incidence of Adverse Reactions
NI Group	127	1 (0.78)	3 (2.36)	1 (0.78)	1 (0.78)	6 (4.72)
Control group	129	2 (1.55)	8 (6.20)	5 (3.876%)	2 (1.55)	17 (13.18)
t						5.593
P						0.018

PS: NI: nutritional intervention.

Table 5. Univariate analysis of factors affecting treatment outcomes in children with ADHD [n (%), $\bar{x}\pm$sd]

	Poor Recovery Group (n=114)	Significant Recovery Group (n=142)	t/χ^2	*P*
Age (yr)	8.57±0.53	8.54±0.56	0.436	0.663
Gender			1.958	0.051
Male	51 (55.17)	81 (50.30)		
Female	63 (44.83)	61 (49.70)		
Course of the disease (yr)	2.50±0.52	2.49±0.50	0.156	0.876
IQ	118.51±6.03	118.60±6.51	0.114	0.910
BMI (kg/m^2)	22.49±0.97	22.50±1.08	0.077	0.939
Maternal education level			0.835	0.659
High school degree	10 (13.79)	18 (10.06)		
College degree	61 (51.72)	79 (54.44)		
Bachelor degree or above	43 (34.48)	45 (35.50)		
Paternal education level			2.018	0.365
High school degree	14 (20.69)	20 (11.83)		
College degree	62 (48.28)	82 (56.80)		
Bachelor degree or above	38 (31.03)	40 (31.36)		
ADHD-RS-IV	25.14±2.17	24.40±1.73	3.036	0.003
CGI-S	4.20±0.59	3.90±0.52	4.320	<0.001
25(OH)D (ng/mL)	12.85±1.27	13.84±1.58	5.428	<0.001
SF (ng/mL)	19.59±1.40	20.81±1.60	6.407	<0.001

PS: NI: nutritional intervention; IQ: Intelligence Quotient; BMI: Body Mass Index; yr: year; ADHD: attention deficit hyperactivity disorder; ADHD-RS-IV: ADHD Rating Scale IV; CGI-SI: Clinical Global Impression Scale-Severity; 25(OH)D: 25-hydroxyvitamin D; SF: serum ferritin.

ment in children [22]. Notably, we additionally analyzed the markedly effective rate because, while the total effective rate reflects the overall scope of benefit from the intervention, it fails to distinguish the "depth of therapeutic response". Specifically, a designation of "effective" indicates only partial symptom improvement, whereas "markedly effective" corresponds to the

Table 6. Assignment of influence factors

Influencing Factors	Assignment
ADHD-RS-IV	0: <26.5
	1: ≥26.5
CGI-S	0: <4.5
	1: ≥4.5
25(OH)D	0: ≥14.26 ng/mL
	1: <14.26 ng/mL
SF	0: ≥19.61 ng/mL
	1: <19.61 ng/mL

PS: ADHD: attention deficit hyperactivity disorder; ADHD-RS-IV: ADHD Rating Scale IV; CGI-SI: Clinical Global Impression Scale-Severity; 25(OH)D: 25-hydroxyvitamin D; SF: serum ferritin.

near-resolution of core symptoms and a ≥50% reduction in ADHD-RS-IV scores. This latter outcome represents a "high-quality therapeutic response" that aligns more closely with optimal clinical outcomes. This analysis allows for a direct assessment of whether vitamin D combined with DHA supplementation offers greater advantages over conventional monotherapy in terms of rapidly alleviating severe symptoms and facilitating in-depth functional recovery in children, thereby preventing the total effective rate from obscuring the unique value of the intervention in achieving robust therapeutic improvements.

Among the serum biomarkers associated with ADHD, 25(OH)D not only regulates neuronal proliferation, differentiation, and neurotransmitter release but also upregulates neurotrophic factor expression by activating the vitamin D receptor signaling pathway, thereby promoting neurodevelopment and enhancing neural function in children with ADHD [23, 24]. As a key coenzyme for tyrosine hydroxylase, reduced serum ferritin (SF) levels are prone to decreasing dopamine synthesis and exacerbating neurological dysfunction [25]. Serum biomarker analysis in this study demonstrated that combined vitamin D and DHA supplementation effectively increased children's serum 25(OH)D and SF levels, consistent with the findings reported by Brennan et al. [26] and Vuholm et al. [27]. This suggests that conventional treatment combined with nutritional supplements can improve children's nutritional status by modulating relevant serum biomarker levels, thereby facilitating neurological function recovery. The study also found that the intervention group had a lower incidence of adverse reactions, with most being mild symptoms such as nausea and headache, indicating that adjuvant nutritional intervention alongside conventional treatment can further enhance treatment safety. Vitamin D and DHA may alleviate gastrointestinal reactions, intestinal mucosal inflammation, and other side effects induced by atomoxetine via modulating the body's metabolic status: DHA's anti-inflammatory properties mitigate intestinal mucosal injury, while vitamin D enhances intestinal barrier function by regulating gut microbiota balance. The synergy between these two nutrients not only improves treatment adherence in children but also supports the feasibility of long-term intervention [28].

