SureScreen Health

# VITAMIN $B_{12}$

WHITEPAPER

## Contents

When it comes to B vitamins, it's easy to presume that they are all very similar.

This is not the case, vitamin $B_{12}$ is one of the most unique essential nutrients that exists and is regarded as a common deficiency, particularly amongst older people whose absorption capabilities decline with age. It is estimated that 1 in 10 over 75s are deficient in $B_{12}$.[1072] Knowing what makes vitamin $B_{12}$ unique from other B vitamins can help you know how and why you should maintain this nutrient at healthy levels.

## What is Vitamin $B_{12}$?

Vitamin $B_{12}$ otherwise known as Cobalamin is an essential vitamin, meaning the body cannot produce it on its own. Therefore, this nutrient must be obtained via the diet or from supplements.

Vitamin $B_{12}$ is the generic term for a group of several compounds that contain the mineral cobalt, known as cobalamins. Their unique role and structure separates them from other vitamins, as they are considered the most chemically complex of all vitamins.

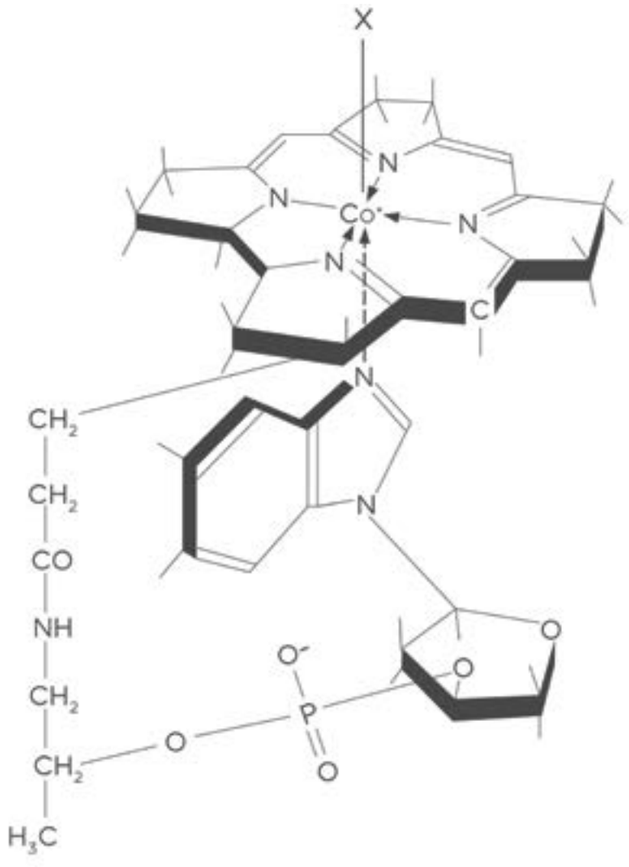



*Figure 1. Chemical structure of cobalamin*

## Function

One of the most well-known functions of vitamin $B_{12}$ is the role it plays in the production of red blood cells. Low amounts of vitamin $B_{12}$ reduces the amount of red blood cells produced and can prevent them from being produced properly, resulting in large red blood cells called megaloblasts. This eventually develops into a disease known as megaloblastic anaemia.[1073]

Vitamin $B_{12}$ also contributes to the normal functioning of the nervous system, psychological function, homocysteine metabolism, the immune system and contributes to the reduction of tiredness and fatigue.[1074, 1075]

Absorption of healthy levels of vitamin $B_{12}$ rely on the adequate supply of intrinsic factor (IF) produced by the parietal cells in the stomach lining, often in short supply in the elderly due to waning stomach acid secretions. Stress can also affect the production of stomach acid and hence intrinsic factor,[1076] as the body deprioritises digestion when responding to stress.

## Benefits and Deficiencies

There are several claims stating that supplementing with Vitamin $B_{12}$ can provide health benefits.[1074, 1075] The truth, however, is that adequate amounts of Vitamin $B_{12}$ are essential to prevent any negative symptoms of the deficiency. Interestingly, any excess beyond enough Vitamin $B_{12}$ provides no added benefits.[1077] For example, when it is claimed that Vitamin $B_{12}$ can provide you with energy, this is only the case if a person is suffering from low energy levels because of a Vitamin $B_{12}$ deficiency. When we discuss the health benefits, we are referring to having healthy levels of Vitamin $B_{12}$ where no side effects are present.[1075,7]

Healthy levels of vitamin $B_{12}$ have been found to:

- