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Synergistic mechanisms of micronutrients in cognitive function and mental health

Karina Shasri Anastasya[1], Meutia Atika Faradilla[2], Aditya Krishna Murthi[3], Deasyka Yastani[4], Mutiara Ferina[5], Nabila Maudy Salma[6]

[1]Department of Nutrition, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[2,4]Department of Biochemistry, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[3]Department of Physiology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[5]Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[6]Department of Anatomy, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

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ABSTRACT

Background: Micronutrients support neuronal metabolism and signaling, but clinical synergy remains uncertain. Objective: To distinguish biological interactions from intervention evidence linking micronutrients with cognition and mental health. Methods: This narrative review synthesized Indonesian and international studies and 35 peer-reviewed references dated 2020–2026, considering design, population, nutrient status, and outcome. Results: Meta-analytic evidence supports benefits of iron for selected cognitive domains in schoolchildren. Randomized multivitamin-mineral studies reported cognitive improvements in older adults. Some vitamin D trials showed reduced adult depressive symptoms, whereas zinc, magnesium, and B-vitamin evidence differed in strength and clinical directness. Iron, zinc, magnesium, vitamin D, and B vitamins converge on energy metabolism, neurotransmission, one-carbon reactions, and inflammatory pathways, but convergence alone does not prove synergy. Conclusion: Adequate diets and targeted deficiency management remain priorities. Specific combinations require factorial trials that test interaction effects. The novelty is a mechanism-to-outcome evidence framework distinguishing biological plausibility, association, and intervention findings.

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Corresponding Author:

Karina Shasri Anastasya,
Faculty of Medicine,
Universitas Trisakti,
Jl. Kyai Tapa No.260 Kampus B, RT.5/RW.9, Tomang, Kec. Grogol Petamburan, Kota Jakarta Barat, Daerah Khusus Ibukota Jakarta, 11440, Indonesia
Email: Karina.shasri@trisakti.ac.id

INTRODUCTION

Mental health and cognitive functioning are interdependent determinants of well-being across the life course. Attention, learning, and memory may be affected by depression, psychological distress, and impaired nutritional status. Nutritional psychiatry increasingly considers dietary quality and micronutrient adequacy alongside psychosocial and clinical determinants; however, observational

associations should not be interpreted as proof that supplementation prevents mental disorders (Martins et al., 2021). A review of the literature places individual nutrients within the multifactorial context of mental well-being rather than presenting supplementation as a substitute for clinical care (Muscaritoli, 2021).

Micronutrients support cerebral energy metabolism, oxygen delivery, one-carbon transfer, neurotransmitter synthesis, and neuronal signaling. Iron participates in oxygen transport and enzymatic reactions; zinc influences synaptic signaling; magnesium is involved in neuronal excitability; and vitamins B6, B9, and B12 are required for interconnected metabolic processes. These functions provide biological plausibility for coordinated action, but a shared pathway is not itself evidence of clinical synergy (Tardy et al., 2020).

Clinical evidence differs by nutrient, outcome, and population. A systematic review of school-aged children found that iron supplementation improved measured intelligence, attention, and memory, but did not demonstrate better school achievement (Gutema et al., 2023). A separate synthesis involving children and adolescents in low- and middle-income countries underscores the importance of baseline iron status and contextual differences (Chen et al., 2022). In contrast, Indonesian cross-sectional evidence illustrates uncertainty: an unadjusted correlation between zinc intake and intelligence was not independent after adjustment, and dietary iron intake was not associated with school performance in a small student sample (Sanjiwani et al., 2020; Puspitasari et al., 2021). For later-life cognition, randomized COSMOS-Mind and COSMOS-Clinic investigations found favorable cognitive outcomes for multivitamin-mineral supplementation compared with placebo (Baker et al., 2023; Vyas et al., 2024). Their findings are promising for multinutrient approaches, but they do not establish that individual components interact synergistically, because the trials did not isolate individual nutrient combinations. Reviews of B-vitamin interventions also suggest that effects differ with duration, cognitive status, and study design (Wang et al., 2022; Suh et al., 2020).

Associations with mental health are likewise nuanced. Meta-analyses of randomized trials have reported reductions in depressive symptoms following vitamin D supplementation in selected adult populations, although the evidence is heterogeneous (Mikola et al., 2023; Srifuengfung et al., 2023). For zinc, evidence involves both observational associations and supplementation trials (Yosaee et al., 2022). Magnesium intake has been inversely associated with depression risk in epidemiological synthesis, but this cannot demonstrate a treatment effect (Hajhashemy et al., 2025). These distinctions are essential when translating biological hypotheses into nutritional advice. Within a life-course framework, micronutrient requirements and neurological vulnerability change with rapid brain development, pregnancy, lactation, adulthood, and aging. Iron deficiency during childhood may affect neurocognitive testing, whereas adult supplementation trials frequently assess mood symptoms or late-life cognition. Thus, the question "Which micronutrient works?" is insufficient without defining the population, deficiency status, exposure, duration, and outcome. Evidence arising from these different settings cannot be treated as interchangeable (Gutema et al., 2023; Baker et al., 2023; William et al., 2025).

Perinatal care provides a clinically relevant and underexplored context for this framework. Pregnancy and postpartum recovery alter nutritional demands, while depressive symptoms can influence diet quality and engagement with health services. In a meta-analysis of randomized perinatal trials, pooled elemental-mineral interventions did not demonstrate a clear improvement in depressive symptoms compared with controls, whereas vitamin D showed a possible benefit in a subgroup of postpartum studies (Tsai et al., 2023). A separate review of postpartum micronutrient deficiencies identified observational associations but emphasized uncertainty about causality (Voros et al., 2025). Long-term child development also challenges a simple "more nutrients equals better cognition" assumption. A cluster-randomized trial in Niger found no significant benefit of prenatal multiple-micronutrient supplementation over iron-folic acid for cognitive, language, or motor outcomes at 24 months (Sudfeld et al., 2022). A later systematic

review of randomized trials suggested that any longer-term cognitive benefits of maternal or early-childhood multiple-micronutrient interventions were generally modest, inconsistent, or limited to specific domains (William et al., 2025). These findings should be interpreted alongside adult multivitamin findings rather than subsumed under a single generalized conclusion.

