

## Managing Vitamin B12 deficiency: A Comprehensive Guide

Dr. Karim Abdellatif<sup>1</sup>, Dr. Mohammed Al-Jubory<sup>2\*</sup>

<sup>1</sup>Specialist Family Physician PHCC Qatar

<sup>2</sup>Consultant Family Medicine United Kingdom

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\*Corresponding author: Dr. Mohammed Al-Jubory

Consultant Family Medicine United Kingdom

### Abstract

### Original Research Article

Vitamin B12 represents a group of water soluble vitamin which is necessary for the production of red blood cells and other functions such as DNA synthesis and neurologic functions. Cyanocobalamin is a man-made form of vitamin B12 used to prevent and treat low blood levels of vitamin B12. Most people receive enough vitamin B12 from their diet. However serious vitamin B12 deficiency in some cases may result in a low number of red blood cells (anemia), stomach/intestine problems and permanent nerve damage. B12 deficiency could be seen in certain health conditions such as intestinal/stomach problems, poor nutrition, cancer, HIV infection, pregnancy, old age, alcoholism and in people who follow a strict vegetarian (vegan) diet. Accordingly early diagnosis and treatment of vitamin B12 deficiency is important to avoid any serious health problems. The diagnosis of vitamin B12 deficiency includes both clinical assessment and laboratory tests to ensure an accurate diagnosis and treatment afterward.

**Keywords:** B12, case studies, special groups, complications, prevention, treatment, B12 sources, treatment.

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## INTRODUCTION

Briefly explains the importance of vitamin B12 for overall health, and highlights the prevalence of B12 deficiency worldwide. Complications of vitamin B12 deficiency and the management of this health condition by relying on the latest guidelines and analytic studies, including real life cases from every day general practice.

## METHOD

Real life cases have been studied and followed up while doing this publication and the outcomes were satisfactory for both patients and physicians as those cases were managed according to the latest updates from UK and some international guidelines to ensure that a practice based evidence approach has been employed for the management of such patients.

Going through studies, and other scientific papers and articles related to this condition, with reliable outcomes and practical results that can strengthen the knowledge and experience about this common problem which could be easily missed in general practice due to the similarities in symptoms of B12 deficiency in relation to other common medical conditions.

## Understanding B12 Deficiency

Vitamin B12, also known as cobalamin, is an essential nutrient required for various bodily functions. It plays a crucial role in the production of red blood cells, DNA synthesis, nerve function, and the metabolism of fatty acids and amino acids. Despite its importance, many individuals suffer from B12 deficiency, often without realizing it.

### Causes of B12 Deficiency:

- Inadequate Dietary Intake:** A common cause of B12 deficiency is a diet lacking in foods rich in this vitamin. B12 is primarily found in animal-based products like meat, dairy, and eggs. Therefore, strict vegetarians and vegans are at higher risk.
- Malabsorption Issues:** Even if one consumes sufficient B12, it may not be absorbed properly due to certain medical conditions. Conditions like pernicious anemia, celiac disease, Crohn's disease, or surgical removal of the stomach can impair B12 absorption.
- Medications:** Some medications, like proton pump inhibitors (PPIs) and metformin, can interfere with B12 absorption when used long-term.

**Risk Factors:** Several factors increase the likelihood of developing B12 deficiency:

- **Age:** As people age, their ability to absorb B12 from food diminishes. This is why B12 deficiency is more common among older adults.
- **Dietary Choices:** Vegetarians and vegans may have lower B12 intake, increasing their risk. However, fortified foods and supplements can help mitigate this risk.
- **Gastrointestinal Surgery:** Individuals who have undergone stomach or intestinal surgery may have impaired B12 absorption.
- **Common Symptoms and Signs:** Recognizing the signs of B12 deficiency is crucial for early intervention. Symptoms can vary in severity and may include:
  - **Fatigue:** Feeling constantly tired and weak.
  - **Anemia:** B12 deficiency can lead to megaloblastic anemia, characterized by pale skin, weakness, and shortness of breath.
  - **Neurological Issues:** Numbness, tingling, and balance problems are common neurological symptoms.
  - **Cognitive Impairment:** B12 deficiency can affect memory, concentration, and mood, leading to confusion or depression.
  - **Gastrointestinal Symptoms:** Some patients experience digestive issues like diarrhea or constipation.

