Review Article

Role of Vitamin B12 in Mental Health Outcomes of Children and Adolescents: A Systematic Review

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Abstract

Objective: To investigate the role of Vitamin B12 in mental health outcomes among children and adolescents.
Methodology: From January-April, 2023, following PRISMA guidelines, a comprehensive search strategy was employed across databases, including PubMed, PsycINFO, Cochrane Library, and Google Scholar to identify relevant studies linking Vitamin B12 levels with mental health outcomes in children and adolescents. The initial search yielded 150 records, leading to the inclusion of 10 quantitative studies, including one cross-sectional, seven case-controls, and two systematic reviews. Parameters recorded included study design, population sample size, age of the participants, place of study, biochemical investigations conducted and mental health disorders as outcomes. The biochemical markers examined across all 10 studies included vitamin B12, folate, homocysteine, ferritin, fatty acids, inorganic phosphorus, and 25-OH vitamin D. These markers were assessed to understand their associations with various mental health disorders such as depression, anxiety, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASD).
Results: Out of the 10 studies included, 6 studies reported significant improvements in symptoms of depression and anxiety with vitamin B12 supplementation. However, 4 studies found no significant association between B12 supplementation and the studied disorders. Three studies out of 6 observed lower levels of vitamin B12 in patients with ADHD and ASD compared to healthy controls, suggesting a potential role for B12 supplementation in these conditions.From the biomarkers identified, lower levels of vitamin B12 were associated with depression among children, while increased intake of certain nutrients such as fiber, omega-3 fatty acids, and vitamin B12 were marginally associated with reduced odds of aggressive behavior. Furthermore, there was a significant decrease in symptoms of depression and anxiety following supplementation with B vitamins and/or vitamin D.
Conclusion: Supplementation of B12, could help improve mental health issues like depression, anxiety, aggression, and ADHD.

Keywords: Adolescents, Children, Vitamin B12, Mental Health,Dietary Patterns.

Introduction

The developmental stages of childhood and adolescence are vital periods for mental health, shaping lifelong well-being and resilience. The World Health Organization's findings in 2021 emphasized the global significance of mental health issues among adolescents, with a substantial burden on their overall health and future prospects.[1] Unaddressed mental health challenges during these formative years can persist into adulthood, impacting various aspects of life, including academic performance and social interactions.Among the multifaceted factors influencing mental health, dietary patterns have emerged as pivotal contributors.[2] Studies highlighting the benefits of diets like the Mediterranean diet on mental and physical well-being signifies the importance of nutrition in mental health maintenance.[3] While numerous nutrients play essential roles, such as vitamin B12, obtained primarily from animal products like meat, fish, and eggs, stand out for its vital biochemical functions.Vitamin B12 operates as an important coenzyme in biochemical pathways vital for neurological and hematological health.[4] Therefore, deficiency in this nutrient can disrupt critical processes, leading to neurological symptoms and potential mental health implications.

Evidence in adults has pointed to correlations between vitamin B12 levels, dietary patterns, and mental health outcomes like depression, anxiety, and schizophrenia.[5] However, there remains a notable gap in understanding these associations in children and adolescents.The prevalence and impact of mental health disorders in this demographic, particularly concerning conditions like autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), anxiety, and depression, it becomes imperative to explore the role of vitamin B12 comprehensively.[6,7]

Thus, this systematic review investigates the existing observational studies to elucidate the relationship between vitamin B12 levels/intake and mental health outcomes in children and adolescents. By synthesizing available data, the study aims to contribute to a deeper understanding of nutritional influences on mental well-being during crucial developmental stages.

Methodology

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]

Search Strategy and Literature Review

For this systematic review, authors employed a comprehensive search strategy following the PRISMA guidelines. Electronic databases in-

cluding PubMed, PsycINFO, Cochrane Library,and Google Scholar, were systematically searched from January to May, 2023 by three authors independently.The search strategy utilized a combination of keywords including Vitamin B12, cobalamin, mental health, children, adolescents, and dietary patterns. Additionally, hand-searching of reference lists from relevant articles and reviews was conducted to identify any additional studies that met the inclusion criteria of study.

Study Selection

Three independent reviewers screened the titles and abstracts of retrieved articles identified potentially relevant studies for inclusion in this review. Full-text articles written in English were then obtained and assessed for eligibility based on predefined inclusion criteria. The review included studies that examined the association between Vitamin B12 status or supplementation and mental health outcomes in children and adolescents. Clinical trials and interventional studies were excluded from review.