Existing mechanistic discussions often use "synergistic" to describe micronutrients that share metabolic pathways, yet biochemical co-operation, statistical interaction, and clinical superiority are three distinct concepts. Functional convergence refers to participation in a common physiological network. Additive benefit indicates the expected combined effect of two independent interventions. Synergy, by contrast, requires empirical evidence that the combined effect exceeds a prespecified additive expectation on an explicitly chosen scale, ideally assessed using a factorial design. A positive result for a combined product versus placebo alone cannot distinguish these possibilities (Tardy et al., 2020; Rodríguez-Morán et al., 2024).

Against this background, the novel contribution of the present review is a life-course mechanism-to-outcome evidence map rather than a claim to have discovered a new pathway or an effective micronutrient cocktail. It triangulates molecular plausibility with randomized, observational, and population-specific clinical findings; tests whether ostensibly positive multinutrient trials actually isolate interaction effects; and proposes research designs able to distinguish deficiency correction from additional benefit in nutrient-replete groups. This synthesis is particularly relevant to midwifery because maternal nutritional assessment and perinatal mental-health screening meet at the same point of care. Exposure to childhood undernutrition also has long-term consequences that cannot be reduced to isolated mineral intake. A systematic review of 30 studies reported consistent associations between childhood malnutrition and impaired neurodevelopment and school achievement, while effects on mental-health diagnoses were less certain. This helps position micronutrient status within the broader context of nutritional vulnerability and early-life adversity (Kirolos et al., 2022).

The central knowledge gap is therefore not whether individual micronutrients have neurological roles, but whether concurrent adequacy or combined supplementation yields benefits greater than expected from the separate nutrients. This narrative review offers a pathway-based framework connecting metabolic cofactors, neuroplasticity-related signaling, and inflammatory/oxidative processes to cognitive and mental-health outcomes, while explicitly distinguishing mechanistic plausibility, observational association, and randomized clinical evidence. The objective is to identify plausible interactions, assess the strength of outcome evidence, and define testable hypotheses for future factorial or biomarker-stratified trials, including possible relevance to adolescent and maternal health services.

LITERATURE REVIEW

The Concept of Micronutrients and the Nervous System

Micronutrients are essential nutrients required by the body in small quantities, yet they play a critical role in maintaining physiological functions, including those of the nervous system. These nutrients consist of vitamins and minerals that function as cofactors in various enzymatic reactions supporting brain metabolism. Within the nervous system, micronutrients are involved in myelin formation, neurotransmitter synthesis, and the maintenance of neuronal structural integrity. Deficiencies in micronutrients may lead to neurological dysfunction, which can adversely affect cognitive performance and mental health (Isang et al., 2024; Rusdi et al., 2025; Yusuf & Helmi, 2022). Furthermore, micronutrients contribute to the regulation of the immune system, which is closely linked to brain function. The interaction between the immune and nervous systems indicates that chronic inflammation resulting from nutritional deficiencies can impair brain function and increase the risk of neuropsychiatric disorders. Therefore, the role of micronutrients extends beyond basic metabolic functions to encompass the complex regulation of interactions between the nervous and immune systems.

Micronutrients and Cognitive Function

Cognitive function encompasses memory, attention, concentration, and learning capacity. Iron is essential for oxygen transport and enzymes involved in neurotransmitter metabolism, and correcting deficiency may be important for neurocognitive health. However, a small Indonesian cross-sectional study of 33 students found no statistically significant association between dietary iron intake and academic achievement ($p = 0.767$). Dietary intake measures must not be equated with iron status or the effects of treating a confirmed deficiency; educational outcomes are multifactorial (Puspitasari et al., 2021; Gutema et al., 2023). Zinc is involved in synaptic signaling and the activity of numerous enzymes relevant to brain development. In a study of schoolchildren in Kupang, the initial association between dietary zinc intake and intelligence was not independent after multivariable analysis, illustrating possible confounding rather than proven cognitive efficacy (Sanjiwani et al., 2020). In older populations, overall nutritional status has been associated with differences in measured cognition, but nutritional associations cannot alone demonstrate the benefits of supplementation (Sa'diyah et al., 2023).

Micronutrients and Mental Health

Mental health refers to a state of psychological well-being that enables individuals to function effectively in their daily lives. Micronutrients play a crucial role in maintaining emotional balance and psychological functioning through their influence on neurotransmitter systems. Vitamin D, for instance, is known to contribute to mood regulation through mechanisms involving the serotonergic system. Empirical evidence indicates that vitamin D deficiency is associated with an increased risk of depression among university students (Mahmudah et al., 2026).

Nutrition and mental health are related through multiple biological and behavioral pathways, including dietary quality, inflammation, and broader contextual factors (Muscaritoli, 2021). Magnesium contributes to physiological processes relevant to neuronal excitability, yet the clinical effects of magnesium supplementation depend on population and study design (Moabedi et al., 2023). Community education on magnesium and psychological screening tools may improve health literacy, but an educational program does not establish the prevention of psychiatric disorders (Biromo et al., 2025).

Biological and Synergistic Mechanisms

Micronutrients may converge on neurotransmission, energy metabolism, and neuroplasticity-related pathways. Iron contributes to monoamine-related enzymatic reactions; zinc regulates synaptic signaling; and B vitamins act in one-carbon and methylation pathways (Tardy et al., 2020; Wang et al., 2022). Brain-derived neurotrophic factor (BDNF) is a relevant neuroplasticity marker, but direct evidence that routine combinations of these nutrients increase human cerebral BDNF and thereby improve clinical outcomes is insufficient. Neuroplasticity-related pathways remain hypotheses requiring trials that link biomarker changes to patient-relevant clinical outcomes (Zhao et al., 2024). Furthermore, micronutrients function as antioxidants that protect neural cells from oxidative stress–induced damage. Antioxidant compounds, particularly those derived from natural micronutrient sources, play a neuroprotective role by mitigating inflammation and preventing neuronal injury (Yanti & Susanti, 2024). These findings highlight that micronutrients do not act in isolation; rather, they exert their effects through synergistic interactions involving multiple biological pathways within the body.