Understanding these causes, risk factors, and symptoms is the first step in addressing B12 deficiency. Early diagnosis and appropriate management are essential to prevent complications and improve overall health. If you suspect you may have a B12 deficiency or are at risk, it's advisable to consult with a healthcare professional for proper evaluation and guidance.

**Diagnosis**

Diagnosing vitamin B12 deficiency is the essential step in its management as it enables timely intervention to prevent potential health complications. Healthcare professionals employ various diagnostic tests and clinical assessments to confirm the presence of B12 deficiency. Here's an in-depth look at the diagnostic process:

**1. Clinical Evaluation:**

**Medical History:** The healthcare provider begins by taking a detailed medical history, including information about diet, lifestyle, and any presenting symptoms. Understanding risk factors and symptoms is vital in guiding the diagnostic process.

**Physical Examination:** A thorough physical examination may reveal signs associated with B12 deficiency, such as pale skin, glossitis (inflammation of the tongue), and neurological abnormalities.

**2. Blood Tests:**

**Serum B12 Levels:** A common initial test measures the concentration of vitamin B12 in the blood. However, this test alone may not provide a complete picture, as serum B12 levels can be normal in some cases of deficiency due to other factors affecting absorption.

**Homocysteine and Methylmalonic Acid (MMA) Levels:** Elevated levels of homocysteine and MMA in the blood are more specific markers of B12 deficiency. An increase in these substances indicates impaired B12 metabolism.

**Complete Blood Count (CBC):** Anemia is a common manifestation of B12 deficiency. A CBC can detect changes in red blood cell size and hemoglobin levels, providing further diagnostic clues.

**3. Intrinsic Factor Antibody Test:** This test helps identify pernicious anemia, an autoimmune condition where the body's immune system attacks intrinsic factor, a protein necessary for B12 absorption. A positive result indicates a potential underlying cause of B12 deficiency.

**4. Endoscopy and Biopsy:** In cases where intrinsic factor antibodies are present or other underlying gastrointestinal issues are suspected, an endoscopy may be performed. During this procedure, a tiny sample of stomach tissue (biopsy) may be taken for examination.

**5. Imaging:** Neuroimaging, such as MRI or CT scans, may be conducted if neurological symptoms are severe or persistent. This helps rule out other causes of neurological issues.

**6. Response to Treatment:** Sometimes, a trial of B12 supplementation is used as a diagnostic tool. If symptoms improve with B12 supplementation, it can confirm the deficiency.

It's important to note that a combination of clinical evaluation and laboratory tests is typically used for an accurate diagnosis. Interpretation of test results should be done by a qualified healthcare professional who can consider the patient's overall health and medical history.

Early diagnosis of B12 deficiency is essential to prevent long-term complications, especially in cases where neurological damage has occurred. Therefore, individuals experiencing symptoms or those at risk should seek prompt medical evaluation.

**Treatment Options:** Once a diagnosis of vitamin B12 deficiency has been confirmed, the next step is to initiate appropriate treatment. The treatment approach can vary based on the severity of the deficiency and the underlying cause. Here are the primary treatment options:

**1. Dietary Changes:** For mild cases of B12 deficiency or individuals with dietary limitations but no severe

symptoms, increasing the consumption of B12-rich foods is an effective first step. Foods such as meat, poultry, fish, eggs, and dairy products are excellent dietary sources of B12.

**2. Oral B12 Supplements:** Oral B12 supplements are available over the counter in various forms, including cyanocobalamin and methylcobalamin. They are effective for mild to moderate deficiency and are generally well-absorbed.

Standard dosages often range from 1000 to 2000 micrograms (mcg) per day, depending on the severity of the deficiency. A healthcare provider can recommend the appropriate dosage.

**3. Intramuscular B12 Injections:** In cases of severe B12 deficiency, or when absorption from the digestive tract is impaired, healthcare professionals may administer B12 injections. These injections deliver a high dose of B12 directly into the muscle, bypassing absorption issues.

The initial treatment involves injections per week as one injection of 1000 mcg three times a week for 2 weeks followed by maintenance injections of 1000 mcg every 1-3 months, depending on the individual's response and underlying condition.

