

# Exploring the Impact of Vitamin B12 Deficiency on Central Nervous System and Cardiovascular Health: A Comprehensive Overview

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## Abstract

Vitamins are organic substances that the body need; it obtains and absorbs them from plants and animals. Cobalamin, another name for vitamin B12, is a substance that belongs to the cobalamin family. Deficiency of cobalamin affects the heart uses energy, causing arrhythmia and enlargement of the left ventricle, demyelination, causing neurological symptoms such as numbness, tingling, and difficulty walking Apathy, anorexia, irritability, growth retardation, and developmental regression. Cardiovascular disease (CVD) is the leading cause of mortality in developed countries. It was determined that B12 is an essential micronutrient for a healthy brain in young people and the elderly. Various conditions are responsible for B12 deficiency. If there is a nutritional shortfall, prompt and appropriate supplementation is required. This supplementation can prevent the damage to nervous system. Deficiency may leads to cognitive decline and vascular risk factors in neuropsychiatric disorders, cardiovascular disease, and heart fail. Some cardiovascular or psychological disorders are related to anxiety, dementia and depression, heart attack which can be improved with B12 supplementation.

**Keywords:** Vitamin B12, Nervous System, Cardiovascular Diseases, Homocysteine.

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## INTRODUCTION

Vitamins are organic substances that the body needs and are outsourced and absorbed through of animal and vegetable. Vitamins can be divided into two categories: fat-soluble (Vitamins A, D, E, and K) and water-soluble (Vitamins B1, B2, B6, Pantothenic acid, Niacin, Biotin, Folic Acid, Vitamin B12, and Vitamin C) [1]. Cobalamin, another name for vitamin B12, is a substance that belongs to the cobalamin family. The liver serves as the body's primary store of adenosyl cobalamin, a water-soluble vitamin that is only produced by microbes and absorbed in the distal ileum. Almost all tissues have a storage capacity of 2 to 5 mg of B12 [2]. Vitamins are commonly used for the prevention of cardiovascular disease (CVD) without clear evidence of benefit or risk. Cardiovascular disease (CVD) is the leading cause of mortality in developed countries [3]. Vitamin B12 is crucial for the production of myelin, a protective sheath around nerves. Deficiency can lead to demyelination, causing neurological symptoms such as numbness, tingling, and difficulty walking [4]. Large

levels of vitamin B12 are stored in the liver after absorption, thus any decrease in vitamin B12 consumption could take 5–10 years to realize clinically [5]. Low levels of vitamin B12 induce substantial cognitive dysfunction if patterns of DNA methylation in redox-related genes and an increased risk of neurodegenerative disorders like dementia and Alzheimer's disease [6]. It disrupts the body's methylation and metabolism of homocysteine (Hcy). Psychiatric symptoms associated with vitamin B12 deficiency have been known for decades. Clinically distinguishable symptoms include slow cerebration, confusion, memory changes, delirium with or without delusions and/or hallucinations, sadness, acute psychotic episodes, and (less frequently) reversible manic and schizophreniform states [7].

Vitamin B12 insufficiency causes about 1% of dementia in the elderly, vegetarians, bariatric surgery patients, and those with gastric malabsorption. However, the sensitivity and specificity of laboratory methods for

diagnosing vitamin B12 deficiency remain challenges [8]. Long-term supplementation is needed to restore normal metabolism in patients with vitamin B12 insufficiency, especially those with restricted vegetarianism [9].

### Vitamin B12 Chemistry

Vitamin B12 is the most complete vitamin biochemically, with a molecular weight of 1.355kDa. Vitamin B12 has a tetrapyrrole ring that surrounds a central cobalt atom, as well as a nucleotide group made up of the base 5,6-dimethylbenzimidazole and phosphorylated ribose esterified with 1-amino, 2-propanol [10].