The initial search yielded a total of 150 records.After removing duplicates, authors screened 100 records based on titles and abstracts, leading to the identification of 35 full-text articles for eligibility assessment. Among these, 25 articles were excluded during full-text assessment due to reasons such as inadequate data reporting, inappropriate study designs, or failure to meet inclusion criteria.Upon thorough assessment, 10 studies were deemed suitable for inclusion.

Data Extraction

Data extraction was conducted using a standardized form to capture key information from the selected studies. Information extracted included study characteristics such as author(s), publication year, study design, participant demographics (e.g., age, sample size), methods used to assess Vitamin B12 status, mental health outcomes measured, main findings, and conclusions. Where available, effect sizes, confidence intervals, and statistical significance were also recorded to facilitate data synthesis and analysis.

Data Synthesis and Analysis

Given the anticipated heterogeneity in study designs and outcomes, a narrative synthesis approach was planned for data synthesis. Findings from individual studies were summarized and synthesized to identify common themes, trends, and areas of consensus or divergence regarding the role of Vitamin B12 in the mental health of children and adolescents.

Reporting

The systematic review adhered to the PRISMA guidelines to ensure transparent reporting and methodological rigor. A PRISMA flow diagram was used to illustrate the study selection process, detailing the number of records identified, screened, assessed for eligibility, and included in the final synthesis. This comprehensive reporting approach enhances the clarity, reproducibility, and overall quality of this systematic review on the role of Vitamin B12 in the mental health of children and adolescents.

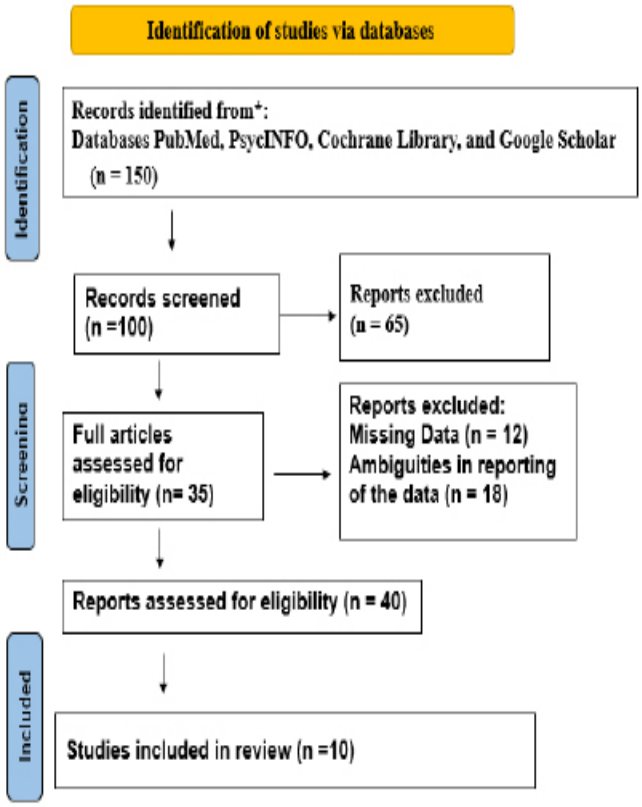

Figure 1: PRISMA Diagram Showing the Study Selection Procedure for investigating the role of Mental Health Outcomes of Children and Adolescents

Results

Out of the 10 studies included, 6 studies reported significant improvements in symptoms of depression and anxiety with vitamin B12 supplementation. However, 4 studies found no significant association between B12 supplementation and the studied disorders. Three studies out of 6 observed lower levels of vitamin B12 in patients with ADHD and ASD compared to healthy controls, suggesting a potential role for B12 supplementation in these conditions.

From the biomarkers identified, lower levels of vitamin B12 were associated with depression among children, while increased intake of certain nutrients such as fiber, omega-3 fatty acids, and vitamin B12 were marginally associated with reduced odds of aggressive behavior. Furthermore, there was a significant decrease in symptoms of depression and anxiety following supplementation with B vitamins and/or vitamin D. Moreover, the studies highlighted the potential of vitamin B12 in modulating behavioral issues, particularly aggressive behavior, when included as part of a broader dietary regimen. The impact of combined nutrient supplementation appeared more pronounced in some studies, indicating a need for further exploration into synergistic effects. Moreover, the studies highlighted the potential of vitamin B12 in modulating behavioral issues, particularly aggressive behavior, when included as part of a broader dietary regimen.