Integrative Theoretical Model

An integrative approach to understanding the role of micronutrients in cognitive function and mental health has gained increasing attention within the field of nutritional neuroscience. The concept of nutritional psychiatry emphasizes that dietary patterns and nutrient intake exert a direct influence on mental health through complex interactions among the brain, immune system, and metabolic processes. Within this framework, micronutrients are not viewed as isolated components but as part of an interconnected system that collectively maintains brain function homeostasis

(Nogueira-de-Almeida et al., 2025). Furthermore, the concept of the brain–nutrition axis highlights a bidirectional relationship between nutrition and brain function, wherein nutritional status influences neural activity, while psychological conditions can, in turn, affect dietary behaviors. This perspective underscores the importance of implementing comprehensive and integrated strategies for micronutrient intake. Existing literature also suggests that optimizing overall nutrient consumption may serve as a preventive approach to addressing mental health challenges (Kristy & Mahmudiono, 2022). Therefore, an integrative theoretical model provides a more holistic framework for understanding the interplay between micronutrients, cognitive function, and mental health.

RESEARCH METHOD

This article is a narrative, mechanism-oriented literature review of micronutrient contributions to cognitive function and mental health. The original manuscript synthesized Indonesian and international studies identified through Google Scholar and national journal portals. For the present revision, targeted additional literature published from 2020 onward was identified and checked against publisher pages and PubMed records, with attention to DOI validity, study design, population, outcomes, and consistency between the cited claim and the source. The review is not registered as a systematic review and does not claim exhaustive retrieval.

Eligible evidence included peer-reviewed human randomized controlled trials, systematic reviews, meta-analyses, and relevant observational investigations that assessed micronutrient status or interventions in relation to cognition, depression, anxiety, or associated biological pathways. Mechanistic reviews were used to inform biological interpretation rather than to establish clinical effectiveness. An older seminal review already present in the original manuscript was retained for historical context, whereas all 15 newly added studies were published from 2020 to 2025. Articles were appraised narratively according to design and directness: randomized interventions informed causal interpretations for specific supplements and measured outcomes; observational studies informed associations only; and molecular or biochemical reviews informed plausible mechanisms. Where multiple analyses derived from COSMOS, they were treated as related investigations rather than wholly independent trials. No formal pooled effect estimate or quantitative risk-of-bias score was generated in this manuscript.

Thematic synthesis used three linked domains: (1) micronutrient-specific functions and deficiency contexts; (2) convergence on energy metabolism, neurotransmission, one-carbon pathways, neuroplasticity, and inflammatory/oxidative regulation; and (3) human evidence on cognitive and psychological outcomes. For this review, "synergy" is reserved for an interaction in which the joint intervention effect exceeds an explicitly defined additive expectation; co-occurrence of pathways or benefit from a multivitamin alone is described as functional convergence, not proven synergy. Findings were interpreted with attention to age, baseline deficiency, nutrient dose and formulation, outcome heterogeneity, and the distinction between dietary adequacy and pharmacological supplementation. The proposed integrative model is an evidence-informed hypothesis and does not establish a new clinically validated treatment regimen.

The additional evidence was selected purposively to address several contrasts rather than to produce a pooled prevalence or treatment-effect estimate: child iron interventions versus academic outcomes; multivitamin trials in older adults versus prenatal supplementation; depressive-symptom trials versus observational biomarkers; and comparative treatment arms versus direct factorial tests of synergy. Selection was guided by relevance, methodological directness, and verified bibliographic metadata. Because sampling was purposive, no PRISMA flow diagram or comprehensive search count is reported, and conclusions are presented as a structured narrative synthesis.

RESULTS AND DISCUSSION

The Role of Individual Micronutrients

Iron has a clear biological role in hemoglobin production, cerebral oxygen delivery, and enzymes implicated in neurotransmitter metabolism. The systematic review by Gutema et al. (2023) reported improvement in intelligence (standardized mean difference [SMD] 0.46), attention/concentration (SMD 0.44), and memory (SMD 0.44) among school-age children receiving iron, but not in school achievement (SMD 0.06; non-significant). This contrasts with neither the null school-performance result nor the observational limitations of the Indonesian study ($p = 0.767$) (Puspitasari et al., 2021). Evidence therefore supports endpoint-specific benefits rather than a general assertion that iron intake improves school grades.

Zinc contributes to synaptic transmission, enzyme activity, and neurodevelopment, but the association between dietary zinc and intelligence in schoolchildren was not statistically independent after adjustment in one Indonesian observational study (Sanjiwani et al., 2020). A dose-response synthesis linked zinc status with depression and assessed supplementation trials, indicating a possible therapeutic signal while leaving questions about study heterogeneity and baseline deficiency (Yosaee et al., 2022). A favorable association with one psychiatric outcome cannot be extrapolated to all cognitive domains or life stages.

Vitamin D and magnesium illustrate the importance of separating mechanistic effects from clinical evidence. Vitamin D has immunomodulatory and neurobiological functions, and some randomized-trial meta-analyses suggest improvement in adult depressive symptoms (Mikola et al., 2023; Srifuengfung et al., 2023). Magnesium modulates neuromuscular and neuronal excitability, but pooled epidemiological evidence on higher magnesium intake and lower depression risk remains observational (Hajhashemy et al., 2025). Together these studies support targeted attention to nutritional status without proving that routine combined supplementation prevents depression or anxiety.

Deficiency-Dependent Effects and Heterogeneous Outcomes

The benefit of supplementation cannot be assumed to be uniform across baseline nutrient status. Iron-based interventions are particularly pertinent where anemia or iron deficiency impairs physiological function. In the school-age iron meta-analysis, intelligence, attention, and memory improved, whereas school achievement did not; this illustrates the difference between neuropsychological test performance and broader educational outcomes shaped by schooling and socioeconomic influences (Gutema et al., 2023). Therefore, biological plausibility should be coupled with outcomes that are sufficiently specific and measurable.

