Vitamin B_{12} deficiency in the elderly: is it worth screening?

CW Wong *

ABSTRACT

Vitamin B_{12} deficiency is common among the elderly. Elderly people are particularly at risk of vitamin B_{12} deficiency because of the high prevalence of atrophic gastritis–associated food-cobalamin (vitamin B_{12}) malabsorption, and the increasing prevalence of pernicious anaemia with advancing age. The deficiency most often goes unrecognised because the clinical manifestations are highly variable, often subtle and non-specific, but if left undiagnosed the consequences can be serious. Diagnosis of vitamin B_{12} deficiency, however, is not straightforward as laboratory tests have certain limitations. Setting a cut-off level to define serum vitamin B_{12} deficiency is difficult; though homocysteine and methylmalonic acid are more sensitive for vitamin B_{12} deficiency, it may give false result in some conditions and the reference intervals are not standardised. At present, there is no consensus or guideline for diagnosis of this deficiency. It is most often based on the clinical symptoms together with laboratory assessment (low serum vitamin B_{12} level and elevated serum homocysteine or methylmalonic acid level) and the response to treatment to make definitive diagnosis. Treatment and replacement with oral vitamin B_{12} can be as effective as parenteral administration even in patients with pernicious anaemia. The suggested oral vitamin B_{12} dose is 1 mg daily for a month, and then maintenance dose of 125 to 250 μg for patients with dietary insufficiency and 1 mg daily for those with pernicious anaemia. Vitamin B_{12} replacement is safe and without side-effects, but prompt treatment is required to reverse the damage before it becomes extensive or irreversible. At present, there is no recommendation for mass screening for vitamin B_{12} in the elderly. Nevertheless, the higher prevalence with age, increasing risk of vitamin B_{12} deficiency in the elderly, symptoms being difficult to recognise, and availability of safe treatment options make screening a favourable option. However, the unavailability of reliable diagnostic tool or gold standard test makes screening difficult to carry out.

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CW Wong *, FHKCP, FHKAM (Medicine)

Department of Medicine and Geriatrics, Caritas Medical Centre, Shamshuipo, Hong Kong

* Corresponding author: chitwaiwong@hotmail.com

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Introduction

Vitamin B_{12} deficiency is a common condition affecting the elderly and tends to increase with age. Acquirement of vitamin B_{12} into our body for cell metabolism involves dietary intake of vitamin B_{12}–enriched foods and the absorption of vitamin B_{12} into our body for utilisation. The main dietary sources of vitamin B_{12} are animal products because animals obtain vitamin B_{12} through microbial symbiosis. The subsequent release of vitamin B_{12} from food for absorption into the body is complex and requires intact function of stomach, pancreas, and ileum. Pathophysiological changes, multiple co-morbidities, coupled with multiple drug intake, and increasing dependency associated with ageing can lead to malnutrition due to inadequate intake and malabsorption of vitamin B_{12}, resulting in deficiency. Vitamin B_{12} is essential for the normal metabolism and functioning of all cells in the body. Vitamin B_{12} deficiency can pose significant adverse effects to organ systems with high cell turnover and metabolism like the bone marrow, gastro-intestinal tract, and brain. Fortunately, vitamin B_{12} deficiency can be readily treated by vitamin B_{12} replacement. Nevertheless, prompt diagnosis and treatment are required to prevent extensive and irreversible damage to the body.

Prevalence of vitamin B_{12} deficiency among the elderly

In general, vitamin B_{12} level declines with age and therefore prevalence of vitamin B_{12} deficiency increases with age.[1] Studies have shown that prevalence of vitamin B_{12} deficiency among elderly can range between 5% and 40% depending on the definition of vitamin B_{12} deficiency used.[1-7] Many studies have used serum vitamin B_{12} level with or without additional tests for its metabolites like homocysteine and methylmalonic acid (MMA) to estimate the prevalence of vitamin B_{12} in the population. The most frequent serum vitamin B_{12} cut-off to diagnose vitamin B_{12} deficiency is 150 pmol/L (203 pg/mL). Using this serum vitamin

老年人的維生素B_{12}缺乏症：是否值得篩檢？

王哲慧

老年人中有維生素B_{12}缺乏症的情況相當普遍。由於老年人經常患有萎縮性胃炎，以致未能從食物中吸收足夠的鈷胺素（即維生素B_{12}），加上年紀愈大愈容易患有惡性貧血病，因此老年人出現維生素B_{12}缺乏的風險較高。這種缺乏症的病徵並不明顯，臨床表現高度變異，症狀對此病的診斷特異性亦不強，所以維生素B_{12}缺乏症很容易會被忽視。但假如未能及時確診，後果可能很嚴重。實驗室的化驗測試有其局限性，所以單靠化驗來診斷維生素B_{12}缺乏症未必可行。事實上，為血清維生素B_{12}缺乏症制定其截取值很難。儘管可以利用高半胱氨酸和甲基丙二酸水平測定維生素B_{12}缺乏症，可惜在某些情況下可能有假陽性的結果出現，而且其參考水平仍未有任何標準。目前對於維生素B_{12}缺乏症尚未有任何診斷指南或共識。一般基於臨床症狀與血清維生素B_{12}的實驗室評估（低血清維生素B_{12}水平以及高半胱氨酸和甲基丙二酸水平上升）及病人對治療的反應來確診。就算對於患有惡性貧血的病人來說，口服維生素B_{12}的效用可媲美腸胃外給藥。建議維生素B_{12}缺乏症患者連續一個月每日服用1毫克的劑量；對於日常飲食未能獲得足夠維生素B_{12}的患者，之後的維持劑量可為每日125至250微克，或者對於患有惡性貧血的患者，維持劑量可為每日1毫克。維生素B_{12}替代療法安全，且無副作用。在維生素B_{12}缺乏症未造成廣泛或不可逆轉的境況前，應及早治療。目前尚未有對老年人作維生素B_{12}缺乏症的大規模篩查的建議。然而，由於此症的發病率會隨着年齡增長而有增高的趨勢，加上老年人風險較高，單憑症狀難以作出診斷，而目前已有安全的治療方案，這一切都顯示維生素B_{12}缺乏症的篩檢是一項有利的選擇，然而現時缺乏可靠的診斷工具或黃金標準測試令篩檢難以施行。