Table 10: Showing Comprehensive description of all the 10 inchluded studies

First Author	Saras-wathy[8]	Wang[9]	Esnafoglu[5]	Jamshid-nia[10]	Mohseni[11]	Sourande[12]	Erden[13]	Topal[14]	Borges[15]	Prades[16]
P-value	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05
Out-comes	Vitamin B-12 and Folate deficiency was not significantly directly associat-ed with Depression and GAD, however indirectly significantly influenc-es the depression and anxiety through mediation of hyperho-mocysteine	Unhealthy dietary pat-terns linked to poor nutritional biochemis-try profiles and ADHD	Vitamin B12 defi-ciency or insuffi-ciency and elevated homocys-teine con-tributes to depression etiopatho-genesis	Lower level of vitamin B-12 is associat-ed with depression among children	Increased intake of simple car-bohydrates, total fat, SFAs, TFAs, and caffeine linked to increased occurrence of AB. Intake of fiber, W3, and vitamin B-12 marginally associated with reduced odds of AB	No associ-ation be-tween lower maternal Vitamin B12 levels and offspring ADHD	Lower vita-min B12 and homocys-teine levels in ASD group, no significant difference in APCA levels	Higher neutrophil levels and neutrophil/ lymphocyte ratio in ASD and ADHD groups. Neutrophil/ lymphocyte ratio correlat-ed with social interaction problems in ASD	Supple-mentation with B vitamins and/or vitamin D signifi-cantly decreased depres-sion score scales and improved symptoms of depres-sion and anxiety	Signifi-cantly lower vi-tamin B12 levels in ASD and ADHD patients vs. healthy controls; higher fo-late levels in ADHD patients post-sup-plementa-tion
Statistical Analysis	Multiple Regres-sion and Correlation Analysis	Structural Equation Model (SEM)	Descrip-tive Analy-sis and T-test	RevMen Analysis for (SMD), Odds Ratio (OR)	Indepen-dent t-test, Mann-Whit-ney test, Chi-square test, Logistic regression models	Logistic regression (adjust-ed odds ratio, 95% confidence interval)	Comparison of means	Comparison of means (neutrophil levels, neutro-phil/lympho-cyte ratio), Correlation analysis (neu-trophil/lym-phocyte ratio and social interaction problems in ASD)	Results aggregated from 20 RCTs	Meta-anal-ysis
Mental Health Disorders Studied	GAD	ADHD	Depres-sion	ASD, ADHD, Depression, Behavioral problems	Aggressive Behavior	ADHD	ASD	ASD, ADHD	Major depressive disorder (MDD), generalized anxiety disorder (GAD)	Various psychiatric disorders including ASD, ADHD
Data Col-lection Tool for Mental Disorders	Patient Health Question-naire and Generalized Anxiety Disorder scale	Clinical Ob-servation	Childhood Depres-sion Inventory, State-Trait Anxiety Inventory	Data Ex-tracted in Excel Sheet	Busse-Perry questionnaire (aggression score)	ADHD di-agnosis (cas-es), matched controls	Childhood Autism Rating Scale (CARS)	Affective Disorders and Schizophrenia for School-Age Children K-SADS-PL, Gilliam Autism Rating Scale-2 (ADHD screening)	Standard-ized rating scales (i.e. depres-sion score scales)	Clinical scales (i.e. symptom rating scales)