By comparison, COSMOS results concern older US adults and a multivitamin-mineral product with numerous constituents. These studies cannot be directly extrapolated to children, individuals with depression, or pregnant women without comparable trials. Apparent variation across life stages may reflect baseline nutritional insufficiency, age-related metabolic changes, dose and duration, differences between biochemical and functional endpoints, and selection of participants. These are possible explanations rather than confirmed effect modifiers (Baker et al., 2023; Vyas et al., 2024; William et al., 2025).

Synergistic Effects of Micronutrients

The main conceptual contribution of this review is a distinction between *functional convergence* and *demonstrated biological synergy*. Several micronutrients participate in connected pathways; nonetheless, a biological interaction is not confirmed merely because combined supplementation improves an outcome. Demonstrating synergy requires comparison of a combination against its separate components, ideally in a factorial randomized trial with a prespecified interaction contrast. The biochemical review by (Tardy et al., 2020) supports pathway convergence, but not a quantified interaction effect.

Multivitamin-mineral trials provide clinically relevant yet indirect evidence for combined formulations. In COSMOS-Mind, a randomized trial reported improved global cognition after multivitamin-mineral supplementation (Baker et al., 2023); the later COSMOS-Clinic study and its pooled analyses found favorable cognitive results across related cognitive assessments (Vyas et al., 2024). These substudies share an underlying COSMOS program and must not be counted as independent replication. Neither study established that zinc, iron, magnesium, and vitamin D specifically caused an effect greater than the sum of their separate actions.

Evidence from targeted intervention reviews remains mixed. Meta-analyses of B vitamins have suggested small benefits for selected cognitive outcomes in non-demented or older populations, with substantial differences by duration and baseline status (Suh et al., 2020; Wang et al., 2022). By contrast, the clinical evidence cannot support a blanket conclusion that a multinutrient strategy is universally superior to a single-nutrient strategy. Existing broad nutritional syntheses (Kristy & Mahmudiono, 2022; Nogueira-de-Almeida et al., 2025) are compatible with a dietary-adequacy perspective, but direct head-to-head and interaction-testing trials are needed.

Direct Combination Trials Versus Proven Synergy

A 2024 open-label randomized study enrolled 60 adults with long-COVID, hypomagnesemia, vitamin D deficiency, and depressive symptoms. The comparison of magnesium plus vitamin D against vitamin D alone favored the combination for improvement in depression scores, but the small sample, selected clinical context, lack of blinding, and absence of a magnesium-only or double-placebo arm limit external validity (Rodríguez-Morán et al., 2024). Importantly, this trial estimates incremental benefit of adding magnesium to vitamin D; it cannot quantify a magnesium-by-vitamin D interaction or establish synergy.

A parallel methodological issue occurs when benefits of multivitamin-mineral formulations are attributed to two or three highlighted nutrients despite a product containing many constituents. Without isolated component arms, neither pharmacodynamic interaction nor the role of correcting multiple deficiencies can be separated. Observed effectiveness of the whole formulation should therefore be reported as a product-level result, while any mechanism-specific interaction remains an inference requiring direct testing (Baker et al., 2023; Vyas et al., 2024).

Impact on Mental Health

Mental-health findings are most interpretable when study designs are distinguished. The meta-analysis by Mikola et al. (2023) supports a possible reduction in depressive symptoms in adults receiving vitamin D, while another randomized-trial meta-analysis found a greater signal in adults than in children or adolescents (Srifuengfung et al., 2023). High between-study heterogeneity limits generalization. Narrative and observational evidence concerning diet quality and depressive symptoms (Muscaritoli, 2021; Mahmudah et al., 2026) does not establish that supplementation prevents a psychiatric diagnosis.

Evidence for zinc and magnesium complements, but does not duplicate, vitamin D evidence. The synthesis by (Yosaee et al., 2022) suggests that zinc-related interventions merit further evaluation in depression. The dose-response analysis by (Hajhashemy et al., 2025) found an inverse relationship between dietary magnesium intake and depression risk, but it pooled epidemiological studies and therefore cannot determine whether magnesium supplementation treats depression. Community education on magnesium awareness (Biromo et al., 2025) is informative for health promotion rather than proof of clinical efficacy.

Guidance for clinical practice should be proportionate to the evidence. The systematic review of B-vitamin and vitamin D treatment trials found variation across interventions and clinical populations (Borges-Vieira & Cardoso, 2023). International clinician guidelines emphasize evidence grading and the use of selected nutraceuticals only as appropriate adjuncts, rather than replacements for established mental-health care (Sarris et al., 2022). Depression, anxiety, and

cognitive impairment require clinical assessment; a nutritional intervention is not a substitute for effective psychiatric or neurological treatment.

Pregnancy, Postpartum Mental Health, and Offspring Cognition

For midwifery, the key patient-centered outcomes are maternal depressive and anxiety symptoms, maternal nutritional status, and downstream child neurodevelopment, rather than biomarkers alone. The randomized-trial meta-analysis by Tsai et al. (2023) pooled studies of dietary interventions during pregnancy or postpartum and found no statistically conclusive overall benefit for iron, zinc, and magnesium interventions on depressive symptoms (SMD −0.42; 95% CI −1.05 to 0.21). In contrast, the subset of vitamin D studies suggested benefit (SMD −0.52; 95% CI −0.84 to −0.20). These are pooled estimates for studied interventions and are not evidence that routine supplementation should treat postpartum depression.

The observational systematic review by Voros et al. (2025) described evidence linking deficiency of certain micronutrients, particularly vitamin D, vitamin B12, and zinc, with postpartum depression, while identifying inconsistent measurements and confounding. A low serum level may indicate inadequate intake, inflammatory illness, altered physiological requirements, or other processes; temporal association does not establish a nutrient-specific causal pathway. Nutritional screening can complement, but cannot replace, validated maternal mental-health assessment and clinical treatment. Offspring cognitive outcomes are equally context sensitive. In the Niger randomized trial, prenatal multiple-micronutrient supplementation did not significantly improve cognitive, motor, or language outcomes at 24 months compared with standard iron-folic acid supplementation (Sudfeld et al., 2022). Reviewing longer-term evidence from several low- and middle-income settings, William et al. (2025) noted mostly nonsignificant findings and some modest improvements in selected cognitive domains. The combined evidence warrants nutritional support based on obstetric indications but does not support guaranteeing later cognitive advantage for a child from additional micronutrients.

Biological Mechanisms

A plausible molecular framework comprises three converging domains. First, iron and B vitamins support neuronal energy delivery, mitochondrial metabolism, and synthesis-related reactions (Tardy et al., 2020). Second, B6, folate, and B12 contribute to one-carbon metabolism, potentially linking methylation status and homocysteine with cognition (Wang et al., 2022). Third, zinc, magnesium, and vitamin D may participate in signaling processes related to neuronal excitability and immune regulation. These are connected physiological functions, not evidence that a specific multi-ingredient supplement acts synergistically in humans.

Neuroplasticity offers a potential intermediary pathway, but biomarker claims require particular caution. In a clinical cross-sectional study, lower folate, vitamin B6, and vitamin B12 status was associated with cognitive impairment among patients with depression; BDNF was assessed in the same investigation (Zhao et al., 2024). These associations cannot demonstrate that supplementation increases BDNF or that any change in BDNF mediates cognitive improvement. The proposed nutrient–BDNF–clinical outcome pathway remains hypothesis-generating and requires controlled testing. Oxidative stress and inflammatory signaling provide additional candidate mechanisms linking nutritional status to neural health. Nevertheless, biochemical plausibility from antioxidant mechanisms or experimental research (Yanti & Susanti, 2024) should not be presented as proof of neuroprotection in clinical populations. A rigorous mechanistic intervention would measure micronutrient status, oxidative or inflammatory indicators, and validated outcomes before and after treatment while adjusting for diet quality, comorbidities, and medications (Martins et al., 2021).

Mechanistic Bridges and the Limits of Biomarker Inference

One-carbon metabolism illustrates a plausible mechanistic bridge: folate and vitamin B12 are required for methyl-group transfer and homocysteine regulation, while vitamin B6 participates

in associated amino-acid pathways. Disruption may influence neural metabolism, but human cognitive and mood outcomes are shaped by multiple non-nutritional determinants. Observational associations among serum folate, B6, B12, and cognitive impairment in patients with depression (Zhao et al., 2024) are therefore hypothesis-generating and do not identify a universal supplement formulation. Inflammatory markers and brain-derived neurotrophic factor (BDNF) should not be used as surrogate proof of clinical effectiveness. BDNF measured in peripheral blood is not identical to direct central nervous system signaling; dietary, exercise, stress, treatment, and preanalytic factors can influence results. A convincing mediation study would require temporally ordered measures, prespecified biomarker hypotheses, validated neuropsychological or depression outcomes, and appropriately controlled comparisons. This mechanistic restraint avoids interpreting correlation as biochemical causation (Tardy et al., 2020; Zhao et al., 2024).

Strength of Evidence and Contradictions

The evidence hierarchy in this review reveals a productive contradiction. Randomized iron trials in children and COSMOS multivitamin trials in older adults show selected benefits, yet prenatal multiple-micronutrient trials do not consistently reproduce clinically meaningful cognitive improvements; similarly, observational nutrient-depression associations do not guarantee benefit from supplementation in perinatal randomized studies (Gutema et al., 2023; Vyas et al., 2024; Sudfeld et al., 2022; Tsai et al., 2023). This heterogeneity is not merely a limitation but a reason to frame nutrient status, life stage, formulation, and outcome as potential effect modifiers. For magnesium specifically, a meta-analysis of seven randomized trials (325 participants) in adults with depressive disorders reported reduced depression scores with supplementation, while cautioning that larger high-quality trials are needed (Moabedi et al., 2023). This signal should not be conflated with the lack of a clear pooled mineral effect in the narrower perinatal population analyzed by Tsai et al. (2023). Contrasting evidence by clinical context is more informative than choosing only the positive result.

Evidence Appraisal and the Novelty of the Integrative Model

Across the included evidence, the strongest support concerns defined interventions and populations: iron supplementation for selected cognitive test domains in schoolchildren, multivitamin-mineral supplementation for cognition in older adults, and selected vitamin D interventions for depressive symptoms in adults (Gutema et al., 2023; Baker et al., 2023; Vyas et al., 2024; Mikola et al., 2023). The remaining pathway and nutrient-status associations support plausibility but do not prove additive or synergistic treatment effects. The novel contribution is this explicit mechanism-to-outcome evidence map and its proposed factorial evaluation, not the discovery of a previously unrecognized biochemical pathway.

Table 1. Evidence contrasts informing the proposed life-course micronutrient model

Population / evidence	Observed clinical finding	Inference for synergy
Schoolchildren: iron RCT synthesis	Selected cognitive tests improved; academic achievement did not (Gutema et al., 2023)	Nutrient-specific benefit; no interaction test
Older adults: COSMOS RCTs	Multivitamin-mineral associated with improved cognition (Baker et al., 2023; Vyas et al., 2024)	Whole-formulation benefit; contributors not isolated
Adults: Mg + vitamin D RCT	Combination better than vitamin D alone in a small long-COVID sample (Rodríguez-Morán et al., 2024)	Incremental benefit, not factorial synergy
Perinatal mental health: RCT meta-analysis	No conclusive mineral benefit; postpartum vitamin D signal (Tsai et al., 2023)	Outcome and population specificity essential
Pregnancy/early childhood: trial and review	No consistent offspring cognitive benefit with prenatal MMN (Sudfeld et al., 2022; William et al., 2025)	Cannot generalize older-adult cognitive findings

Practical Implications

For clinical and community health practice, the most defensible recommendation is to encourage diverse diets and to identify and manage documented deficiencies. In children and

adolescents, iron-related cognitive benefit was observed in trial-based synthesis, but academic achievement was not consistently improved (Gutema et al., 2023; Chen et al., 2022). In older adults, the COSMOS findings justify further study of multivitamin-mineral supplementation for cognitive outcomes (Baker et al., 2023; Vyas et al., 2024), not indiscriminate supplementation for all ages. Appropriate dosage, safety, and indication remain essential.