Multivariate logistic regression analysis identified high baseline ADHD-RS-IV and CGI-S scores, as well as low serum 25(OH)D and SF levels, as independent risk factors for ADHD treatment failure. The underlying reasons are as follows: ADHD-RS-IV and CGI-S scores are closely associated with disease progression and symptom severity in children with ADHD; higher scores indicate disease exacerbation and worsening symptoms [29]; lower serum 25(OH)D and SF levels reflect underlying neurological dysfunction and neurodevelopmental abnormalities [30, 31]. ROC curve analysis of the training set revealed that each of these four risk factors exhibited acceptable diagnostic efficacy, with combined detection demonstrating significantly superior performance compared to individual indicators. Results from the validation set were consistent with those of the training set, indicating that the model's predictive value for ADHD symptom exacerbation in children closely aligns with actual outcomes, reflecting excellent predictive accuracy. Based on these findings, clinicians can assess treatment-related risks in children by measuring ADHD-RS-IV and CGI-S scores alongside relevant serum biomarkers, and subsequently adjust intervention strategies, for example, by moderately increasing nutritional supplement doses in high-risk children or extending the intervention duration.

There are several limitations to this study: First, it is a single-center retrospective study, which is inherently prone to selection bias. Additionally, the optimal supplemental doses of vitamin D

Table 7. Multivariate logistic regression analysis of factors influencing treatment outcomes in children with ADHD

Factors	β	StdError	Wald x^2	P	OR	95% CI	
						Lower	Upper
ADHD-RS-IVS≥26.5	1.046	.430	5.911	0.015	2.846	1.225	6.614
CGI-S≥4.5	1.139	.437	6.795	0.009	3.125	1.327	7.360
25(OH)D<14.26 ng/mL	1.847	0.375	24.225	<0.001	6.343	3.040	13.237
SF<19.61 ng/mL	1.381	0.332	17.282	<0.001	3.978	2.075	7.629

PS: ADHD: attention deficit hyperactivity disorder; ADHD-RS-IV: ADHD Rating Scale IV; CGI-SI: Clinical Global Impression Scale-Severity; 25(OH)D: 25-hydroxyvitamin D; SF: serum ferritin.

