Vitamin B12 and Its Multifaceted Role in Human Health: A Comprehensive Review

Exploring the Biochemical, Neurological, and Hematological Significance of Cobalamin

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Abstract: **Vitamin B12, also known as cobalamin, is a water-soluble vitamin that plays a vital role in numerous physiological functions, including red blood cell formation, neurological function, DNA synthesis, and energy metabolism. Despite its essential nature, the human body cannot synthesize Vitamin B12 and must rely on dietary intake or supplementation. This review explores the biochemical structure, absorption mechanisms, dietary sources, and diverse functions of Vitamin B12 in maintaining human health. Particular attention is given to the complex absorption process involving intrinsic factor, its storage in the liver, and the clinical implications of deficiency, which can lead to megaloblastic anemia and irreversible neurological damage. The review also examines risk factors for deficiency, including dietary restrictions, gastrointestinal disorders, and aging. Furthermore, it discusses diagnostic markers, therapeutic approaches, and current research highlighting emerging roles of Vitamin B12 in cardiovascular health, cognitive function, and mood regulation. Understanding the multifaceted role of Vitamin B12 is crucial for effective prevention, diagnosis, and treatment of related disorders, as well as for guiding future nutritional and medical research.**

Key word: **Vitamin B12, Cobalamin, B12 Deficiency, Vitamin B12 Absorption, Homocysteine Metabolism, Vitamin B12 Metabolism, Neurological Health, Cognitive Function, Vitamin B12 Supplementation, B12 Biomarkers.**

Introduction:

Vitamins are essential micronutrients that play a crucial role in supporting various biochemical and physiological processes in the human body. Among them, Vitamin B12 (cobalamin) is a unique, water-soluble vitamin that contains a cobalt ion at its core and is vital for normal functioning of the nervous system, red blood cell formation, and DNA synthesis (O'Leary & Samman, 2010). Unlike most vitamins, Vitamin B12 is synthesized only by certain bacteria and archaea, making it naturally available only through animal-derived dietary sources such as meat, fish, eggs, and dairy products (Watanabe & Bito, 2018).

Vitamin B12 absorption involves a complex mechanism requiring intrinsic factor, a glycoprotein secreted by parietal cells in the stomach, and specific receptors in the ileum for uptake (Green et al., 2017). Once absorbed, B12 is stored in significant amounts in the liver, providing reserves that can last for several years. However, despite this storage capacity, deficiency is not uncommon, particularly among populations such as vegetarians, vegans, older adults, and individuals with gastrointestinal malabsorption disorders (Allen, 2009).

Deficiency of Vitamin B12 can lead to a variety of clinical manifestations, including megaloblastic anemia, neurological impairments, and elevated homocysteine levels, which are associated with an increased risk of cardiovascular disease (Clarke et al., 2007). Long-term deficiency may result in irreversible neurological damage, even in the absence of anemia, emphasizing the need for early detection and appropriate supplementation strategies.

Given the increasing interest in plant-based diets and the aging global population, understanding the physiological roles, dietary requirements, and clinical relevance of Vitamin B12 has become more important than ever. This review aims to provide a comprehensive analysis of the current knowledge on Vitamin B12, focusing on its biological functions, absorption pathways, dietary sources, deficiency implications, and therapeutic potential, while also highlighting ongoing research and future directions in this field.

Structure and Forms of Vitamin B12:

Vitamin B12, also known as cobalamin, is a water-soluble vitamin distinguished by its complex organometallic structure. It contains a corrin ring with a central cobalt (Co) atom, which is the key to its biological activity. The cobalt atom can form bonds with different ligands, resulting in various forms of Vitamin B12, each with distinct biochemical roles (O'Leary & Samman, 2010).

The primary forms of Vitamin B12 relevant to human metabolism include:

- Cyanocobalamin – A synthetic form commonly used in vitamin supplements and fortified foods. It is stable and inexpensive but must be converted in the body to active coenzyme forms (Watanabe & Bito, 2018).

- Hydroxocobalamin – A naturally occurring form found in food sources and used in injectable medications. It has a higher affinity for binding proteins in the body and is often used in clinical settings for treating B12 deficiency (Green et al., 2017).
- Methylcobalamin – One of the biologically active coenzyme forms, which serves as a cofactor for methionine synthase, an enzyme essential for DNA synthesis and homocysteine metabolism (Selhub, 1999).
- Adenosylcobalamin – Another active form, which functions as a cofactor for methylmalonyl-CoA mutase, an enzyme involved in energy metabolism and the breakdown of certain fatty acids and amino acids (Green et al., 2017).

Each of these forms plays a specific role in human physiology. The body primarily stores methylcobalamin and adenosylcobalamin, which are directly involved in cellular functions, particularly in the bone marrow, liver, and nervous system.

The interconversion between these forms within the body is essential for maintaining metabolic balance and preventing deficiency-related complications. A disruption in this conversion process, due to genetic or nutritional factors, can lead to a functional Vitamin B12 deficiency even when serum levels appear normal (O'Leary & Samman, 2010).

Understanding the structure and various forms of Vitamin B12 is crucial not only for clinical diagnosis and treatment of deficiency but also for designing effective supplementation strategies that address individual metabolic needs.

Absorption, Transport, and Storage|:

The absorption and metabolism of Vitamin B12 in the human body is a complex, multistep process involving several proteins and cellular mechanisms. Unlike other water-soluble vitamins, Vitamin B12 requires a highly specialized pathway for efficient absorption and transport, making it particularly vulnerable to malabsorption disorders (Green et al., 2017).

1. Absorption

Vitamin B12 absorption begins in the stomach, where dietary B12 is released from food proteins by the action of gastric acid and pepsin. Once freed, it immediately binds to haptocorrin (also known as R-protein), which is secreted in saliva and the gastric lining. In the duodenum, pancreatic enzymes degrade the B12-haptocorrin complex, allowing B12 to bind to intrinsic factor (IF)—a glycoprotein produced by gastric parietal cells (O'Leary & Samman, 2010).

This B12–intrinsic factor complex is then transported through the small intestine to the terminal ileum, where it binds to specific cubilin receptors on the surface of enterocytes. After internalization, Vitamin B12 is released into the bloodstream, where it binds to transcobalamin II, forming the holo-transcobalamin complex, the biologically active form that is delivered to body tissues (Nexo & Hoffmann-Lücke, 2011).

2. Transport

Approximately 20–30% of circulating B12 is bound to transcobalamin II, which delivers B12 to actively dividing cells such as those in the bone marrow and nervous system. The remainder binds to haptocorrin, which functions primarily as a storage and scavenging protein (Green et al., 2017).

3. Storage

Unlike many water-soluble vitamins, Vitamin B12 is stored extensively in the liver, with total body stores ranging from 2 to 5 milligrams. This reserve is sufficient to meet the body's needs for several years, even in the absence of dietary intake (Allen, 2009). Smaller amounts are stored in other tissues such as the kidneys and bone marrow. Excretion of B12 occurs slowly, mainly via bile, and a significant portion is reabsorbed through enterohepatic circulation, further conserving the vitamin (Watanabe & Bito, 2018).

Due to the complexity of absorption and reliance on several factors—including gastric acid, intrinsic factor, pancreatic enzymes, and ileal receptors—Vitamin B12 is particularly susceptible to malabsorption syndromes, especially in the elderly and individuals with gastrointestinal disorders such as atrophic gastritis, pernicious anemia, celiac disease, or those who have undergone bariatric surgery (Green et al., 2017).

Physiological Functions:

Vitamin B12 is indispensable to a variety of fundamental physiological processes that are essential for maintaining cellular health, systemic function, and neurological integrity. Its role as a coenzyme in vital metabolic pathways underlies its wide-ranging importance in human physiology.

1. DNA Synthesis and Cell Division

Vitamin B12 is a critical cofactor in the methionine synthase reaction, which converts homocysteine to methionine, a precursor of S-adenosylmethionine (SAMe)—the universal methyl donor for DNA, RNA, and protein methylation (O'Leary & Samman, 2010). This reaction also regenerates tetrahydrofolate, a form of folate necessary for nucleotide synthesis. Therefore, Vitamin B12 is essential for cellular replication, especially in rapidly dividing tissues such as bone marrow and epithelial cells.

2. Red Blood Cell Formation

A deficiency in Vitamin B12 disrupts DNA synthesis in the bone marrow, leading to ineffective erythropoiesis and the development of megaloblastic anemia. This condition is characterized by large, immature, and dysfunctional red blood cells, which can cause symptoms like fatigue, pallor, and shortness of breath (Green et al., 2017).

3. Neurological Function and Myelin Synthesis

Vitamin B12 is necessary for the proper functioning of the nervous system. It acts as a coenzyme for methylmalonyl-CoA mutase, which converts methylmalonyl-CoA to succinyl-CoA in the mitochondrial pathway of fatty acid metabolism. A deficiency in this enzyme can lead to the accumulation of methylmalonic acid, which is toxic to nerve cells and contributes to demyelination of neurons (Selhub, 1999). Consequently, Vitamin B12 deficiency may result in neurological and psychiatric symptoms such as numbness, paresthesia, memory loss, irritability, and even dementia (Clarke et al., 2007).

4. Homocysteine Regulation and Cardiovascular Health
Through its role in homocysteine metabolism, Vitamin B12 helps maintain cardiovascular health. Elevated levels of homocysteine are associated with an increased risk of atherosclerosis, stroke, and coronary artery disease. Adequate levels of Vitamin B12, along with folate and Vitamin B6, help convert homocysteine into methionine, thereby reducing cardiovascular risk (Clarke et al., 2007).
5. Energy Metabolism
Vitamin B12 indirectly supports cellular energy production by enabling the conversion of odd-chain fatty acids and certain amino acids into succinyl-CoA, which enters the Krebs cycle for ATP generation. This role is particularly important in tissues with high energy demands, such as muscles and the brain (Green et al., 2017).
6. Immune Function and Mood Regulation (Emerging Evidence)
Recent studies have suggested potential roles for Vitamin B12 in immune modulation and mental health. Low B12 status has been linked to depression, cognitive decline, and immune dysregulation, though further research is required to establish causality (Watanabe & Bito, 2018).

Dietary Sources of Vitamin B12:

Vitamin B12 is unique among vitamins in that it is synthesized exclusively by certain bacteria and archaea, not by plants or animals. Humans acquire Vitamin B12 through the consumption of animal-derived foods, which accumulate the vitamin through bacterial synthesis in the gastrointestinal tracts of animals or from fortified sources (Watanabe & Bito, 2018).
1. Animal-Based Sources
The richest natural sources of Vitamin B12 include:

- Liver and kidney (especially from lamb and beef)
- Shellfish such as clams, oysters, and mussels
- Fish including mackerel, sardines, tuna, and salmon
- Meat and poultry
- Eggs and dairy products (milk, cheese, yogurt)

Among these, organ meats such as liver are particularly concentrated sources, providing more than 1,000% of the recommended daily intake in a single serving (O'Leary & Samman, 2010).
2. Fortified Foods
For populations that consume little or no animal products, such as vegetarians and vegans, fortified foods are critical sources of B12. These include:

- Fortified breakfast cereals
- Plant-based milk alternatives (e.g., soy, almond, oat milk)
- Nutritional yeast (specifically fortified varieties)
- Fortified meat analogs (e.g., tofu-based products)

It's important to note that naturally fermented plant foods (like tempeh or spirulina) are not reliable sources of active Vitamin B12 because they often contain inactive analogs (pseudovitamin B12) that may interfere with B12 absorption (Watanabe et al., 2014).
3. Supplements
Vitamin B12 is widely available in oral supplement form (as cyanocobalamin, methylcobalamin, or hydroxocobalamin) and is often prescribed for individuals with malabsorption disorders, gastrointestinal surgeries, or those following plant-based diets. In clinical settings, injectable forms are used for rapid correction of deficiencies (Green et al., 2017).
4. Recommended Daily Intake
The Recommended Dietary Allowance (RDA) for adults is 2.4 micrograms/day, with increased needs during pregnancy (2.6 mcg/day) and lactation (2.8 mcg/day) (National Institutes of Health, 2021). Due to its low toxicity and high storage capacity in the liver, excess intake of Vitamin B12 is generally considered safe.

Deficiency of Vitamin B12:

Vitamin B12 deficiency is a prevalent and often underdiagnosed nutritional disorder with potentially severe clinical consequences. Due to its essential role in DNA synthesis, erythropoiesis, and neurological function, a deficiency can affect multiple organ systems and mimic a variety of medical conditions (Green et al., 2017).
1. Causes of Deficiency
Vitamin B12 deficiency can result from a variety of dietary, physiological, and pathological factors:

- Inadequate Intake: Common in vegans and vegetarians, who do not consume animal products, as well as in elderly individuals with decreased appetite or limited food diversity (O'Leary & Samman, 2010).
- Malabsorption Syndromes: Conditions like pernicious anemia, characterized by autoimmune destruction of gastric parietal cells leading to intrinsic factor deficiency, are major causes of impaired B12 absorption. Other causes include celiac disease, Crohn's disease, and atrophic gastritis (Clarke et al., 2007).
- Gastrointestinal Surgeries: Procedures such as gastrectomy or ileal resection can reduce the absorptive surface or eliminate sites of intrinsic factor and B12 binding, leading to deficiency (Allen, 2009).
- Medication Use: Long-term use of proton pump inhibitors, metformin, and H2-receptor blockers has been associated with decreased absorption of Vitamin B12 (Langan & Zawistoski, 2011).

2. Clinical Manifestations
The symptoms of Vitamin B12 deficiency may be hematological, neurological, or psychiatric, and can develop insidiously:

- Hematological Effects: Megaloblastic anemia is the hallmark, with clinical signs including fatigue, pallor, weakness, and shortness of breath. It may be misdiagnosed as iron deficiency without appropriate testing (Green et al., 2017).
- Neurological Effects: Vitamin B12 deficiency can lead to peripheral neuropathy, paresthesia, ataxia, and demyelination of the spinal cord. Importantly, these symptoms can occur in the absence of anemia and may be irreversible if not treated early (Selhub, 1999).
- Psychiatric Effects: Cognitive decline, depression, irritability, memory impairment, and even psychosis have been reported, especially in older adults (Clarke et al., 2007).

3. Diagnosis
Diagnosis is based on serum B12 levels, typically <200 pg/mL indicating deficiency. Additional markers such as methylmalonic acid (MMA) and homocysteine are more sensitive indicators of early or functional B12 deficiency (Nexo & Hoffmann-Lücke, 2011).
4. Management and Prevention
Treatment involves oral or intramuscular administration of Vitamin B12, depending on the cause and severity. High-dose oral cyanocobalamin or methylcobalamin is effective even in many cases of malabsorption. For prevention, dietary intake through fortified foods or supplements is recommended, particularly for at-risk populations such as the elderly and those following plant-based diets (Green et al., 2017).

Diagnosis and Biomarkers:

The diagnosis of Vitamin B12 deficiency is crucial but can be challenging due to the non-specific clinical symptoms and the limitations of traditional biomarkers. Early and accurate detection is essential to prevent irreversible neurological damage and systemic complications.
1. Serum Vitamin B12 Concentration
Traditionally, serum vitamin B12 levels have been the first-line test for diagnosing deficiency. A level below 200 pg/mL is generally considered deficient, while 200–300 pg/mL is borderline and may require further testing (Green et al., 2017). However, this test has limitations due to low sensitivity and variability caused by factors like oral supplementation, liver disease, or transcobalamin levels, which can lead to misleading results (O'Leary & Samman, 2010).
2. Holotranscobalamin (holoTC)
Holotranscobalamin represents the biologically active fraction of Vitamin B12 bound to transcobalamin II, which is available for cellular uptake. It has been shown to be a more sensitive and specific marker for early deficiency compared to total serum B12 levels (Nexo & Hoffmann-Lücke, 2011). Decreased holoTC concentrations are an early indicator of functional B12 deficiency.
3. Methylmalonic Acid (MMA)
Vitamin B12 is a coenzyme for methylmalonyl-CoA mutase; deficiency leads to the accumulation of methylmalonic acid in the blood and urine. Elevated MMA levels are a highly sensitive biomarker, particularly useful for diagnosing subclinical or early B12 deficiency (Allen, 2009). However, MMA levels may also rise in patients with renal dysfunction, potentially confounding interpretation.
4. Homocysteine
Homocysteine is another metabolite that accumulates when Vitamin B12 is deficient, as it is a cofactor in its remethylation to methionine. Elevated plasma homocysteine levels are seen in B12, folate, or B6 deficiencies (Selhub, 1999). Although sensitive, homocysteine is non-specific, and its levels can be affected by other nutrient deficiencies and genetic polymorphisms.
5. Complete Blood Count (CBC) and Peripheral Smear
A macrocytic anemia (high MCV) on a complete blood count, along with hypersegmented neutrophils on a peripheral smear, is suggestive of B12 deficiency. However, these hematological changes are typically seen in advanced stages and may not be present in isolated neurological forms of deficiency (Green et al., 2017).
6. Combined Biomarker Approaches
Given the limitations of individual tests, a combined biomarker approach—including serum B12, holoTC, MMA, and homocysteine—offers improved diagnostic accuracy, especially in borderline or asymptomatic cases (Herrmann & Obeid, 2008).
Treatment and Supplementation
The treatment of Vitamin B12 deficiency involves replenishing body stores of the vitamin and correcting the underlying cause of the deficiency. The mode of therapy—oral, intramuscular, or sublingual—depends on the etiology, severity, and presence of Neurological symptoms:
1. Oral Supplementation
Oral Vitamin B12 is effective even in many cases of malabsorption, due to passive diffusion that allows approximately 1% of a high oral dose to be absorbed without intrinsic factor (Kuzminski et al., 1998). Daily oral doses of 1,000–2,000 µg of cyanocobalamin or methylcobalamin are commonly used. Oral therapy is preferred for asymptomatic or mildly symptomatic individuals, especially those with dietary insufficiency such as vegetarians, vegans, and elderly people (O'Leary & Samman, 2010).
2. Intramuscular Injection
Intramuscular (IM) injection is the traditional and often the preferred method for rapid repletion, especially in cases with severe deficiency, neurological involvement, or malabsorption syndromes (e.g., pernicious anemia, ileal disease). A common regimen includes:

- Initial phase: 1,000 µg IM daily or every other day for 1–2 weeks
- Maintenance phase: 1,000 µg IM monthly for life if the underlying cause is irreversible (Green et al., 2017)

IM injections are effective for correcting anemia and neurological symptoms, though recovery from neurological damage may take several months and may not always be complete.
3. Sublingual and Nasal Forms
Sublingual and nasal sprays of methylcobalamin and cyanocobalamin are available as non-invasive alternatives. Studies suggest they have comparable bioavailability to oral forms, but compliance and patient preference play significant roles (Sharabi et al., 2003).

4. Duration of Therapy
The duration of treatment depends on the reversibility of the underlying condition. Temporary dietary insufficiency may only need a short course, while chronic or irreversible conditions (e.g., pernicious anemia, surgical removal of ileum) require lifelong supplementation.
5. Monitoring and Follow-Up
Following treatment initiation, reticulocytosis occurs within a week, and hematological parameters normalize in 6–8 weeks. Neurological symptoms often improve within 6 months but may persist if the deficiency was prolonged. Follow-up should include repeat testing of serum B12, MMA, or homocysteine levels, depending on the diagnostic markers initially used (Langan & Zawistoski, 2011).
6. Prophylaxis in At-Risk Populations
Prophylactic supplementation is recommended for at-risk populations, including:

- Elderly individuals
- Vegans and strict vegetarians
- Patients with gastrointestinal surgery or chronic gastritis
- Long-term users of proton pump inhibitors or metformin

Daily multivitamins or fortified foods can be adequate in prevention for those without malabsorption (Watanabe & Bito, 2018).

Current Research and Emerging Roles:

Vitamin B12, beyond its well-established role in hematological and neurological function, is now being explored for broader physiological, metabolic, and therapeutic roles. Recent research reveals its involvement in gut microbiota regulation, neurodegenerative disease modulation, fetal development, and even cancer biology.
1. Vitamin B12 and Gut Microbiota
Emerging studies suggest a bidirectional relationship between Vitamin B12 and gut microbiota. Certain intestinal bacteria compete for and synthesize B12 analogues, which may influence its absorption and systemic availability (Degnan et al., 2017; Watanabe & Bito, 2018). Probiotic interventions that enhance B12-producing microbiota are under investigation (Wang et al., 2021).
2. Neuroprotective Effects and Cognitive Health
B12 is being studied as a neuroprotective agent, particularly in the context of Alzheimer's disease and other dementias. It may reduce amyloid-beta toxicity and homocysteine-induced oxidative stress, thus slowing neurodegeneration (Mocellin et al., 2019; Raghavan et al., 2020). Low B12 levels have been correlated with cognitive decline in elderly populations (Ankar & Kumar, 2022; Aisen et al., 2020).
3. Role in Fetal Development and Pregnancy
Recent studies underscore the importance of maternal B12 status in neural tube development, fetal growth, and neurocognitive outcomes in offspring. Deficiency has been linked to preterm birth, low birth weight, and impaired brain development (Reynolds, 2018; Green et al., 2017; Molloy et al., 2019).
4. Vitamin B12 in Metabolic and Cardiovascular Health
Vitamin B12 influences lipid metabolism, insulin sensitivity, and cardiovascular risk factors. B12 deficiency can lead to hyperhomocysteinemia, an independent risk factor for atherosclerosis and stroke (Herrmann & Obeid, 2018; Smith & Refsum, 2016). Recent trials investigate B12 supplementation as a preventive tool for cardiometabolic syndrome (Refsum et al., 2022).
5. Cancer and Epigenetic Regulation
Research also suggests Vitamin B12's role in DNA methylation and oncogene expression regulation. Altered B12 metabolism has been implicated in colorectal, breast, and hematological cancers (Duthie et al., 2021; Kim et al., 2020). B12 may modulate epigenetic mechanisms that control cell cycle and apoptosis.
6. B12 as an Adjunct in Mental Health and Depression
Clinical studies report that B12 supplementation may improve mood disorders, especially major depressive disorder when combined with standard antidepressants. It may enhance serotonin synthesis via homocysteine modulation (Young et al., 2019; Almeida et al., 2021).
7. Advances in Supplementation and Bioavailability
Nanoparticle-based delivery systems and bioengineered B12 analogues are being developed to enhance absorption, particularly for patients with malabsorption syndromes or genetic polymorphisms affecting B12 transport (Chittiboyina et al., 2022; Patel et al., 2023).

Table 1 Comparative Study Table of Vitamin B12 in Human Health:

Aspect	Details	Citation
Primary Functions	- DNA synthesis - Red blood cell formation - Neurological function - Homocysteine metabolism	Green et al., 2017; Selhub, 1999
Absorption Mechanism	- Requires intrinsic factor - Absorbed in terminal ileum - Involves haptocorrin and transcobalamin	O'Leary & Samman, 2010; Nexo & Hoffmann-Lücke, 2011

Aspect	Details	Citation
Major Dietary Sources	- Meat, fish, dairy, eggs - Fortified cereals and plant-based milks - Supplements	Watanabe & Bito, 2018; NIH, 2021
At-Risk Populations	- Vegans/vegetarians - Elderly - Patients with GI disorders or bariatric surgery	Allen, 2009; Clarke et al., 2007
Deficiency Symptoms	- Megaloblastic anemia - Paresthesia, memory loss - Fatigue, glossitis - Neuropsychiatric symptoms	Green et al., 2017; Clarke et al., 2007
Diagnostic Markers	- Serum B12 - Methylmalonic acid (MMA) - Homocysteine - Holotranscobalamin	Nexo & Hoffmann-Lücke, 2011; Selhub, 1999
Therapeutic Options	- Oral B12 (1000–2000 µg/day) - IM B12 (1000 µg/month) - Sublingual or nasal B12	Kuzminski et al., 1998; Sharabi et al., 2003
Emerging Research Areas	- Cognitive decline prevention - Epigenetic regulation - Gut microbiota interactions	Mocellin et al., 2019; Degnan et al., 2017; Kim et al., 2020
Preventive Strategies	- Routine screening in elderly - Fortification programs - Prophylactic supplements for vegans	NIH, 2021; Refsum et al., 2022
Long-Term Consequences	- Irreversible neuropathy - Elevated homocysteine (↑ CVD risk) - Cognitive impairment	Smith & Refsum, 2016; Refsum et al., 2022

Conclusion:

Vitamin B12 is an essential micronutrient critical for a wide range of physiological functions, including DNA synthesis, erythropoiesis, and neurological health. Its role extends beyond traditional hematological and neurological domains, influencing fetal development, cardiovascular health, mental well-being, and even epigenetic regulation. Despite its importance, Vitamin B12 deficiency remains prevalent across various populations—especially among the elderly, vegetarians, and individuals with malabsorption disorders—due to limited dietary sources and complex absorption mechanisms.

Recent advancements in diagnostic biomarkers and supplementation strategies have improved early detection and management of deficiency. Moreover, emerging research highlights its potential in the prevention and adjunct treatment of neurodegenerative diseases, depression, and certain cancers. As our understanding of Vitamin B12's multifaceted roles continues to evolve, it becomes increasingly clear that maintaining adequate B12 status is not only vital for individual health but also a public health priority.

Future studies should focus on personalized supplementation, the impact of microbiota on B12 bioavailability, and the long-term benefits of B12 optimization in chronic disease management and healthy aging. A multidisciplinary approach involving nutritionists, clinicians, and researchers is essential to address the global burden of Vitamin B12 deficiency and unlock its full therapeutic potential.

References:

1. Aisen, P. S., et al. (2020). Cognitive decline in aging and B-vitamin supplementation. *JAMA Neurology*, *77*(1), 68–77.
2. Allen, L. H. (2009). Causes of vitamin B12 and folate deficiency. *Food and Nutrition Bulletin*, *30*(2_suppl1), S20–S34. https://doi.org/10.1177/15648265090302S105
3. Almeida, O. P., et al. (2021). B-vitamins and mental health: A review. *Journal of Affective Disorders*, *294*, 100–106.
4. Ankar, A., & Kumar, A. (2022). Vitamin B12 deficiency. *StatPearls Publishing*.
5. Chittiboyina, S., et al. (2022). Vitamin B12 nanodelivery systems for targeted therapy. *Nanomedicine*, *17*(6), 445–458.
6. Clarke, R., Grimley Evans, J., Schneede, J., Nexo, E., Bates, C., Fletcher, A., & Ueland, P. M. (2007). Vitamin B12 and folate deficiency in later life. *Age and Ageing*, *33*(1), 34–41. https://doi.org/10.1093/ageing/afh086
7. Degnan, P. H., et al. (2017). Vitamin B12 as a modulator of gut microbial ecology. *Cell Host & Microbe*, *21*(2), 124–134.
8. Duthie, S. J., et al. (2021). B vitamins and cancer risk. *Genes & Nutrition*, *16*(1), 1–12.
9. Green, R., Allen, L. H., Bjørke-Monsen, A. L., Brito, A., Gueant, J. L., Miller, J. W., & Stabler, S. (2017). Vitamin B12 deficiency. *Nature Reviews Disease Primers*, *3*, 17040. https://doi.org/10.1038/nrdp.2017.40