Adolescent and reproductive-health services provide a relevant translational setting for nutritional assessment and education, especially where iron deficiency, poor diet quality, or psychological distress may coexist. Existing Indonesian health-promotion evidence (Anggriany et al., 2026) suggests an opportunity to integrate nutritional literacy with mental-health screening. However, the adult depression trials and older-adult cognitive trials synthesized here do not establish benefits for pregnant or postpartum populations; maternal outcomes require dedicated studies and clinically appropriate care. A testable translational design would stratify participants by baseline deficiency and assign factorial groups receiving nutrient A, nutrient B, both, or neither, with prespecified cognitive and validated psychiatric scales as endpoints. Biomarkers could include ferritin or hemoglobin for iron status, 25-hydroxyvitamin D, zinc or magnesium indices where appropriate, and exploratory measures of inflammatory signaling and BDNF. Comparing joint and separate intervention effects would distinguish genuine synergy from simple co-treatment, while accounting for interaction risks and adherence (Sarris et al., 2022).

Taken together, the evidence supports an integrative assessment of dietary adequacy and deficiency correction, rather than a generalized efficacy claim for micronutrient cocktails. The proposed pathway-based model links clinically measured outcomes to physiological mechanisms and identifies where evidence is experimental, observational, or randomized. This distinction is the primary novelty of the narrative synthesis and provides explicit hypotheses for future research.

Novelty: A Testable, Life-Course Mechanism-to-Outcome Framework

The original aspect of this narrative synthesis is the explicit alignment of four elements: (1) a defined physiological pathway; (2) baseline biomarker status or deficiency; (3) a population- and life-stage-specific functional outcome; and (4) the experimental comparison needed to evaluate a hypothesized interaction. Rather than presenting all micronutrients as mutually beneficial by default, the framework distinguishes observed randomized effects, observational correlations, and mechanistic propositions. It also captures why a treatment can be biologically plausible yet clinically ineffective in a different population.

This model yields falsifiable hypotheses. For a two-nutrient 2 × 2 factorial trial, the prespecified interaction contrast is [mean outcome under A+B − mean under A only] − [mean under B only − mean under neither]; a confidence interval excluding zero on the chosen scale would provide statistical evidence of interaction. Clinical synergy requires that the direction and magnitude of interaction also be clinically meaningful. Separate analyses are needed for participants with documented deficiency versus adequate baseline status, and for cognitive performance versus depressive symptom scores. In a maternal-health application, antenatal iron status and postpartum 25-hydroxyvitamin D could be characterized where clinically indicated, but research must distinguish standard-of-care supplementation from any additional intervention and avoid withholding essential treatment. Predefined maternal outcomes could include validated depression and anxiety scales, while longer-term offspring studies could use age-appropriate standardized cognitive tasks. Such designs connect molecular hypotheses to midwifery endpoints and establish a clearer research agenda than broad claims that multivitamin combinations invariably outperform single nutrients (Tsai et al., 2023; William et al., 2025).

CONCLUSION

The available evidence supports nutrient-specific and population-dependent effects rather than an unqualified benefit of all micronutrient combinations. Meta-analyses of iron trials report improved

selected cognitive domains in schoolchildren; multivitamin-mineral trials show favorable cognitive results in older adults; and selected vitamin D or magnesium interventions may reduce depressive symptoms in particular adult settings. By contrast, prenatal multiple-micronutrient trials have yielded inconsistent child cognitive outcomes, and randomized studies of perinatal depression do not support all mineral interventions (Gutema et al., 2023; Vyas et al., 2024; Tsai et al., 2023; Sudfeld et al., 2022; William et al., 2025).

This review proposes a life-course mechanism-to-outcome model that distinguishes functional convergence from statistically demonstrated synergy. Although micronutrients share pathways involving energy metabolism, neurotransmission, immune signaling, and neuroplasticity, no generalized claim that combined supplementation is clinically superior to individual nutrients can be justified without trials that isolate the components and explicitly test interaction. Its novelty lies in the transparent alignment of proposed molecular mechanisms, clinical evidence, and an experimentally testable synergy definition.

Practical recommendations prioritize diverse diets, appropriate assessment and treatment of clinically relevant deficiencies, and standard mental-health care where indicated. In pregnancy and postpartum practice, supplementation should follow established obstetric guidance rather than untested strategies to optimize a child's intelligence or to replace therapy for maternal depression. Future trials should prespecify age, baseline nutritional status, factorial comparisons, validated outcomes, and clinically meaningful interaction thresholds.

References

Anggriany, N., Fajriani, L. N., Sukanty, N. M. W., Anisah, A., Isasih, W. D., Ardian, J., & Saputra, I. P. B. A. (2026). Kesehatan Fisik dan Mental Remaja: Hubungan Status Gizi dan Tingkat Stres Di Sekolah Menengah Kejuruan. Bakti Sekawan: Jurnal Pengabdian Masyarakat, 6(1), 79–85. https://doi.org/10.35746/bakwan.v6i1.931

Baker, L. D., Manson, J. E., Rapp, S. R., Sesso, H. D., Gaussoin, S. A., Shumaker, S. A., & Espeland, M. A. (2023). Effects of cocoa extract and a multivitamin on cognitive function: A randomized clinical trial. Alzheimer's & Dementia, 19(4), 1308–1319. https://doi.org/10.1002/alz.12767

Biromo, A. R., Santoso, A. H., Destra, E., Setia, N., & Anthony, L. (2025). Peran Edukasi Konsumsi Magnesium dan Instrumen DASS-42 untuk Deteksi Dini dan Pencegahan Terjadinya Gangguan Psikologis di Cengkareng. Jurnal Pengabdian Sosial, 2(9), 4274–4279. https://doi.org/10.59837/4b11xe94

Borges-Vieira, J. G., & Cardoso, C. K. S. (2023). Efficacy of B-vitamins and vitamin D therapy in improving depressive and anxiety disorders: A systematic review of randomized controlled trials. Nutritional Neuroscience, 26(3), 187–207. https://doi.org/10.1080/1028415X.2022.2031494