Biochemical Tests for Deficiency Analysis/ Interventional Supplementation	DNA extraction and MTHFR C677T gene polymorphism Analysis	Serum levels of nutritional markers (vitamin B12, folate, vitamin B6, ferritin, fatty acids, inorganic phosphorus)	Serum levels of folate, vitamin B12, homocysteine, and 25-OH vitamin D	Vitamin B12 Levels	Fiber, W3 (omega-3), vitamin B-12	Chemiluminescence microparticle immunoassay (maternal serum)	Enzyme-linked immunosorbent assay (ELISA)	Serum Levels	Blood level measurements	Serum levels of water-soluble vitamins specifically folate and vitamin B12
Micronutrient Deficiencies	Vitamin B-12 and Folate	Vitamin B12, folate, vitamin B6, ferritin, monounsaturated fatty acids (MUFA)	Vitamin B-12 and Folate & Vitamin D	Vitamin B12	Vitamin B12	Vitamin B12	Vitamin B12	Vitamin B12, Folate, Ferritin	B vitamins (folic acid, L-methylfolate, B1, B12, methylcobalamin), vitamin D	Water-soluble vitamins specifically folate and vitamin B12
Country	India	Taiwan	Turkey	China	Iran	Finland	UK	Turkey	Multiple countries	Multiple countries
Age of Participants	up to 25 Years	Elementary school children	Mean age: 15.08 (SD 1.46) for depression group, 14.41 (SD 2.32) for control group	Less than 25 Years	9-13 years old	Singleton children born in Finland (1998-1999)	Patient Group's Age (month) mean(±SD) 51.67 (23.63), Control Group's Age (month) mean(±SD) 57.94 (19.26)	School-age children	≥ 18 years old	≤ 18 years old
Population & Sample Size	303 Both Male and Female	432 (216 ADHD, 216 controls)	Depression (n=89) and healthy controls (n=43) Children and adolescents	Children and adolescents (56 studies with 37,932 participants)	Adolescent girls (primary school students) 212 (106 with aggressive behavior, 106 healthy)	Singleton children born in Finland (1998-1999) with ADHD cases and matched controls (1026 cases, 1026 controls)	Children with ASD and controls (69 (36 ASD, 33 controls)	Children with ASD, ADHD, and Healthy Controls (203 ASD = 72, ADHD = 61, HC = 70)	Patients ≥ 18 years old with (MDD), (GAD), or depressive and anxiety symptoms (20 RCTs, 2,256 subjects)	(CAD) with psychiatric disorders [42 articles, 29 examining (ASD)
Research Design	Cross-sectional Study	Case-Control Study	Case-control Study	Systematic review and meta-analysis	Case-control study	Case-control study	Case-Control Study	Case-Control Study	Systematic review of (RCTs)	Systematic review and meta-analysis

Discussion

This systematic review involved 10 quantitative studies, including one cross-sectional, seven case-controls, and two systematic reviews(Table 1, figure 1).The primary findings highlighted that vitamin B-12 and folate deficiencies were not directly linked to depression and Generalized Anxiety Disorders.However, they did indirectly influence these conditions, particularly depression and anxiety, through the mediation of hyperhomocysteinemia. [8-13] This suggests a complex interplay between nutritional deficiencies and mental health markers. Some studies also highlighted the significant impact of unhealthy dietary patterns on poor nutritional biochemistry profiles, notably in relation to ADHD.[17,18] It also pointed out that vitamin B-12 deficiency coupled with elevated homocysteine levels might contribute to depression's etiopathogenesis, offering insights into potential mechanisms underlying mental health disorders.

The studies included in this review encompassed a diverse range of methodologies for data collection and analysis. Clinical observations using tools like the Childhood Depression Inventory and State-Trait Anxiety Inventory complemented biochemical tests such as DNA extraction and MTHFR C677T gene polymorphism analysis.[5,10,13,14] Additionally, serum levels of various nutritional markers including vitamin B12, folate, vitamin B6, ferritin, fatty acids, inorganic phosphorus, and 25-OH vitamin D were measured to assess micronutrient deficiencies and their implications.[8] The study's scope extended across different countries such as India, Taiwan, and Turkey, covering age groups ranging from elementary school children to adults aged upto 25 years of age. Sample sizes were diverse, reflecting populations with depression, ADHD, and controls. Various research designs including cross-sectional studies and case-control studies were employed, with different authors leading the investigations.[15] The reported p-values ≤0.05 across analyses suggest statistically sig-

nificant findings, reinforcing the robustness of the associations identified. Overall, the study's detailed approach sheds light on the multifaceted connections between nutritional status, dietary patterns, and mental health outcomes, contributing valuable insights to the field of psychiatric and nutritional research.

Through these studies, it was observed that lower levels of vitamin B-12 were associated with depression among children, highlighting the potential impact of nutritional deficiencies on mental health. Additionally, the study revealed that increased intake of simple carbohydrates, total fat, saturated fatty acids, trans fatty acids , and caffeine was linked to a higher occurrence of aggressive behavior.16Conversely, higher intake of fiber, omega-3 fatty acids (W3), and vitamin B-12 showed a marginal association with reduced odds of AB, emphasizing the importance of dietary patterns in behavioral outcomes.[10]

Moreover, lower vitamin B12 and homocysteine levels were observed in the ASD group, , indicating specific patterns of nutrient deficiencies in ASD individuals.[14] The statistical analyses of the studies investigated in this review included RevMen Analysis for Standardized Mean Difference and Odds Ratio , as well as independent t-tests, Mann-Whitney tests, Chi-square tests, and logistic regression models, highlighting a robust methodological approach to assess associations and differences across various variables.