B_{12} cut-off alone, the prevalence of vitamin B_{12} deficiency is estimated to be in the range of 5% to 15%.[3-6] However, when higher serum vitamin B_{12} cut-off at 258 pmol/L (350 pg/mL) or using elevated serum homocysteine or MMA level in addition to a low or low-to-normal serum vitamin B_{12} level to diagnose vitamin B_{12} deficiency, the prevalence of deficiency increases to 40.5%.[1,3] Also, the prevalence of vitamin B_{12} deficiency appears to increase with age among the elderly population.[4,5] Furthermore, reports have indicated that institutionalised elderly with multiple co-morbidities and with increasing dependency are more prone to vitamin B_{12} deficiency than non-institutionalised (free-living) elderly. In such individuals, the prevalence of vitamin B_{12} deficiency has been reported to reach 30% to 40%.[8,9] In our unpublished study on 2096 institutionalised elderly residents aged >65 years, the prevalence of serum vitamin B_{12} level of <150 pmol/L was 34.9%, whilst in another local study conducted on non-institutionalised (free-living) elderly residents aged over 70 years, the prevalence of vitamin B_{12} level of <140 pmol/L was only 6.6%.[7]

Diagnosis of vitamin B_{12} deficiency

There is no precise or 'gold standard' test to diagnose vitamin B_{12} deficiency. The diagnosis is usually based on identifying a low level of serum vitamin B_{12} with clinical evidence of deficiency, which responds to vitamin B_{12} replacement therapy. When there is a clinical suspicion of vitamin B_{12} deficiency, the initial laboratory assessment includes serum vitamin B_{12} levels, complete blood count, and blood film examination.[10-12] Although the blood picture and classical finding of vitamin B_{12} is megaloblastic anaemia, often times this is not seen especially in mild cases of vitamin B_{12} deficiency. The investigations for vitamin B_{12} deficiency are traditionally recommended for patients with macrocytosis, but macrocytosis with or without anaemia is neither specific nor sensitive to confirm the diagnosis.[10-12] The reason for this is that macrocytosis can also be found in other conditions like folate deficiency and myelodysplastic disorders, and up to 84% of cases would be missed if macrocytosis is used as the only parameter to screen for vitamin B_{12} deficiency.[13]

Tests to measure and quantify serum vitamin B_{12} levels in the body are readily available and inexpensive. However, the screening test has some limitations and drawbacks. The main drawback is that there is no universally accepted serum vitamin B_{12} cut-off to define deficiency although the value of <150 pmol/L (200 pg/mL) is often used, and at this serum vitamin B_{12} level or below, metabolites like serum homocysteine, serum and urine MMA, become elevated. The World Health Organization has suggested to use this cut-off to define vitamin B_{12} deficiency since the year 2008.[14] However, some have argued that the cut-off value of 150 pmol/L is too low and inevitably does not reflect a sufficient level of vitamin B_{12} in the body, and more so the clinical symptoms of vitamin B_{12} deficiency like neurological symptoms can occur even if serum vitamin B_{12} is above 150 pmol/L. Thus, a higher cut-off value of 220 to 258 pmol/L (298-350 pg/mL) based on more sensitive indicators of vitamin B_{12} status like elevated serum homocysteine and MMA levels has been suggested.[3,15] It should be noted that not all the vitamin B_{12} circulating in the blood is in metabolically active form and a low serum vitamin B_{12} level is not necessarily equivalent to tissue deficiency. The falsely low vitamin B_{12} level can be related to the disturbance in vitamin B_{12} metabolism but may not be associated with any tissue vitamin B_{12} deficiency. Such situations can occur in people with folate deficiency, multiple myeloma, and transcobalamin I deficiency.[10-12] On the other hand, falsely normal serum vitamin B_{12} level may occur in the presence of liver disease, myeloproliferative disorder, congenital transcobalamin II deficiency, and intestinal bacterial overgrowth.[10-12]

When serum vitamin B_{12} results are normal but still the clinical suspicion of deficiency exists, additional 'confirmatory testing' may help to identify