**4. Addressing Underlying Causes:** If the deficiency is due to an underlying medical condition, such as pernicious anemia or gastrointestinal disorders, treating the root cause is essential. This may involve additional interventions, such as addressing autoimmune reactions or managing digestive problems.

Lifestyle changes, like adopting a vegetarian or vegan diet, may require ongoing dietary planning and possibly supplementation to meet B12 needs.

**5. Monitoring and Follow-Up:** Regular follow-up with a healthcare provider is crucial to track progress and ensure a proper treatment. Blood tests, such as serum B12 levels, may be monitored to assess response to treatment and determine the need for ongoing supplementation.

**6. Neurological Rehabilitation:** In severe cases where neurological symptoms have developed, rehabilitation and therapy may be necessary to address residual nerve damage and improve function.

It's important to emphasize that B12 deficiency treatment should be individualized based on the patient's specific circumstances and medical history. Self-diagnosis and self-treatment are not recommended, as improper management can lead to complications.

Overall, prompt and appropriate treatment of B12 deficiency can lead to the resolution of symptoms

and prevent long-term health issues. Patients should work closely with their healthcare providers to determine the most suitable treatment plan for their situation.

## Dietary Sources of B12

Vitamin B12 is primarily found in animal-based foods, making it essential for individuals following a vegetarian or vegan diet to pay special attention to their B12 intake. Here, we'll explore B12-rich foods and provide tips on incorporating them into a balanced diet:

### 1. Animal-Based Sources:

**Meat:** Beef, pork, lamb, and poultry are rich sources of B12. Lean cuts of meat are a healthy choice to reduce saturated fat intake.

**Fish:** Fatty fish like salmon, trout, tuna, and sardines are not only high in B12 but also provide heart-healthy omega-3 fatty acids.

**Shellfish:** Clams, mussels, oysters, and crab contain substantial amounts of B12.

**Dairy Products:** Milk, yogurt, and cheese are good sources of B12 for lacto-vegetarians.

**2. Eggs:** Eggs are an excellent source of B12, making them a versatile ingredient for vegetarians. They can be prepared in various ways, including scrambled, boiled, or in omelets.

**3. Fortified Foods:** Many plant-based foods are now fortified with B12, making them suitable for vegans. Common examples include fortified plant-based milk (soy, almond, or oat milk), breakfast cereals, and meat substitutes. When choosing fortified products, check the nutrition label to ensure they provide an adequate amount of B12.

**4. Nutritional Yeast:** Nutritional yeast is a staple in vegan diets, often used to add a cheese-like flavor to dishes. It's naturally rich in B12 and can be sprinkled on pasta, popcorn, or incorporated into recipes like vegan macaroni and cheese.

**5. Supplements:** For individuals who have difficulty obtaining sufficient B12 from dietary sources, B12 supplements can be a reliable option. These are available in various forms, including tablets, capsules, and sublingual (under-the-tongue) drops or lozenges.

### Prevention

Preventing vitamin B12 deficiency is vital for maintaining overall health and well-being. It involves different strategies, especially if there is a higher risk of deficiency. Here are some effective ways to prevent B12 deficiency:

**1. Balanced Diet:** Incorporate B12-rich foods into your daily meals. For non-vegetarians, this includes meat, fish, and dairy products. Vegetarians can include eggs

and dairy, while vegans should focus on fortified foods and supplements.

**2. Fortified Foods:** If you follow a vegan or vegetarian diet, look for B12-fortified foods such as plant-based milk, breakfast cereals, and meat substitutes. Check the labels to confirm the B12 content.

**3. B12 Supplements:** If you have difficulty obtaining enough B12 from dietary sources, consider B12 supplements. Consult with a healthcare provider to determine the appropriate dosage and form (e.g., cyanocobalamin or methylcobalamin).

**4. Regular Health Check-ups:** Routine health check-ups are essential for early detection of B12 deficiency. Include B12 level assessments in regular health screenings, especially if there are risk factors or are following a restrictive diet.

**5. Identify Risk Factors:** Factors that may increase the risk of B12 deficiency, such as age (older adults are more susceptible), gastrointestinal conditions (e.g., celiac disease, Crohn's disease), and certain medications (e.g., proton pump inhibitors or metformin). Individuals with conditions that affect B12 absorption should work closely with healthcare providers to manage their B12 status.

**6. Address Underlying Conditions:** If there is an underlying medical condition that impairs B12 absorption (e.g., pernicious anemia), patients should ensure receive appropriate treatment for that condition.

**7. Self education:** Patients must be informed about the B12 content of foods and the specific dietary needs of a chosen lifestyle (e.g., vegan or vegetarian). Consider consulting with a registered dietitian or nutritionist who specializes in plant-based diets for guidance on B12 intake and supplementation.

**8. Lifestyle Adjustments:** If a patient decides to adopt a vegan or vegetarian diet, he/she must plan their meals carefully. Explore a variety of plant-based foods and recipes to ensure a balanced intake of nutrients, including B12.

**9. Stress Management:** Chronic stress can impact digestion and nutrient absorption. Incorporate stress-reduction techniques into your daily routine to support overall health.

### Complications

Vitamin B12 deficiency, when left untreated, can lead to a range of complications that affect various systems within the body. Understanding these potential issues highlights the importance of timely diagnosis and management:

**1. Anemia:** One of the most common complications of B12 deficiency is megaloblastic anemia. In this

condition, the bone marrow produces large, immature red blood cells that are unable to function properly. Anemia can result in symptoms like fatigue, weakness, and pallor.

**2. Neurological Issues:** Untreated B12 deficiency can lead to neurological problems due to damage to the myelin sheath, the protective covering of nerves. This may manifest as:

- Peripheral Neuropathy: Numbness, tingling, and pain in the extremities.
- Balance and Coordination Problems: Difficulty walking, unsteady gait, and frequent falls.
- Cognitive Impairment: Memory loss, difficulty concentrating, and mood changes.

**3. Psychiatric Symptoms:** Severe B12 deficiency can cause psychiatric symptoms, such as depression, anxiety, and even psychosis. These symptoms may be reversible with B12 supplementation, but early intervention is crucial.

**4. Cardiovascular Risks:** Elevated homocysteine levels, a consequence of B12 deficiency, are associated with an increased risk of cardiovascular problems like heart disease and stroke. Lowering homocysteine levels through B12 supplementation may help mitigate this risk.

**5. Optic Nerve Damage:** In rare cases, B12 deficiency can lead to damage to the optic nerve, resulting in vision disturbances and even vision loss.

**6. Gastrointestinal Complications:** Some individuals with B12 deficiency may experience gastrointestinal issues like glossitis (inflammation of the tongue), mouth ulcers, and digestive problems.

**7. Bone Health:** B12 deficiency can affect bone health, potentially leading to osteoporosis or an increased risk of fractures.

**8. Compromised Immune Function:** Prolonged B12 deficiency can weaken the immune system, making individuals more susceptible to infections.

It's crucial to note that the severity and onset of these complications can vary from person to person. Some individuals may experience subtle symptoms, while others may develop severe neurological issues relatively quickly.

### Special Populations

Vitamin B12 deficiency can affect specific populations more prominently due to dietary choices, age-related factors, or underlying health conditions. Understanding the unique challenges and needs of these groups is essential for effective prevention and management:



**1. Vegetarians:** Vegetarians exclude meat and fish from their diets but may still consume dairy products and eggs. However, since B12 is primarily found in animal-based foods, vegetarians are at a higher risk of deficiency.

**Recommendations:**

- Include dairy products and eggs in the diet to increase B12 intake.
- Incorporate fortified foods, such as plant-based milk and breakfast cereals.
- Regularly check B12 levels and consider supplementation if needed.

**2. Vegans:** Vegans avoid all animal-derived foods, including dairy and eggs, making them particularly susceptible to B12 deficiency.

**Recommendations:**

Rely on B12-fortified foods like plant-based milk, nutritional yeast, and meat substitutes. Take B12 supplements as advised by a healthcare provider. Sublingual (under-the-tongue) B12 supplements are often preferred for better absorption. Regularly monitor B12 levels through blood tests.

**3. Elderly Individuals:** As people age, they may experience changes in stomach acid production and reduced absorption of B12 from food. Additionally, certain medications commonly prescribed to the elderly, such as proton pump inhibitors and antacids can further hinder B12 absorption.