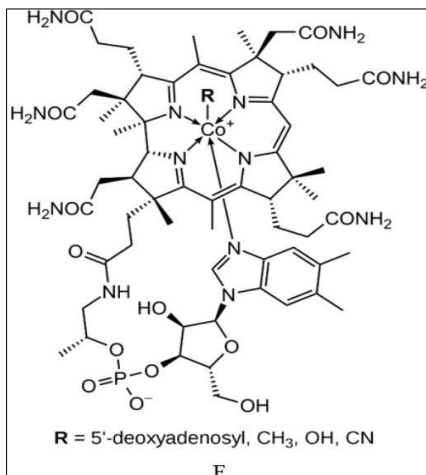


Figure 01: Vitamin B12 Structure [11]

### Absorption and Metabolism Process

Active absorption starts when B-12 is released from food and is bound by salivary transcobalamin-I (haptocorrin), active absorption begins. Histamine, gastrin, and cholinergic stimulation cause the production of both IF and hydrochloric acid by the gastric parietal cells simultaneously [12]. In the stomach, haptocorrin protects vitamin B-12 from acidic breakdown. However, pancreatic trypsin partially breaks down the protein once it reaches the duodenum, promoting its transfer to IF, which is more proteolysis-resistant [13]. The distal ileum is the main site of receptor-mediated, calcium-dependent active transport's absorption of the B-12-IF complex. The complex binds to the cubam receptor, which contains cubilin and receptor-associated proteins.

Haptocorrin protects vitamin B-12 from stomach acidic degradation, but pancreatic trypsin partially degrades it, transferring it to IF, which is resistant to proteolysis [14]. IF enters the ileal enterocyte, degrades in lysosomes, and releases free B-12. Bile excretes B-12 daily, and enterohepatic circulation recycles it. Avoid alcohol and tobacco use for optimal vitamin B12 absorption. Avoid high-fiber meals and avoid medications like nemycin, colchicine, aminosalicic acid, and metformin [15]. Vitamin B12 has low body requirement and efficient circulation. Malabsorption is a common cause of vitamin B12 deficiency, making it essential for patients with malnutrition, the elderly, restricted vegans, depressive disorders, alcoholics, and those with bariatric surgery [16].