The review focused on mental health disorders such as ASD and ADHD, depression, and behavioral problems, employing tools like the Busse-Perry questionnaire for aggression scores, ADHD diagnosis protocols, and the Childhood Autism Rating Scale for assessing autism symptoms. Biochemical tests for deficiency analysis and interventional supplementation included measuring vitamin B12 levels and utilizing assays such as chemiluminescence microparticle immunoassay and enzyme-linked immunosorbent assay. With a diverse participant demographic including populations from China, Iran, Finland, and the UK across different age groups and research designs such as systematic meta-analysis and case-control studies led by various authors, the study provides valuable insights into the complex relationships between nutrition, mental health, and behavioral outcomes. Furthermore, the higher neutrophil levels and a higher neutrophil to lymphocyte ratio were observed in groups with ASD and ADHD.[14] The study also found that the neutrophil to lymphocyte ratio correlated with social interaction problems specifically in the ASD group, indicating a potential biomarker for social difficulties in ASD. Moreover, supplementation with B vitamins and/or vitamin D led to a significant decrease in depression scores and improvements in symptoms of depression and anxiety, highlighting the therapeutic potential of these nutrients in mental health management.The analysis also revealed significantly lower levels of vitamin B12 in ASD and ADHD patients compared to healthy controls, alongside higher folate levels in ADHD patients post-supplementation, leading to a decrease in symptoms. These findingshighlights the importance of micronutrients like vitamin B12 and folate in mental health outcomes and the potential benefits of targeted supplementation strategies.[11] The study focused on a range of mental health disorders including ASD, ADHD, MDD, GAD, and depressive/anxiety symptoms, utilizing standardized rating scales and clinical assessments for data collection. Biochemical tests for deficiency analysis and interventional supplementation encompassed serum levels measurements, blood level measurements for micronutrients like vitamin B12, folate, and ferritin, as well as interventions with various B vitamins, vitamin D, and water-soluble vitamins.[12] Therefore, the study included participants across different age groups and regions, reflecting a diverse population and enhancing the generalizability of the findings. Various authors contributed to this research effort, bringing together a multidisciplinary approach to understanding and addressing mental health challenges through nutrition.

Strengths and Limitations

This review highlightsthe therapeutic potential of targeted nutrient supplementation in managing mental health conditions, particularly in cases where deficiencies or insufficiencies are identified.Furthermore, the research identified potential biomarkers such as neutrophil to lymphocyte ratios correlating with social interaction problems in conditions like ASD and ADHD. These biomarkers offer insights into underlying physiological mechanisms and potential avenues for targeted interventions or monitoring strategies. However, this review has certain limitations. With an inclusion of only 10 studies, and even those with three different study designs might have led to biases and inability to establish robust causation. The sample sizes with these 10 studies varied considerably, from very limited to enormous, and that too could have lack of ability to detect association between inadequate levels of B12 on mental health. The heterogeneity among the sample population, settings, and methodologies. Confounding factors, such as genetic, environmental, social, and other nutritional influences, were challenging to control. Publication bias might have favoured positive findings. Moreover, accurate assessment of dietary intake is difficult, potentially leading to misclassification of Vitamin B12 status. Additionally, the broad age range and different developmental stages of children and adolescents were not specifically addressed in this review. Also worth mentioning is the lack of contemplation of the long-term effects of Vitamin B12 status on mental health through this review. Further studies are advised to investigate these gaps, to further strengthen the impact of Vitamin B12 on mental well-being of children and adolescents.

Conclusion

Lower levels of Vitamin B12 were found to be associated with depression among children. Supplementation of B12, could help improve mental health issues like depression, anxiety, aggression, and ADHD. This highlights the potential impact of nutritional deficiencies, specifically in essential vitamins like B12, on mental health outcomes, particularly in younger populations. Dietary patterns and intake were also significant factors influencing mental health outcomes. Increased intake of certain nutrients such as fiber, omega-3 fatty acids (W3), and Vitamin B12 showed marginal associations with reduced odds of aggressive behavior (AB) and improved symptoms of depression and anxiety.

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