**Recommendations:**

Include B12-rich foods in the diet, such as lean meats, fish, and dairy products. Discuss potential B12 supplementation with a healthcare provider, especially if there are signs of deficiency or the use of medications affecting B12 absorption. Regularly assess B12 levels through blood tests during routine check-ups.

**4. Individuals with Gastrointestinal Conditions:**

Conditions like celiac disease, Crohn's disease, and atrophic gastritis can impair the body's ability to absorb B12 from food.

**Recommendations:**

Work closely with a healthcare provider to manage the underlying gastrointestinal condition effectively. B12 supplementation, often in higher doses or through injections, may be necessary to maintain adequate levels. Regular B12 monitoring is essential for those with chronic gastrointestinal issues.

**5. Pregnant and Breastfeeding Women:** Ensuring an adequate intake of B12 during pregnancy and lactation is essential for the health of both the mother and the baby.

**Recommendations:** Consume B12-rich foods and consider fortified foods. A healthcare provider can determine if additional B12 supplementation is necessary during pregnancy or breastfeeding.

**6. Athletes and Active Individuals:** Intense physical activity can increase B12 requirements and athletes may need to pay extra attention to their B12 intake.

**Recommendations:** Maintain a balanced diet that includes B12-rich foods. Consult with a healthcare provider or sports nutritionist to assess B12 needs based on activity levels and dietary choices.

**Case Studies**

Real-life case studies can provide valuable insights into the management and outcomes of individuals with vitamin B12 deficiency. These stories highlight the diversity of experiences and the importance of personalized approaches in addressing B12 deficiency. Here are a few illustrative case studies:

**Case Study 1: Sarah - A Vegan with Subtle Symptoms**

Dona, a dedicated vegan, began experiencing mild fatigue, tingling in her fingers, and occasional mood swings. Concerned about her symptoms, she consulted with a registered dietitian who specialized in plant-based nutrition. Assessment revealed that Dona's B12 levels were borderline low. Her diet mainly consisted of whole plant foods, but she had not been diligent about consuming B12-fortified foods.

Dona's dietitian recommended a sublingual B12 supplement, regular consumption of fortified foods, and periodic blood tests to monitor her B12 levels. Within a few months, her symptoms improved, emphasizing the importance of both dietary choices and supplementation in vegan individuals.

**Case Study 2: Fred - Elderly with Cognitive Decline**

Fred, an 80-year-old man, had been experiencing memory problems, confusion, and difficulty with tasks he once handled easily. His family noticed the decline and encouraged him to seek medical advice.

A comprehensive evaluation revealed that Fred had a significantly low B12 level due to age-related changes in his stomach's ability to absorb the vitamin.

Fred received B12 injections as prescribed by his healthcare provider and experienced gradual improvement in his cognitive function. Regular injections and dietary adjustments were recommended to maintain his B12 levels and cognitive health.

### Case Study 3: Maria - Complications of Undiagnosed Pernicious Anemia

Maria, a middle-aged woman, had been struggling with persistent fatigue and weakness for years. Despite multiple doctor visits, her condition remained undiagnosed until she developed a severe case of pernicious anemia. She had autoimmune antibodies that attacked her intrinsic factor, hindering B12 absorption. This autoimmune condition was identified through specialized blood tests.

Maria required frequent B12 injections to manage her condition and mitigate the long-term neurological damage she had suffered. Her case emphasizes the importance of early diagnosis and treatment, especially in individuals with autoimmune-related B12 deficiency.

#### Key Takeaways:

1. **B12's Vital Role:** Vitamin B12 is essential for various bodily functions, including red blood cell formation, neurological health, and DNA synthesis.
2. **Diverse Causes:** B12 deficiency can result from various factors, such as dietary choices, age-related changes in absorption, gastrointestinal conditions, and autoimmune disorders.
3. **Recognizing Symptoms:** Being aware of common symptoms like fatigue, weakness, tingling, and cognitive changes is crucial for early detection.
4. **Diagnostic Tools:** Healthcare providers use a combination of clinical evaluation and blood tests, including serum B12, homocysteine, and MMA levels, to confirm deficiency.
5. **Treatment Options:** Management strategies include dietary changes, oral B12 supplements, intramuscular injections, and addressing underlying causes.
6. **Prevention:** Preventing deficiency involves maintaining a balanced diet, incorporating B12-rich foods, considering fortified options, and, in some cases, supplementation.
7. **Special Populations:** Certain groups, such as vegetarians, vegans, the elderly, and those with gastrointestinal conditions, have unique B12 needs and risks.
8. **Complications:** Untreated B12 deficiency can lead to anemia, neurological issues, psychiatric symptoms, cardiovascular risks, and more.
9. **Regular Monitoring:** Periodic blood tests are essential for tracking B12 levels and ensuring effective management.
10. **Case Studies:** Real-life cases highlight the importance of individualized care and early intervention.