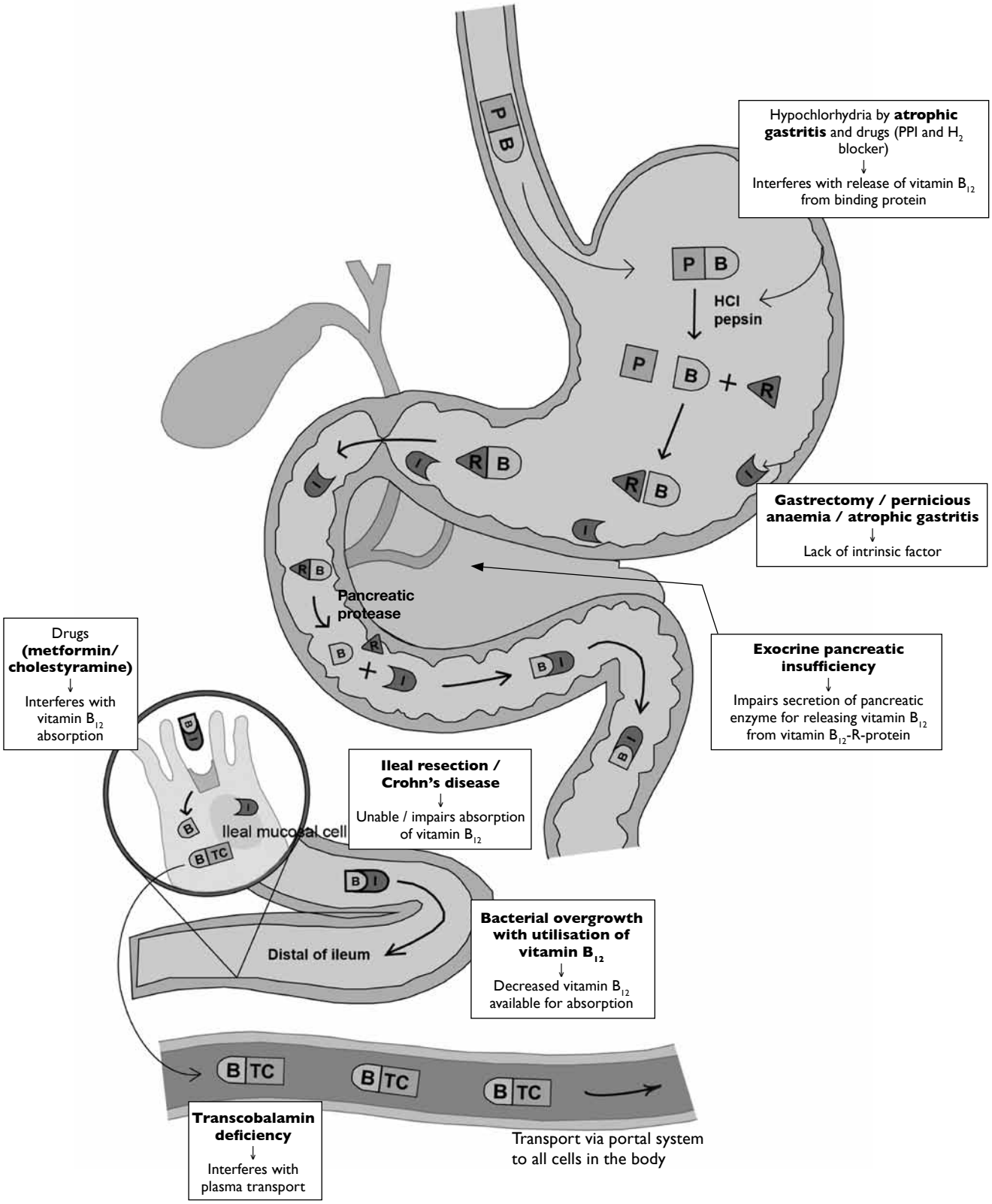

FIG 1. Sites of vitamin B_{12} absorption and causes of deficiency

Abbreviations: B = vitamin B_{12}; HCl = hydrochloric acid; I = intrinsic factor; P = animal protein; PPI = proton pump inhibitor; R = protein; TC = transcobalamin

Adapted from Reference 29, with permission from Prof E Andrès

vitamin B_{12} deficiency. There is compensatory elevation of homocysteine and MMA levels preceding the drop in serum vitamin B_{12} level and these are regarded as more sensitive indicators of vitamin B_{12} deficiency than just low serum vitamin B_{12} level.[11,12,16,17] Elevated serum homocysteine and MMA level (>3 standard deviations above the mean in normal subjects) has a sensitivity of 95.9% and 98.4%, respectively to diagnose vitamin B_{12} deficiency.[16] However, the reference intervals for serum MMA and homocysteine are variable among different laboratories. Serum MMA of 100 to 750 nmol/L, urine MMA of 1 to 4 nmol/L, and serum homocysteine of 6 to 29 μmol/L are the reference ranges for most methods.[10] If the normalisation of elevated serum homocysteine and MMA levels in response to vitamin B_{12} replacement therapy is used as a diagnosis of deficiency, up to 50% of patients may be missed when the diagnosis is based on low vitamin B_{12} level (150 pmol/L) alone.[18,19] Rise in homocysteine level before increase in MMA is an early indicator of vitamin B_{12} deficiency. However, this is less specific than elevated MMA level for vitamin B_{12} deficiency, since such elevated homocysteine levels can occur even in vitamin B_6 and folate deficiency states. Both homocysteine and MMA levels can be elevated in renal insufficiency, hypovolaemia, and inherited metabolic defects.[12] Although elevated homocysteine and MMA levels can aid in the diagnosis of vitamin B_{12} deficiency in people with 'normal' serum vitamin B_{12} levels, there are concerns about these metabolite assays. Some have reported that serum MMA and homocysteine levels increase with age and the prevalence of elevated MMA and homocysteine levels is higher than the prevalence of low vitamin B_{12} or clinically evident vitamin B_{12} deficiency in the elderly.[19-22] In this regard, using the assay for metabolites alone may result in overdiagnosis and overtreatment. The rationale for these findings is uncertain and some have suggested that it may be related to the increased prevalence of subclinical vitamin B_{12} deficiency in the elderly. Moreover, these add to the controversies about whether to use metabolite estimation as the initial test to diagnose vitamin B_{12} deficiency. Besides, other important considerations are that they are more expensive, not readily available, and reference intervals are not standardised. Currently, the initial test for vitamin B_{12} deficiency is to assess serum vitamin B_{12} levels, and only when there is low normal vitamin B_{12} level, metabolite assay is most often suggested.[11,12] However, the consensus for vitamin B_{12} threshold levels for ordering the additional tests has not yet been reached.

In addition to elevation in homocysteine and MMA levels, a decrease in serum holotranscobalamin level is also considered an early marker for vitamin B_{12} deficiency. Holotranscobalamin is composed of vitamin B_{12} attached to a transport protein, transcobalamin II. It is a biologically active fraction of vitamin B_{12} that can be readily taken up by all cells and represents only 6% to 20% of total serum vitamin B_{12}.[23] In vitamin B_{12} deficiency, serum level of holotranscobalamin decreases even before elevation in homocysteine and MMA levels occurs.[24] It has been shown that holotranscobalamin is the most sensitive marker for vitamin B_{12} deficiency, followed by MMA.[23,25] Like homocysteine and MMA, holotranscobalamin cannot be tested in renal patients as its level increases in renal impairment.[23] Furthermore, higher cost and lesser availability than homocysteine and MMA testing make it difficult to acquire wide clinical acceptance.

Causes of vitamin B_{12} deficiency in the elderly

As we know elderly people are particularly at risk of vitamin B_{12} deficiency. The main aetiologies can be divided under two main categories: inadequate dietary intake and impaired absorption of vitamin B_{12} (Table 1).

It is believed that in developed countries, the most common cause for vitamin B_{12} deficiency in the elderly is inadequate dietary intake.[1,15] However, studies have shown that this is far from real. A French study showed that among 172 elderly patients with vitamin B_{12} deficiency, only 2% accounted for inadequate intake,[26] while in a hospital-based Chinese study on 52 patients, only 3.8% (median age, 73.5 years) with megaloblastic anaemia (98% had vitamin B_{12} deficiency) had inadequate dietary intake.[27] However, this can be a problem in strict vegans because animal products are the only dietary source of vitamin B_{12}. Usually, 2 to 3 mg of vitamin B_{12} reserves are stored in the body primarily in the liver, and our daily requirement of vitamin B_{12} is only about 2 to 3 μg. Thus, even with vegan diets, deficiency generally takes several years to develop. According to a local study on 119 older Chinese vegetarian women, the

TABLE 1. Causes of vitamin B_{12} deficiency

Cause	Particulars
Inadequate intake	Alcohol consumption
	Vegetarian diet
Malabsorption	Food vitamin B_{12} malabsorption
	Lack of intrinsic factor or parietal cell • Pernicious anaemia • Atrophic gastritis • Post-gastrectomy
	Ileal malabsorption • Ileal resection • Crohn's disease
	Bacterial overgrowth
Defective transport	Transcobalamin deficiency (genetic)

prevalence of deficiency was 42%.[28] Besides, factors like poor health conditions, especially in those living in institutions, lead to inadequate nutritional intake and vitamin B_{12} deficiency.

Often, vitamin B_{12} deficiency can be seen even among the elderly consuming meat and animal proteins and this is because of malabsorption. Vitamin B_{12} in animal food is bound to a protein, and after ingestion, it is broken down in the stomach by pepsin and hydrochloric acid to release free vitamin B_{12} (Fig 1[29]). The free vitamin B_{12} is then bound to R-protein (transcobalamin I) found in saliva and gastric juice. The vitamin B_{12}-R-protein complex is also secreted in bile from the enterohepatic circulation. These complexes are then degraded by pancreatic enzyme to release free vitamin B_{12} in the duodenum. The free vitamin B_{12} is then bound to intrinsic factor secreted by the gastric parietal cells, and then they travel undisturbed until the distal 80 cm of ileum where they bind to mucosal cell receptors. Subsequently, vitamin B_{12} is carried by transport protein, transcobalamin, via the portal system to all cells in the body for utilisation. About 60% of vitamin B_{12} from food is absorbed through this pathway, and any pathophysiological changes in stomach, pancreas, and intestine result in disturbance of vitamin B_{12} absorption. Food-cobalamin (vitamin B_{12}) malabsorption, first described by Carmel in 1995,[30] is the most common cause of vitamin B_{12} deficiency in the elderly and accounts for about 40% to 70% of cases.[26,29,31] It is characterised by the inability to release vitamin B_{12} from food or from its binding protein and thus, preventing vitamin B_{12} from being taken up by intrinsic factor for absorption. It is defined by vitamin B_{12} deficiency in the presence of sufficient dietary vitamin B_{12} intake, negative Schilling test, and lack of anti-intrinsic factor antibodies.[30] Clinically, it is diagnosed by exclusion of other disorders or factors causing vitamin B_{12} deficiency. It can be corrected simply with oral vitamin B_{12} supplement since free vitamin B_{12} absorption is not affected.[31] Any process that interferes with the release of free vitamin B_{12}, such as decreased production of gastric acid and pepsin for releasing vitamin B_{12} from food, and impaired secretion of pancreatic enzyme for releasing vitamin B_{12} from vitamin B_{12}-R-protein complex, can lead to malabsorption. Atrophic gastritis is the main cause of food-cobalamin malabsorption in the elderly. In the stomach, hypochlorhydria associated with atrophic gastritis interferes with vitamin B_{12} release from the food and causes intestinal bacterial overgrowth to compete for vitamin B_{12} uptake, resulting in a decline in vitamin B_{12} in the body. The prevalence of atrophic gastritis in the elderly ranges from 20% to 50% and generally increases with age.[26,32] According to Framingham Heart Study, the prevalence in age-group of 60 to 69 years was 24% and increased to 37% in people aged >80 years.[33] Chronic *Helicobacter pylori* infection is strongly associated with atrophic gastritis,[34,35] and a study reported that *H pylori* was found in 56% of people with vitamin B_{12} deficiency.[35] Other causes of food-cobalamin malabsorption include long-term consumption of proton pump inhibitors,[36] histamine H_2 blockers,[36] chronic alcohol consumption, gastric bypass surgery, and pancreatic insufficiency in patients with alcohol abuse and cystic fibrosis. Food-cobalamin malabsorption often produces a slow, progressive depletion of vitamin B_{12}. Clinical manifestations tend to be subtle and mild,[2] although progression to more severe form, like pernicious anaemia (PA), can still occur in a minority of patients.[26]

Pernicious anaemia, a result of autoimmune atrophic gastritis (type A atrophic gastritis), is most often diagnosed in the elderly. Earlier studies suggested that PA was restricted to Northern Europeans, but subsequent studies indicate that PA affects virtually all ethnic groups.[37] Pernicious anaemia was considered a classical cause of vitamin B_{12} deficiency before food-cobalamin malabsorption was described, and accounted for 15% to 25% of vitamin B_{12} deficiency in the elderly in studies.[9] In a local study on 296 Chinese patients, definite PA was diagnosed in 61% of patients having megaloblastic anaemia with vitamin B_{12} or folate deficiency.[38] Pernicious anaemia is characterised by destruction of gastric mucosa, especially fundal mucosa, primarily by a cell-mediated mechanism.[39] There is progressive destruction and eventual loss of intrinsic factor producing gastric parietal cells. Moreover, auto-antibodies in gastric juices bind and block the vitamin B_{12}–binding site of intrinsic factor and prevents the uptake of vitamin B_{12}. The end result is gastric atrophy and depletion of intrinsic factor leading to poor absorption of food-bound, free, and biliary vitamin B_{12}.[2] Malabsorption is more complete and severe in PA compared to food-cobalamin malabsorption which is more partial in nature,[2] and so the manifestations are more overt and severe in PA. Two antibodies, anti-parietal cell antibody and anti-intrinsic factor antibody, have been described in PA. Anti-parietal cell antibody is more sensitive (90%) but less specific (50%) for diagnosis of PA as it can also be found in other autoimmune diseases.[29,39] On the other hand, anti-intrinsic factor antibody is less sensitive (50%) but more specific (98%), and its presence is almost diagnostic of PA.[29,39] Schilling test, traditionally used to diagnose intrinsic factor–related malabsorption, is now rarely performed. Although PA is associated with excess risk of gastric carcinoma and gastric carcinoid tumour,[40] the benefit of endoscopic surveillance has still not been established. Once the patient is diagnosed with PA, single endoscopic screening for gastric cancer or carcinoid tumours is recommended, but subsequent

routine endoscopic surveillance recommendation is inconclusive.[41]

In the elderly, long-term use of medications for co-morbidities can interfere or reduce vitamin B_{12} absorption. These include proton pump inhibitors and histamine H_2 blockers, which suppress gastric acid secretion and prevent release of vitamin B_{12} from food.[42] Other drugs like metformin reduces intestinal availability of free calcium ions for vitamin B_{12}–intrinsic factor complex uptake by ileal cell membrane receptors,[43] and cholestyramine interferes with vitamin B_{12} absorption from intestine.[44]

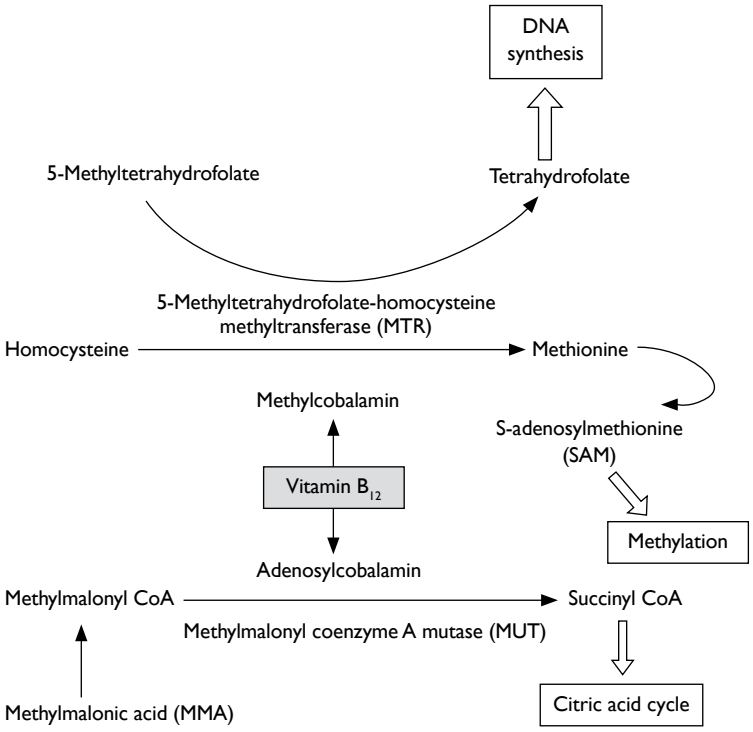

FIG 2. Metabolism of vitamin B_{12}

Clinical manifestations of vitamin B_{12} deficiency

Vitamin B_{12} is essential for metabolism of all cells in our body. In humans, two enzymatic reactions are dependent on vitamin B_{12}—methylmalonyl coenzyme A mutase (MUT) reaction and 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR) reaction (Fig 2). The MUT reaction is an important step in the extraction of energy from protein and fat in the mitochondrial citric acid cycle. In the MTR reaction, vitamin B_{12} and folic acid are required for the conversion of homocysteine to methionine that is important for maintaining the integrity of nervous system. Tetrahydrofolate is also regenerated via the MTR reaction for DNA synthesis. Hence, in vitamin B_{12} deficiency, multi-organ systems can be affected and hence associated with wide spectrum of clinical manifestations. However, clinically overt vitamin B_{12} deficiency with classical feature of macrocytic anaemia and neuropathy is infrequently seen in the elderly.[2] Very often they have mild, subclinical deficiency, which are usually asymptomatic.[2]

Clinical manifestations of vitamin B_{12} deficiency are usually non-specific and are highly variable according to severity or organ systems involved.[9] There is no one clinical feature unique to all patients with vitamin B_{12} deficiency. Non-specific symptoms and signs are loss of appetite, diarrhoea, fatigue and weakness, shortness of breath, low blood pressure, confusion, and change in mental states.[9,29] Classical manifestations include Hunter's glossitis, megaloblastic anaemia, and subacute combined degeneration of spinal cord (Table 2[9]).

TABLE 2. Clinical manifestations of vitamin B_{12} deficiency*

Type	Clinical manifestations
Haematological	Macrocytosis (frequent)
	Isolated thrombocytopenia and neutropenia, pancytopenia (rare)
Neuropsychiatric	Combined degeneration of the cord (classic)
	Peripheral neuropathy (frequency)
	Ataxia
	Optic atrophy (rare)
	Dementia
	Psychosis, depression
Digestive	Hunter's glossitis, angular stomatitis, jaundice, lactate and bilirubin elevation (classic)
Hyperhomocysteinaemia	Cardiovascular and thromboembolic risk

* Adapted from Reference 9

Vitamin B_{12} deficiency and atherosclerotic vascular disease

Hyperhomocysteinaemia, as an independent risk factor for cardiovascular disease, has been receiving increased attention. Elevated homocysteine level is associated with an increased risk for atherosclerotic and thrombotic events.[45] Meta-analysis of 30 studies involving 5073 ischaemic heart disease (IHD) events suggested that elevated homocysteine level was at most a modest independent predictor of IHD and stroke risk in healthy populations, and a 25% reduction in homocysteine levels was associated with 11% and 19% reduction in IHD and stroke, respectively.[46] Another meta-analysis also provided a strong evidence of the causal association between homocysteine and cardiovascular disease, and

showed that lowering homocysteine level by 3 μmol/L could reduce the risk of IHD by 16% and stroke by 24%.[47]

Vitamin B_{12}, folic acid, and vitamin B_6 are required for homocysteine metabolism, and often nutritional deficiency of these vitamins can cause hyperhomocysteinaemia. In contrast to severe hyperhomocysteinaemia associated with genetic disorders, hyperhomocysteinaemia resulted from nutritional deficiency is mild but is still associated with increased risk of atherothrombosis. The proposed mechanism for hyperhomocysteinaemia on inducing endothelial dysfunction and thus atherosclerosis includes homocysteine-induced endoplasmic reticulum stress, oxidative stress, and proinflammatory response.[48] Animal models of hyperhomocysteinaemia have confirmed the causal relationship between hyperhomocysteinaemia and the development of endothelial dysfunction and accelerated atherosclerosis.[48]

Although meta-analyses have shown reduction of cardiovascular risk with reduction of homocysteine levels,[46,47] vitamin supplementation (with vitamin B_6, vitamin B_{12}, and folic acid) to lower homocysteine in the body may not be transformed into clinically beneficial vascular outcomes. In a double-blind, randomised controlled trial of 3680 adults with non-disabling cerebral infarction, subjects who received a combination of vitamin B_6, vitamin B_{12}, and folic acid showed moderate reduction in total homocysteine levels, but there was no effect on vascular outcomes (recurrent ischaemic stroke and coronary heart disease) during 2 years of follow-up.[49] Probably a longer duration of treatment may be necessary or there may be other factors governing the clinical response. Therefore, we need more controlled trials to explore the vascular benefits of vitamin supplementation.

Vitamin B_{12} deficiency and neuropsychiatric illness

Neuropsychiatric manifestations in the absence of haematological abnormalities are commonly seen in the elderly.[2,50] These include paraesthesia, weakness, gait abnormalities, and cognitive or behavioural changes. Although the exact mechanism of how vitamin B_{12} deficiency causes neuropsychiatric disorder is unclear, the disruption of both MUT and MTR vitamin B_{12}–dependent reactions seem to play a role. Vitamin B_{12} deficiency disrupts MUT reaction with accumulation of MMA; MMA is a myelin destabiliser and can affect normal myelin formation. Besides, disruption of MTR reaction leads to insufficient supply of methionine and S-adenosylmethionine (SAM), which is essential for the myelination of myelin sheath, phospholipids and neurotransmitter synthesis, for maintaining brain and nervous system function.[51] Furthermore, high levels of homocysteine due to vitamin B_{12} deficiency are associated with an increased risk of atherosclerotic vascular disease, and this in turn may increase the risk of cognitive impairment or dementia. It has been shown that low serum vitamin B_{12} is associated with a 2- to 4-fold higher risk of cognitive impairment.[50] The prevalence of low serum vitamin B_{12} has been reported to be significantly higher in the people with Alzheimer's disease (AD).[52] However, the causal relationship between vitamin B_{12} deficiency and the development of AD remains controversial. Amyloid deposition and hyperphosphorylation of tau protein are believed to be involved in the mechanism of AD. The SAM-dependent methylation is involved in the regulation of mechanism of presenilin I expression, γ-secretase activity, and thus amyloid levels; SAM is also involved in the regulation of tau phosphorylation.[51] Moreover, hyperhomocysteinaemia has been shown to be associated with a significant increase in amyloid level and amyloid deposition on cortex and hippocampus in mouse models of AD.[53] Overall, vitamin B_{12} deficiency may have implications in the neuropathological process of AD.

Depression is a common psychiatric manifestation of vitamin B_{12} deficiency. Involved in the synthesis of neurotransmitters, SAM may be implicated in mood disorders. In a population-based study of 3884 elderly people, deficiency of vitamin B_{12} was associated with almost 70% more likelihood of having a depressive disorder.[54] In another cross-sectional study of 700 community-dwelling, physically disabled women aged ≥65 years, vitamin B_{12}–deficient women were twice more likely to have severe depressive symptoms.[55] Although controlled studies to show response to vitamin B_{12} replacement therapy in depression are lacking, it is recommended that all patients with vitamin B_{12} deficiency should be managed as part of depression treatment. Psychosis, including delusion and hallucination, has also been reported in vitamin B_{12}–deficient patients. Although the exact mechanism is unknown, vitamin B_{12} replacement even after a prolonged period (at least up to 2 years) has shown good outcomes in patients with psychosis.[56]

Therapeutic management

In general, vitamin B_{12} replacement therapy helps to reverse the haematological abnormalities and psychiatric disorders. However, even after correcting serum vitamin B_{12} and its metabolite levels, or haematological abnormalities, the ability to reverse cognitive impairment (dementia) and neurological disorders is not promising.[50-52] The longer the time the neurological disorder or cognitive impairment presents before treatment, the less likely it can be reversed. It is suggested that prompt correction of deficiency should be done within 6 to 12 months of cognitive impairment in order to obtain maximum

response.[57] Nevertheless, continuous replacement therapy may still help to prevent symptoms from deteriorating. Treatment for subtle or subclinical deficiency is still debatable although prompt diagnosis and treatment might prevent the progress to clinically overt deficiency.