Chen, Z., Yang, H., Wang, D., Sudfeld, C. R., Zhao, A., Xin, Y., Chen, J. C., Fawzi, W. W., Xing, Y., & Li, Z. (2022). Effect of oral iron supplementation on cognitive function among children and adolescents in low- and middle-income countries: A systematic review and meta-analysis. Nutrients, 14(24), 5332. https://doi.org/10.3390/nu14245332

Gutema, B. T., Sorrie, M. B., Megersa, N. D., Yesera, G. E., Yeshitila, Y. G., Pauwels, N. S., De Henauw, S., & Abbeddou, S. (2023). Effects of iron supplementation on cognitive development in school-age children: Systematic review and meta-analysis. PLOS ONE, 18(6), e0287703. https://doi.org/10.1371/journal.pone.0287703

Hajhashemy, Z., Shirani, F., & Askari, G. (2025). Dietary magnesium intake in relation to depression in adults: A GRADE-assessed systematic review and dose-response meta-analysis of epidemiologic studies. Nutrition Reviews, 83(2), 217–229. https://doi.org/10.1093/nutrit/nuae056

Isang, M. R., Dinatha, N. M., Maku, K. R. M., Bay, M. S. T., & Wea, M. S. (2024). Pentingnya Gizi Mikro Untuk Anak Usia Dini. Jurnal Edukasi Citra Olahraga, 4(3), 145–152. https://doi.org/10.38048/jor.v4i3.4006

Kirolos, A., Goyheneix, M., Kalmus Eliasz, M., Chisala, M., Lissauer, S., Gladstone, M., & Kerac, M. (2022). Neurodevelopmental, cognitive, behavioural and mental health impairments following childhood malnutrition: A systematic review. BMJ Global Health, 7(7), e009330. https://doi.org/10.1136/bmjgh-2022-009330

Kristy, N. C., & Mahmudiono, T. (2022). Mengoptimalkan asupan zat gizi sebagai upaya preventif dalam mengatasi masalah kesehatan mental: Sebuah tinjauan literatur. Media Gizi Kesmas, 11(2), 548–555. https://doi.org/10.20473/mgk.v11i2.2022.548-555

Mahmudah, A., Dewi, A. D. A., & Mutiasari, D. R. (2026). Hubungan Asupan Vitamin D Dengan Tingkat Depresi Pada Mahasiswa Di Yogyakarta. Borneo Nursing Journal (BNJ), 8(1), 2967–2974. https://doi.org/10.61878/bnj.v8i1.459

Martins, L. B., Braga Tibães, J. R., Sanches, M., Jacka, F., Berk, M., & Teixeira, A. L. (2021). Nutrition-based interventions for mood disorders. Expert Review of Neurotherapeutics, 21(3), 303–315. https://doi.org/10.1080/14737175.2021.1881482

Mikola, T., Marx, W., Lane, M. M., Hockey, M., Loughman, A., Rajapolvi, S., Rocks, T., O'Neil, A., Mischoulon, D., Valkonen-Korhonen, M., Lehto, S. M., & Ruusunen, A. (2023). The effect of vitamin D supplementation on depressive symptoms in adults: A systematic review and meta-analysis of randomized controlled trials. Critical Reviews in Food Science and Nutrition, 63(33), 11784–11801. https://doi.org/10.1080/10408398.2022.2096560

Moabedi, M., Aliakbari, M., Erfanian, S., & Milajerdi, A. (2023). Magnesium supplementation beneficially affects depression in adults with depressive disorder: A systematic review and meta-analysis of randomized clinical trials. Frontiers in Psychiatry, 14, 1333261. https://doi.org/10.3389/fpsyt.2023.1333261

Muscaritoli, M. (2021). The impact of nutrients on mental health and well-being: Insights from the literature. Frontiers in Nutrition, 8, 656290. https://doi.org/10.3389/fnut.2021.656290

Nogueira-de-Almeida, C. A., Gutiérrez, C. A. C., Ramos, L. R., Katz, M., Gonzalez, M. M., Angel Badillo, B., Gómez Santa María, O. A., Reyes Torres, C. A., O'Neill, S., Reyes, M. G., & Mustapic, L. (2025). Role of Micronutrient Supplementation in Promoting Cognitive Healthy Aging in Latin America: Evidence-Based Consensus Statement. Nutrients, 17(15). https://doi.org/10.3390/nu17152545

Puspitasari, D. I., Hardiyanto, D., & Hamardika, N. A. (2021). Asupan zat besi dengan prestasi belajar siswa SMA Muhammadiyah 1 Surakarta. Darussalam Nutrition Journal, 5(2), 121–128. https://doi.org/10.21111/dnj.v5i2.6564

Rodríguez-Morán, M., Guerrero-Romero, F., Barragán-Zuñiga, J., Gamboa-Gómez, C. I., Weyman-Vela, Y., Arce-Quiñones, M., Simental-Mendía, L. E., & Martínez-Aguilar, G. (2024). Combined oral supplementation with magnesium plus vitamin D alleviates mild to moderate depressive symptoms related to long-COVID: An open-label randomized, controlled clinical trial. Magnesium Research, 37(3), 49–57. https://doi.org/10.1684/mrh.2024.0535

Rusdi, F. Y., Helmizar, H., & others. (2025). Peran Vitamin dan Mineral terhadap Status Gizi Bayi: Studi pada Anak Usia 6--11 Bulan di Kota Padang. Jurnal Kesehatan Perintis, 12(1), 33–43. https://doi.org/10.33653/en3m3a94

Sa'diyah, H., Yulia, A. N., & Widayanti, D. M. (2023). Hubungan Antara Status Nutrisi dan Fungsi Kognitif Pada Lansia dengan Penyakit Penyerta Selama Masa Pandemi Covid-19 di Puskesmas Kenjeran Surabaya. Jurnal Keperawatan Dan Kesehatan Masyarakat Cendekia Utama, 12(1), 48–58. https://doi.org/10.31596/jcu.v12i1.1422

Sanjiwani, P. A., Shinta, D., & Fahmida, U. (2020). Asupan zink dan tingkat kecerdasan anak sekolah dasar di Kota Kupang, Nusa Tenggara Timur. Media Gizi Mikro Indonesia, 12(1), 53–62. https://doi.org/10.22435/mgmi.v12i1.1998

Sarris, J., Ravindran, A., Yatham, L. N., Marx, W., Rucklidge, J. J., McIntyre, R. S., Akhondzadeh, S., Benedetti, F., Caneo, C., Cramer, H., Cribb, L., de Manincor, M., Dean, O., Deslandes, A. C., Freeman, M. P., Gangadhar, B., Harvey, B. H., Kasper, S., Lake, J., ... Berk, M. (2022). Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals: The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce. World Journal of Biological Psychiatry, 23(6), 424–455. https://doi.org/10.1080/15622975.2021.2013041

Srifuengfung, M., Srifuengfung, S., Pummangura, C., Pattanaseri, K., Oon-Arom, A., & Srisurapanont, M. (2023). Efficacy and acceptability of vitamin D supplements for depressed patients: A systematic review and meta-analysis of randomized controlled trials. Nutrition, 108, 111968. https://doi.org/10.1016/j.nut.2022.111968

Sudfeld, C. R., Bliznashka, L., Salifou, A., Guindo, O., Soumana, I., Adehossi, I., Langendorf, C., Grais, R. F., & Isanaka, S. (2022). Evaluation of multiple micronutrient supplementation and medium-quantity lipid-based nutrient supplementation in pregnancy on child development in rural Niger: A secondary analysis

of a cluster randomized controlled trial. PLOS Medicine, 19(5), e1003984. https://doi.org/10.1371/journal.pmed.1003984

Suh, S. W., Kim, H. S., Han, J. H., Bae, J. B., Oh, D. J., Han, J. W., & Kim, K. W. (2020). Efficacy of vitamins on cognitive function of non-demented people: A systematic review and meta-analysis. Nutrients, 12(4), 1168. https://doi.org/10.3390/nu12041168

Tardy, A.-L., Pouteau, E., Marquez, D., Yilmaz, C., & Scholey, A. (2020). Vitamins and minerals for energy, fatigue and cognition: A narrative review of the biochemical and clinical evidence. Nutrients, 12(1), 228. https://doi.org/10.3390/nu12010228

Tsai, Z., Shah, N., Tahir, U., Mortaji, N., Owais, S., Perreault, M., & Van Lieshout, R. J. (2023). Dietary interventions for perinatal depression and anxiety: A systematic review and meta-analysis of randomized controlled trials. The American Journal of Clinical Nutrition, 117(6), 1130–1142. https://doi.org/10.1016/j.ajcnut.2023.03.025

Voros, C., Sapantzoglou, I., Athanasiou, D., Mavrogianni, D., Bananis, K., Athanasiou, A., Athanasiou, A., Papadimas, G., Tsimpoukelis, C., Gkirgkinoudis, A., Papapanagiotou, I., Vaitsis, D., Koulakmanidis, A.-M., Ivanidou, S., Stepanyan, A. J., Daskalaki, M. A., Thomakos, N., Theodora, M., Antsaklis, P., ... Daskalakis, G. (2025). Invisible links: Associations between micronutrient deficiencies and postpartum depression—A systematic review. Life, 15(10), 1566. https://doi.org/10.3390/life15101566

Vyas, C. M., Manson, J. E., Sesso, H. D., Cook, N. R., Rist, P. M., Weinberg, A., Moorthy, M. V., Baker, L. D., Espeland, M. A., Yeung, L.-K., Brickman, A. M., & Okereke, O. I. (2024). Effect of multivitamin-mineral supplementation versus placebo on cognitive function: Results from the clinic subcohort of the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized clinical trial and meta-analysis of 3 cognitive studies within COSMOS. American Journal of Clinical Nutrition, 119(3), 692–701. https://doi.org/10.1016/j.ajcnut.2023.12.011

Wang, Z., Zhu, W., Xing, Y., Jia, J., & Tang, Y. (2022). B vitamins and prevention of cognitive decline and incident dementia: A systematic review and meta-analysis. Nutrition Reviews, 80(4), 931–949. https://doi.org/10.1093/nutrit/nuab057

William, A., Lachat, C., Petalios, D., Deshons, A., Hadush, K. T., Broin, M., & Abbeddou, S. (2025). Long-term effects of multiple-micronutrient supplementation during pregnancy, lactation, and early childhood on the cognitive development of children aged 4–14 years: A systematic review of randomized controlled trials. Nutrients, 17(24), 3966. https://doi.org/10.3390/nu17243966

Yanti, N. K. D. C. S., & Susanti, N. M. P. (2024). Potensi Antioksidan dan Neuroprotektif Bunga Telang (Clitoria ternatea L.): Literature Review. Prosiding Workshop Dan Seminar Nasional Farmasi, 3, 435–443. https://doi.org/10.24843/WSNF.2024.v03.p42

Yosaee, S., Clark, C. C. T., Keshtkaran, Z., Ashourpour, M., Keshani, P., & Soltani, S. (2022). Zinc in depression: From development to treatment: A comparative/dose response meta-analysis of observational studies and randomized controlled trials. General Hospital Psychiatry, 74, 110–117. https://doi.org/10.1016/j.genhosppsych.2020.08.001

Yusuf, R. N., & Helmi, H. (2022). Perkembangan Otak dan Fungsi Kognitif Anak: Peran Nutrisi dan Sistem Imun pada Awal Kehidupan. Bioscientist: Jurnal Ilmiah Biologi, 10(2), 1036–1045. https://doi.org/10.33394/bioscientist.v10i2.6289

Zhao, L., Guan, L., Sun, J., & Li, X. (2024). Serum levels of folate, vitamin B6, and vitamin B12 are associated with cognitive impairments in depression patients. Acta Neuropsychiatrica, 36(1), 44–50. https://doi.org/10.1017/neu.2023.41