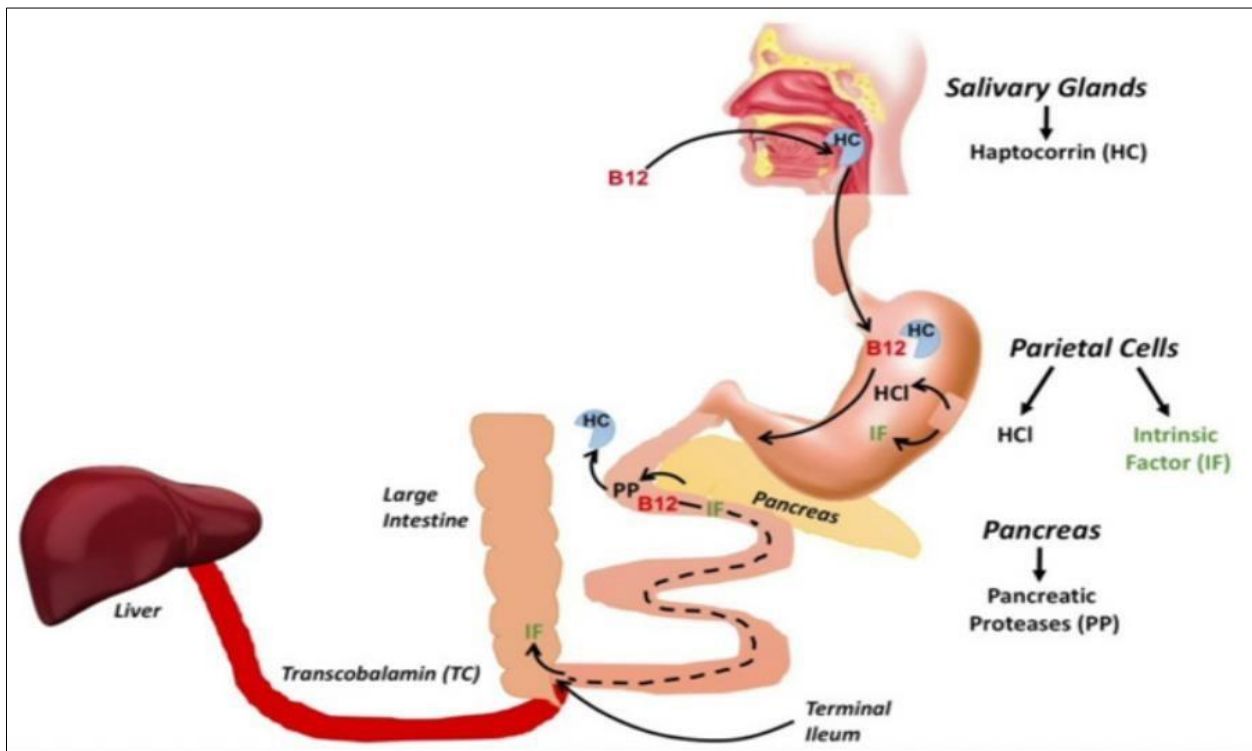


Figure 02: Absorption process [17]

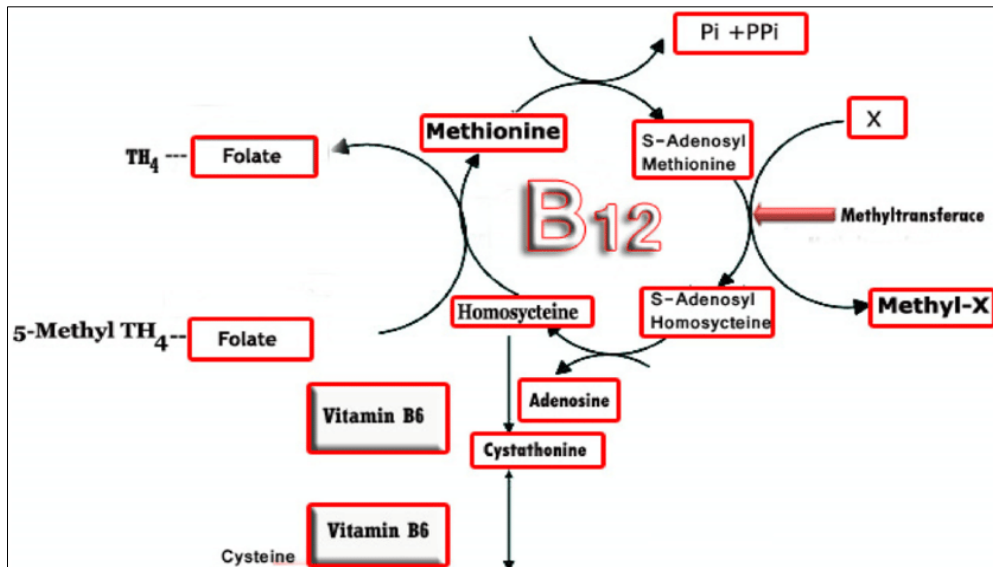


Figure 03: Metabolic pathway of vitamin B 12 [18]

### Vitamin B12 Deficiency Effect on Nervous System and Cause Diseases

Individuals of all ages have psychiatric problems, extreme anxiety, and depression. These individuals are prescribed expensive benzodiazepines, opioids, or psychiatric medications; nevertheless, the true cause is a B12 deficiency [19].

### Myeloneuropathy

Myelopathy symptoms resulting from low B12 concentrations develop slowly, it is classified as subacute combined degeneration. Additionally, it is "combined" as this deterioration causes the development of numerous neurological symptoms [19]. One of the main areas of damage is the spinal column's posterior column. The most crucial component is this one, which gives the brain control over and transmission of sensory data about position, light touch, and vibrations. People experience tingling and numbness due to B12 deficiency causes neurological damage [20].

Since the autonomic nerves pass via the spinal cord, they may also sustain harm. Furthermore, it could also impair smell and vision. Individuals may experience the terminal stages of dementia [21].

### Demyelination

B12 is a cofactor in myelination and has significant immunomodulatory and neurotrophic effects. Both multiple sclerosis (MS) and vitamin B12 deficiency share pathophysiological conditions such as inflammatory and neurodegenerative disorders. Similarities between the MRI appearance and clinical findings, it is highly challenging to distinguish between multiple sclerosis and a B12 deficit. Furthermore, a patient with multiple sclerosis showed a decline in B12 levels [22].