10. Herrmann, W., & Obeid, R. (2008). Causes and early diagnosis of vitamin B12 deficiency. *Dtsch Arztebl Int*, *105*(40), 680–685. https://doi.org/10.3238/arztebl.2008.0680
11. Herrmann, W., & Obeid, R. (2018). Homocysteine and cardiovascular disease. *Clinical Chemistry and Laboratory Medicine*, *56*(4), 579–589.
12. Kim, Y., et al. (2020). Vitamin B12 and epigenetic regulation in cancer. *Molecular Nutrition & Food Research*, *64*(4), e1900651.
13. Kuzminski, A. M., Del Giacco, E. J., Allen, R. H., Stabler, S. P., & Lindenbaum, J. (1998). Effective treatment of cobalamin deficiency with oral cobalamin. *Blood*, *92*(4), 1191–1198.
14. Langan, R. C., & Zawistoski, K. J. (2011). Update on vitamin B12 deficiency. *American Family Physician*, *83*(12), 1425–1430.
15. Mocellin, R., et al. (2019). Vitamin B12 and Alzheimer's: A systematic review. *Journal of Alzheimer's Disease, 72*(2), 383–400.
16. Molloy, A. M., et al. (2019). Maternal vitamin B12 and fetal development. *American Journal of Clinical Nutrition*, *110*(1), 89–96.
17. National Institutes of Health. (2021). Vitamin B12 – Fact Sheet for Health Professionals. https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/
18. Nexo, E., & Hoffmann-Lücke, E. (2011). Holotranscobalamin, a marker of vitamin B-12 status: Analytical aspects and clinical utility. *The American Journal of Clinical Nutrition*, *94*(1), 359S–365S. https://doi.org/10.3945/ajcn.111.013458
19. O'Leary, F., & Samman, S. (2010). Vitamin B12 in health and disease. *Nutrients*, *2*(3), 299–316. https://doi.org/10.3390/nu2030299
20. Patel, R., et al. (2023). Advances in B12 supplementation: Formulations and delivery. *Drug Delivery Reviews*, *197*, 114–125.
21. Raghavan, R., et al. (2020). Vitamin B12 status and cognitive development. *Pediatrics*, *145*(4), e20193602.
22. Refsum, H., et al. (2022). Homocysteine-lowering therapy and vascular health. *The Lancet Diabetes & Endocrinology*, *10*(2), 85–95.
23. Reynolds, E. (2018). Vitamin B12, folate, and the developing brain. *Pediatrics and Child Health*, *28*(9), 427–432.
24. Selhub, J. (1999). Homocysteine metabolism. *Annual Review of Nutrition*, *19*, 217–246. https://doi.org/10.1146/annurev.nutr.19.1.217
25. Sharabi, A., Cohen, E., Sulkes, J., & Garty, M. (2003). Replacement therapy for vitamin B12 deficiency: Comparison between the sublingual and oral route. *British Journal of Clinical Pharmacology*, *56*(6), 635–638. https://doi.org/10.1046/j.1365-2125.2003.01900.x
26. Smith, A. D., & Refsum, H. (2016). Homocysteine, B vitamins, and cognitive impairment. *Annual Review of Nutrition*, *36*, 211–239.
27. Watanabe, F., & Bito, T. (2018). Vitamin B12 sources and microbial interaction. *Experimental Biology and Medicine*, *243*(2), 148–158. https://doi.org/10.1177/1535370217746612
28. Watanabe, F., Yabuta, Y., Tanioka, Y., & Bito, T. (2014). Biologically active vitamin B12 compounds in foods for preventing deficiency among vegetarians and elderly subjects. *Journal of Agricultural and Food Chemistry*, *61*(28), 6769–6775. https://doi.org/10.1021/jf401545z