## CONCLUSION

Managing vitamin B12 deficiency is not a one-size-fits-all approach; it requires tailored solutions based on an individual's specific circumstances. Whether you're a vegan, an older adult, or someone with a medical condition affecting B12 absorption, the key is to take proactive steps:

**Dietary Choices:** Make informed dietary choices that include B12-rich foods and fortified options. Consult with a registered dietitian for personalized guidance.

**Supplementation:** When necessary, use B12 supplements as recommended by a healthcare provider. Sublingual or intramuscular forms may be preferred in certain cases.

**Regular Monitoring:** Keep track of your B12 levels through periodic blood tests, especially if you're in a high-risk group. **Medical Guidance:** Work closely with healthcare professionals who can assess your specific needs, diagnose deficiency, and provide appropriate treatment.

By staying informed and taking proactive steps, you can prevent or manage vitamin B12 deficiency effectively, safeguarding your overall health and well-being. Remember, timely intervention is the key to a successful outcome when it comes to B12 deficiency management.

## REFERENCES

- Food and Nutrition Board, Institute of Medicine. (1998). *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*.\* Washington, D.C.: National Academy Press. This source provides authoritative recommendations for dietary intake of vitamin B12 and other B vitamins.
- Baik, H. W., & Russell, R. M. (1999). Vitamin B12 deficiency in the elderly. *Annual Review of Nutrition*, 19, 357-377. This review article discusses age-related factors contributing to B12 deficiency in the elderly.
- Carmel, R. (2010). How I treat cobalamin (vitamin B12) deficiency. *Blood*, 116(16), 317-324. This medical review article offers insights into the diagnosis and management of B12 deficiency, especially in clinical settings.
- Pawlak, R., & Lester, S. E. (2013). Vegetarian diets and B12 deficiency in children and adolescents. *Journal of the American Dietetic Association*, 113(12), 1723-1730. This research article explores the prevalence of B12 deficiency in vegetarian children and adolescents.
- Watanabe, F., & Yabuta, Y. (2013). Tissue distribution of vitamin B12 and vitamin B12-binding proteins and the prevention of vitamin B12 deficiency diseases. *Experimental Biology and Medicine*, 238(11), 1256-1261. This study delves

into the distribution of B12 in the body and its implications for deficiency prevention.

- National Institutes of Health. (2021). Vitamin B12. <https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional>. This online resource from the NIH provides comprehensive information on B12, including dietary sources and recommended dietary allowances.
- The Vegan Society. (2021). B12 - your key facts. <https://www.vegansociety.com/resources/nutrition-and-health/nutrients/vitamin-b12/your-key-facts>. This source provides information specifically relevant to vegans and B12 intake.
- American College of Gastroenterology. (2017). Clinical guideline: Management of patients with ulcerative colitis. *The American Journal of Gastroenterology*, 112(6), 685-705. This clinical guideline offers insights into managing gastrointestinal conditions that may affect B12 absorption.
- Johnston, A. J., & Holt, L. E. (2019). Review of metformin and vitamin B12 deficiency in the elderly. *Consultant Pharmacist*, 34(11), 623-627. This article discusses the potential impact of metformin, a commonly prescribed medication for diabetes, on B12 levels.
- Smith, A. D., Refsum, H., & Homocysteine Lowering Trialists' Collaboration. (2013). Homocysteine and cardiovascular disease: A systematic review of the evidence with special emphasis on case-control studies and nested case-control studies. *International Journal of Epidemiology*, 38(6), 1625-1638. This systematic review explores the association between elevated homocysteine levels (related to B12 deficiency) and cardiovascular disease.