Classical treatment for vitamin B_{12} deficiency is parenteral administration, usually intramuscular injection, to correct the deficiency and build up tissue storage. There are two forms of vitamin B_{12} for parenteral administration: cyanocobalamin and hydroxocobalamin. It is believed that hydroxocobalamin is converted to active enzyme more easily and retained in the body for a longer period of time than cyanocobalamin, and therefore be administered in intervals of 3 months. The regimen for vitamin B_{12} therapy varies across countries and between individual practices. Generally, the schedule for vitamin B_{12} replacement is 1 mg daily for a week or 1 mg 3 times a week for 2 weeks, followed by 1 mg per week for 1 month, and then 1 mg per month as maintenance dose.[9]

Around 1% to 5% of free vitamin B_{12} can be absorbed along the entire intestine by passive diffusion. Oral vitamin B_{12} replacement is theoretically as effective as parenteral administration even in patients with PA or ileal disease, provided that the dosage is high. However, the unpredictable absorption by passive diffusion makes recommendation of a standard dose difficult. A Cochrane review supports the use of high-dose vitamin B_{12} (1 mg and 2 mg daily) in elevating serum vitamin B_{12} level and achieving haematological and neurological responses, even in patients with PA or with ileal resection.[58] The recommendation for oral replacement is 1 mg daily for a month, and then 125 to 250 μg daily as maintenance dose for patients with dietary insufficiency and food-cobalamin malabsorption, while for PA the maintenance dose is 1 mg daily.[29]

Vitamin B_{12} does not have side-effects even when prescribed in large doses.[59] However, hypokalaemia, resulting from uptake of circulating potassium by newly growing and dividing haematopoietic cells, can be severe or sometimes life-threatening. Transient potassium replacement at the initial stage of vitamin B_{12} replacement, especially in those with low-normal serum potassium, can prevent subsequent hypokalaemia.

Correction of risk factors associated with vitamin B_{12} deficiency, like antibiotics for *H pylori* infection and intestinal bacterial overgrowth, stopping or replacing offending medications are also important in the management and prevention of vitamin B_{12} deficiency. Some institutions have even recommended universal vitamin B_{12} supplement for people aged ≥60 years in view of the high prevalence of vitamin B_{12} deficiency among this popualation.[15]

Conclusion

Vitamin B_{12} deficiency is prevalent among the elderly. Elderly people are particularly at risk of deficiency because of the increasing prevalence with increasing age of atrophic gastritis–associated food-cobalamin malabsorption, PA, and due to drug intake for co-morbidities. Symptoms and signs of vitamin B_{12} deficiency are usually vague and unrecognised. Treatment may always be useful to correct clinical abnormalities like vitamin B_{12}–related haematological abnormalities, psychiatric and depressive symptoms. For neurological disease and dementia, prompt vitamin replacement is necessary before it becomes irreversible or permanent. Both oral and parenteral administration of vitamin B_{12} are effective and without untoward side-effects. Overall, we are in support of screening for vitamin B_{12} deficiency in the elderly. However, accurate diagnosis of vitamin B_{12} deficiency remains controversial. To diagnose vitamin B_{12} deficiency, laboratory tests have their limitations, and this makes it difficult to choose a reliable and easily available tool for screening. Although there is no formal recommendation for screening for vitamin B_{12} deficiency in asymptomatic elderly people, the high prevalence, higher risk of deficiency in the elderly, easy and safe treatment availability warrant more liberal testing and vitamin supplementation in the elderly.

References

1. Baik HW, Russell RM. Vitamin B_{12} deficiency in the elderly. Annu Rev Nutr 1999;19:357-77.
2. Carmel R. Current concepts in cobalamin deficiency. Annu Rev Med 2000;51:357-75.
3. Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH. Prevalence of cobalamin deficiency in the Framingham elderly population. Am J Clin Nutr 1994;60:2-11.
4. Clarke R, Refsum H, Birks J, et al. Screening for vitamin B-12 and folate deficiency in older persons. Am J Clin Nutr 2003;77:1241-7.
5. Clarke R, Grimley Evans J, Schneede J, et al. Vitamin B_{12} and folate deficiency in later life. Age Ageing 2004;33:34-41.
6. Loikas S, Koskinen, Irjala K, et al. Vitamin B_{12} deficiency in the aged: a population-based study. Age Ageing 2007;36:177-83.
7. Chui CH, Lau FY, Wong R, et al. Vitamin B_{12} deficiency—need for a new guideline. Nutrition 2001;17:917-20.
8. Matthews JH. 12 Cobalamin and folate deficiency in the elderly. Baillieres Clin Haematol 1995;8:679-97.
9. Dali-Youcef N, Andrè E. An update on cobalamin deficiency in adults. QJM 2009;102:17-28.
10. Guidelines on the investigation and diagnosis of cobalamin and folate deficiencies. A publication of the British Committee for Standards in Haematology. BCSH General Haematology Test Force. Clin Lab Haematol 1994;16:101-15.
11. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B_{12} and folate. Clin Chem 2000;46:1277-83.