### Hypo-Methylation

Decrease in the availability of S-adenosyl-methionine (SAM), a universal methyl group donor. Methionine synthase is inhibited by a lack of vitamin B12. As a result, methionine synthesis is inhibited, resulting in a decrease in SAM concentration. Vitamin B12 insufficiency causes funicular spinal cord illness (myelosis), which is a common neurological complication. Vitamin B12 deficiency can cause psychiatric and neurological diseases, as well as cognitive difficulties, depression, and dementia, which can occur years before hematological anomalies appear, and sometimes such anomalies do not appear [23].

### Neuropsychiatric Abnormalities

Vitamin B12 insufficiency is linked to psychiatric issues in individuals 40–90 years of age; it rarely affects those younger. Psychiatric symptoms include altered thinking (such as memory loss), sadness, hallucinations, dementia, and delusions [24]. The processes include increased homocysteine and methylmalonic acid (MMA) levels in B12 deficient individuals, as well as unstable neurotransmitter synthesis [25].

### Atrophy or Brain Shrinkage

The loss or shrinkage of cells is referred to as atrophy. In brain atrophy, the brain shrinks relative to its normal size as a result of neurons and their connections wasting away and identified homocysteine (Hcy) increase in plasma as an additional risk factor [26, 27]. The process of converting histone to its metabolites, glutathione and S-adenosyl methionine, requires the cofactor activity of three vitamins. B9 (methyl folate), B12 (cobalamin), and B6 (pyridoxine) are some of these vitamins inadequate intake of B vitamins, decreased remethylation of hydroxycytidine via methionine synthase, and increased hydroxycytidine in plasma [28, 29].

### Peripheral Neuropathy

Prolonged deficiency may lead to peripheral neuropathy, causing pain, tingling, and weakness in the extremities [29].

### Vitamin B12 Deficiency on Cardiovascular Health

Heart failure (HF) is the last stage of cardiovascular illness, characterized by the heart's incapacity to pump blood effectively. Asian continues to have high rates of heart failure (HF)-related death and morbidity [31, 32]. Cobalamin deficiencies are still focused on its relationship with oxidative stress and thermogenesis, such as smoking, hypertension, dyslipidemia, obesity, and diabetes mellitus. One of the risk factors cardiovascular illnesses are dietary intake imbalance. Thus, deficiency in Cobalamin may lead to lack of dietary methyl donors, which will alter the heart metabolism [33-35]. A lack of Cobalamin may also evaluate to an increased plasma Hcy level (Hcy)/hyperhomocysteinemia. The high levels of Hcy have been linked to oxidative stress, dyslipidemia, and atherogenesis. Congestive heart failure (CHF) that is circulating Hcy concentration, it's above the sex-specific median [36].

### Homocysteine and Atherogenesis

Hyperhomocysteinemia, or HHcy, is a condition in which there is an excess of Hcy in the blood, which can lead to endothelial dysfunction, smooth muscle cell proliferation, and cardiovascular remodeling [37]. HHcy additionally causes oxidative stress-induced decreased cardiac O<sub>2</sub> consumption, which can result in the heart metabolic illness. Vitamin B12 is involved in the metabolism of homocysteine. Deficiency can lead to elevated levels of homocysteine, which is associated with an increased risk of cardiovascular diseases [38].

### Atherosclerosis

High levels of homocysteine, which can result from B12 deficiency, contribute to the development of atherosclerosis. Atherosclerosis is characterized by the accumulation of fatty deposits (plaques) on the inner walls of arteries, leading to vessel narrowing and reduced blood flow. This condition is a major risk factor for heart disease [39].

### Increased Thrombosis Risk & Coronary Heart Disease

Elevated homocysteine levels may contribute to an increased risk of blood clot formation (thrombosis). This can further exacerbate the risk of heart attacks and strokes. Nitric oxide molecule that helps dilates blood vessels, improve blood flow, and regulate blood pressure [40]. B12 deficiency can impair no synthesis, potentially contributing to hypertension and other cardiovascular problems. Coronary artery disease (CAD), also known as coronary heart disease or ischemic heart disease, is a condition in which the blood vessels supplying the heart muscle (coronary arteries) become narrowed or blocked

and as a result in reduced blood flow to the heart muscle, leading to various cardiovascular problems [41, 42]. Deficiency of vitamin B12 can lead to anemia and neurological symptoms, heart diseases such as coronary artery disease (CAD). Coronary artery disease can include chest pain (angina), shortness of breath, fatigue, and, in severe cases, heart attacks [43].

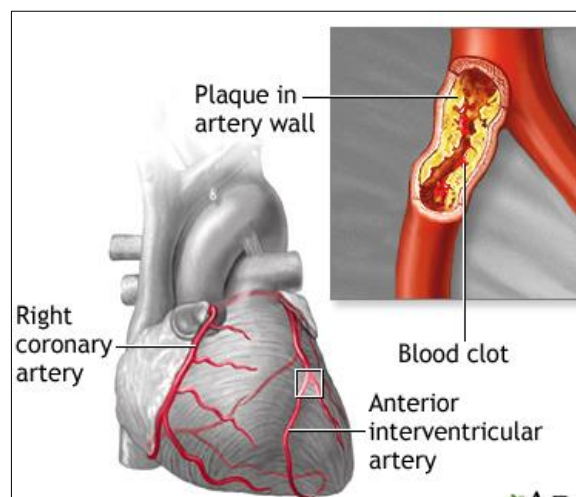


Figure 04: Coronary cardiovascular disease [42]

### Serum Value of Vitamin B12

Vitamin B12 deficiency in patients can be easily missed when total serum vitamin B12 is the only status indicator. Functional biomarkers, homocysteine and MMA, to determine the serum value of vitamin B12 deficiency. Elevated MMA and/or homocysteine results may help establish a potential diagnosis of deficiency, particularly in those with borderline vitamin B12 levels (140-300 pmol/L). Vitamin B12's function in our bodies can explain how these indicators may show cobalamin insufficiency [44].

In two enzymatic processes, vitamin B12 is a crucial cofactor, preventing enzymes from working properly and causing substrate buildup [45, 46]. If the function of methylmalonyl-Coenzyme A (CoA) mutase is compromised, elevated levels of methylmalonyl-CoA and MMA will result. High MMA and homocysteine levels in vitamin B12 deficient patients remain uncertain, and MMA levels are higher in those with compromised renal function. Epidemiological studies show only 73% of low serum vitamin B12 levels have elevated MMA and homocysteine levels and normal amounts of MMA can be measured even in extremely low levels [47, 48].

### Clinical Manifestation

Vitamin B12 deficiency is a common condition in the elderly that gets worse over time with age. The appearance of clinical symptoms, and associated complications of causing a chronic deficiency of vitamin B12, which, if maintained for a long time, can lead to irreversible neuropsychiatric manifestations, is a very relevant factor that potentiates problems arising from its

deficiency [49]. Clinical symptoms may not appear for up to 10 years after the onset of the insufficiency due to the significant hepatic storage of vitamin B12 [50]. Vitamin B12 deficiency can cause abnormal erythropoiesis, leading to decreased haptoglobin levels, increased lactate dehydrogenase, and elevated reticulocyte count. Patients may also experience neurological symptoms of mental illness and cognitive disorders [51].

Clinical manifestations range from mild to severe, with severe forms causing subacute combined spinal cord degeneration. Neurological abnormalities are present in 75-90% of patients with clinically meaningful vitamin B12 deficiency [52]. Vitamin B12 deficiency leads to low platelet count, decreased haemoglobin, megaloblastic anemia, and brain damage. It also causes memory deficits, cognitive dysfunction, dementia, and depressive disorders.

Research has shown that vitamin B12 deficiency can cause neurological impairment in both adults and children. Infants born to mothers with vitamin B12 deficiency may experience impaired psychomotor function and brain development [53]. Additionally, vitamin B12 deficiency increases plasma homocysteine concentrations, a condition known as Hyperhomocysteinemia, an independent risk factor for atherosclerosis. Homocysteine-induced endothelial cell injury resulted in arteriosclerosis via platelet-mediated intimal proliferation of smooth muscle cells, which is considered a marker of degenerative diseases in the brain and cardiovascular [54].