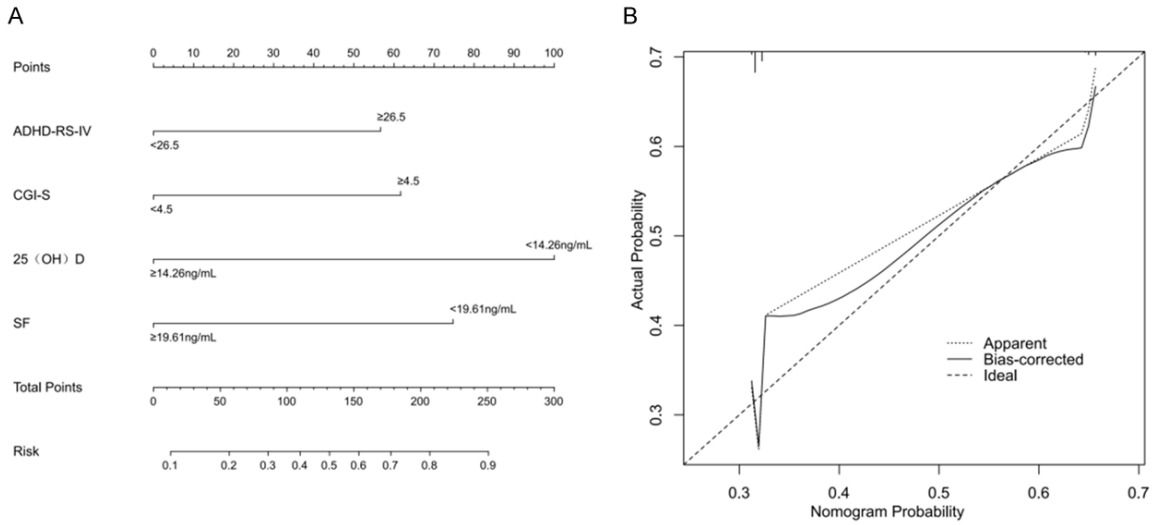

Figure 4. Construction and diagnostic performance evaluation of the Nomogram model: (A) Nomogram for Predicting Risk Factors for Treatment Outcomes in Pediatric Patients; (B) Calibration Curve for Validating the Nomogram. PS: ADHD-RS-IV: ADHD Rating Scale IV; CGI-SI: Clinical Global Impression Scale-Severity; 25(OH)D: 25-hydroxyvitamin D; SF: serum ferritin.

and DHA, as well as the optimal intervention duration, remain unaddressed. Second, the follow-up period was limited to 3 months, so the impact of the intervention on children's long-term cognitive function and social competence was not assessed. Future studies should therefore conduct prospective randomized controlled trials to investigate the efficacy of different doses of vitamin D and DHA, and simultaneously extend the follow-up duration to systematically evaluate the effects of combined supplementation on children's long-term growth and mental health, thereby providing more robust evidence for the precise management of ADHD.

In conclusion, combined vitamin D and DHA supplementation synergistically alleviates clinical symptoms, enhances serum nutritional biomarker levels, improves treatment outcomes, and reduces the incidence of adverse events in children with ADHD. ADHD-RS-IV scores, CGI-SI scores, serum 25-hydroxyvitamin D [25(OH)D], and serum ferritin (SF) levels are key factors influencing treatment efficacy. Clinicians can assess ADHD-RS-IV scores, CGI-S scores, and relevant serum biomarkers to develop personalized intervention strategies.

Disclosure of conflict of interest

None.

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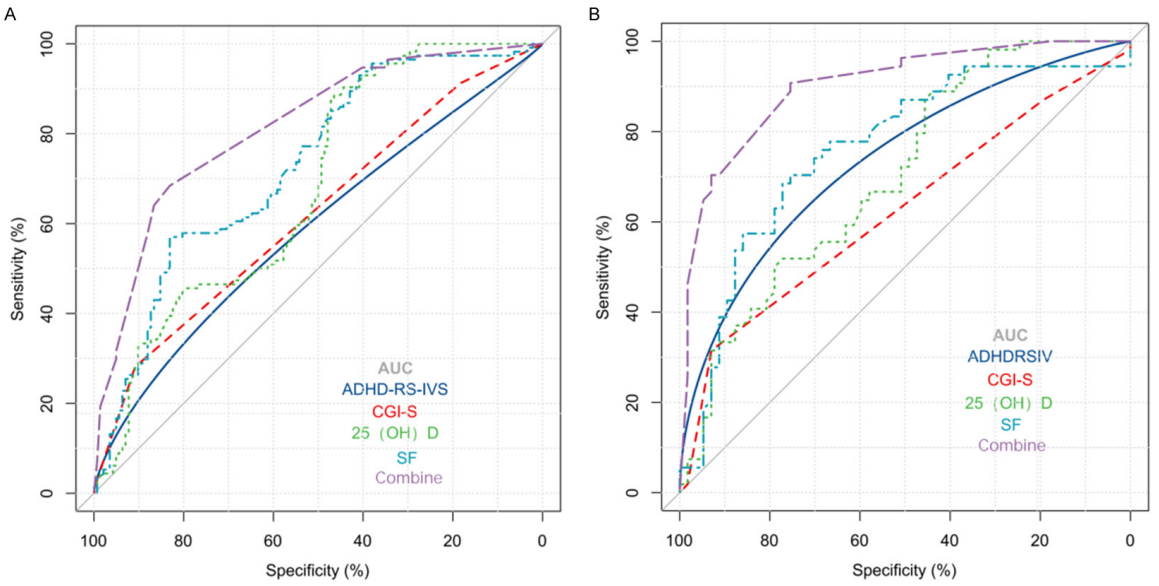

Figure 5. ROC curves predicting treatment outcomes for various risk factors: (A) Training set; (B) Validation set. PS: ROC: receiver operating characteristic; AUC: area under the curve; ADHD-RS-IV: ADHD Rating Scale IV; CGI-SI: Clinical Global Impression Scale-Severity; 25(OH)D: 25-hydroxyvitamin D; SF: serum ferritin.

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