12. Snow CF. Laboratory diagnosis of vitamin B_{12} and folate deficiency: a guide for the primary care physician. Arch Intern Med 1999;159:1289-98.
13. Oosterhuis WP, Niessen RW, Bossuyt PM, Sanders GT, Sturk A. Diagnostic value of the mean corpuscular volume in the detection of vitamin B_{12} deficiency. Scand J Clin Lab Invest 2000;60:9-18.
14. Conclusions of a WHO technical consultation on folate and vitamin B_{12} deficiencies. Food Nutr Bull 2008;29:S238-44.
15. Wolters M, Ströhle A, Hahn A. Cobalamin: a critical vitamin in the elderly. Prev Med 2004;39:1256-66.
16. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. Am J Med 1994;96:239-46.
17. Lindenbaum J, Savage DG, Stabler SP, Allen RH. Diagnosis of cobalamin deficiency: II. Relative sensitivities of serum cobalamin, methylmalonic acid, and total homocysteine concentrations. Am J Hematol 1990;34:99-107.
18. Stabler SP. Screening the older population for cobalamin (vitamin B_{12}) deficiency. J Am Geriatr Soc 1995;43:1290-7.
19. Pennypacker LC, Allen RH, Kelly JP, et al. High prevalence of cobalamin deficiency in elderly outpatients. J Am Geriatr Soc 1992;40:1197-204.
20. Joosten E, Lesaffre R, Riezler R. Are different reference intervals for methylmalonic acid and total homocysteine necessary in elderly people? Eur J Haematol 1996;57:222-6.
21. Joosten E, van den Berg A, Riezler R, et al. Metabolic evidence that deficiencies of vitamin B-12 (cobalamin), folate, and vitamin B-6 occur commonly in elderly people. Am J Clin Nutr 1993;58:468-76.
22. Chanarin I, Metz J. Diagnosis of cobalamin deficiency: the old and the new. Br J Haematol 1997;97:695-700.
23. Herrmann W, Obeid R, Schorr H, Geisel J. Functional vitamin B_{12} deficiency and determination of holotranscobalamin in populations at risk. Clin Chem Lab Med 2003;41:1478-88.
24. Herbert V. Staging vitamin B-12 (cobalamin) status in vegetarians. Am J Clin Nutr 1994;59(5 Suppl):1213S-22S.
25. Nexo E, Hoffmann-Lücke E. Holotranscobalamin, a marker of vitamin B-12 status: analytical aspects and clinical utility. Am J Clin Nutr 2011;94:359S-65S.
26. Andrès E, Affenberger S, Vinzio S, et al. Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. Am J Med 2005;118:1154-9.
27. Chan CW, Liu SY, Kho CS, et al. Megaloblastic anaemia in Chinese patients: a review of 52 cases. Hong Kong Med J 1998;4:296-74.
28. Kwok T, Cheng G, Woo J, Lai WK, Pang CP. Independent effect of vitamin B_{12} deficiency on hematological status in older Chinese vegetarian women. Am J Hematol 2002;70:186-90.
29. Andrès E, Loukili NH, Noel E, et al. Vitamin B_{12} (cobalamin) deficiency in elderly patients. CMAJ 2004;171:251-9.
30. Carmel R. Malabsorption of food cobalamin. Baillieres Clin Haematol 1995;8:639-55.
31. Carmel R. Cobalamin, the stomach, and aging. Am J Clin Nutr 1997;66:750-9.
32. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr 2000;71:614S-20S.
33. Krasinski SD, Russell RM, Samloff IM, et al. Fundi atrophic gastritis in an elderly population. Effect on hemoglobin and several serum nutritional indicators. J Am Geriatr Soc 1986;34:800-6.
34. Blaser MJ, Parsonnet J. Parasitism by the "slow" bacterium *Helicobacter pylori* leads to altered gastric homeostasis and neoplasia. J Clin Invest 1994;94:4-8.
35. Kaptan K, Beyan C, Ural AU, et al. *Helicobacter pylori*—is it a novel causative agent in Vitamin B_{12} deficiency? Arch Intern Med 2000;160:1349-53.
36. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B_{12} deficiency in older adults. J Clin Epidemiol 2004;57:422-8.
37. Carmel R. Ethnic and racial factors in cobalamin metabolism and its disorders. Semin Hematol 1999;36:88-100.
38. Chan CW, Liu SY, Kho CS, et al. Pernicious anemia in Chinese: a study of 181 patients in a Hong Kong hospital. Medicine (Baltimore) 2006;85:129-38.
39. Toh BH, van Driel IR, Gleeson PA. Pernicious anemia. N Engl J Med 1997;337:1441-8.
40. Hsing AW, Hansson LE, McLaughlin JK, et al. Pernicious anemia and subsequent cancer. A population-based cohort study. Cancer 1993;71:745-50.
41. Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of upper GI tract. Gastrointest Endosc 2006;63:570-80.
42. Schümann K. Interactions between drugs and vitamins at advanced age. Int J Vitam Nutr Res 1999;69:173-8.
43. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B_{12} malabsorption induced by metformin. Diabetes Care 2000;23:1227-31.
44. Desouza C, Keebler M, McNamara DB, Fonseca V. Drugs affecting homocysteine metabolism: impact on cardiovascular risk. Drugs 2002;62:605-16.
45. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998;338:1042-50.
46. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 2002;288:2015-22.
47. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002;325:1202.
48. Austin RC, Lentz SR, Werstuck GH. Role of hyperhomocysteinemia in endothelial dysfunction and atherothrombotic disease. Cell Death Differ 2004;11 Suppl 1:S56-64.
49. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565-75.
50. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988;318:1720-8.
51. Vogel T, Dali-Youcef N, Kaltenbach G, Andrès E. Homocysteine, vitamin B_{12}, folate and cognitive functions: a systematic and critical review of the literature. Int J Clin Pract 2009;63:1061-7.
52. Malouf R, Areosa Sastre A. Vitamin B_{12} for cognition.

Cochrane Database Syst Rev 2003;(3):CD004326.
53. Zhou JM, Praticò D. Acceleration of brain amyloidosis in an Alzheimer's disease mouse model by a folate, vitamin B_6 and B_{12}-deficiency diet. Exp Gerontol 2010;45:195-201.
54. Tiemeier H, van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, Breteler MM. Vitamin B_{12}, folate, and homocysteine in depression: the Rotterdam study. Am J Psychiatry 2002;159:2099-101.
55. Penninx BW, Guralnik JM, Ferrucci L, Fried LP, Allen RH, Stabler SP. Vitamin B_{12} deficiency and depression in physically disabled older women: epidemiologic evidence from Women's Health and Aging Study. Am J Psychiatry 2000;157:715-21.
56. Sabeen S, Holroyd S. Vitamin B_{12} and psychiatric illness. Ann Longterm Care 2009;17:32-6.
57. Martin DC, Francis J, Protech J, Huff FJ. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. J Am Geriatr Soc 1992;40:168-72.
58. Vidal-Alaball J, Butler CC, Cannings-John R, et al. Oral vitamin B_{12} versus intramuscular vitamin B_{12} for vitamin B_{12} deficiency. Cochrane Database Syst Rev 2005;(3):CD004655.
59. Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998.