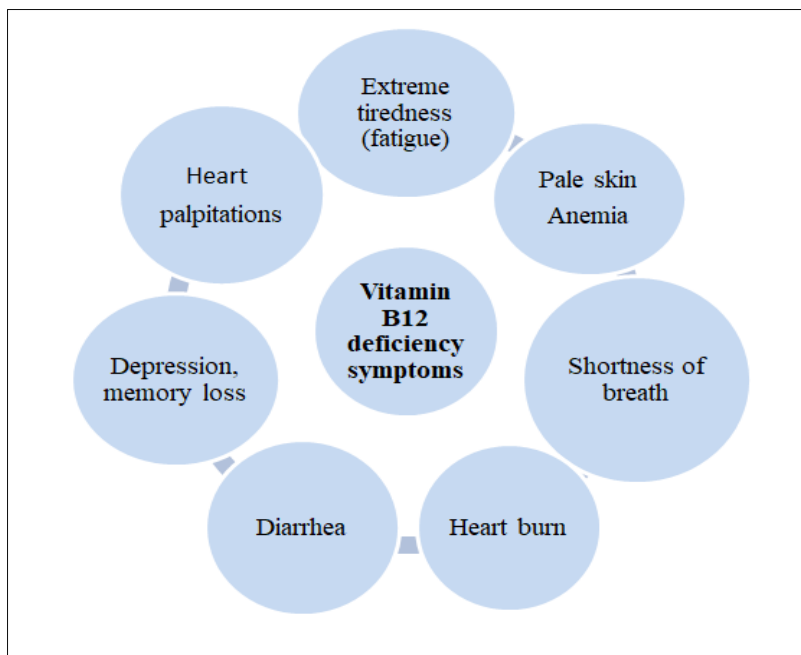
**Causes of Vitamin B12 Deficiency**

Vitamin B12 deficiency can occur for various reasons, and it is essential for several bodily functions, including the production of red blood cells and the maintenance of the nervous system [55].

**Table 1**

Causes	References
Inadequate Dietary Intake: Vitamin B12 is primarily found in animal products such as meat, fish, eggs, and dairy. Vegetarians and vegans do not consume these sources are at a higher risk of B12 deficiency.	[56, 57]
Gastritis: Gastritis is inflammation of the stomach lining, and it’s a common cause of vitamin B12 deficiency. It can cause vitamin B12 deficiency due to a lack of hydrochloric acid in your stomach, which is needed for vitamin B12 absorption	[58]
Pernicious anemia: Pernicious anemias, a rare medical condition, are not able to make intrinsic factor, a protein made by your stomach.	[59, 60]
Digestive diseases: Diseases that affect the digestive system, like Crohn’s disease and celiac disease, can prevent your body from fully absorbing vitamin B12.	[61]
Alcohol use disorder: This condition can damage your digestive system and cause vitamin B12 deficiency.	[62]

**Vitamin B12 Deficiency Symptoms**



**Figure 05: Deficiency Symptoms [43, 60]**

### Treatment of Vitamin B12 Deficiency

Supplementation with B12 is conducted to treat deficiency either orally (if vegan diet) or parenterally (if atrophy gastritis) Vitamin B12 intramuscular injections

(a shot that goes into the muscle). Vitamin B12 nasal gel, and nasal spray is also used for treatment. Monitoring is necessary with treatment, and cognition should return to normal [63].

**Table 2: Age wise requirement of vitamin B12 in humans [64]**

Age	Requirement per day
0–6 months	0.4
7–12 months	0.5
1–3 years	0.9
4–8 years	1.2
9–13	1.8
14 years and older man	2.4
14 years and older women	2.4
Pregnant women	2.6
Breast feeding women	2.8

### CONCLUSION

Vitamin B12, also known as cyanocobalamin, is crucial for the human body, playing a role in metabolic pathways, neurotrophic functions, and red blood cell maturation. Cardiovascular disease (CVD) is the leading cause of mortality in developed countries. Deficiency of vitamin B12 can lead to health issues such as anemia, cardiovascular disorders, and cognitive degeneration.

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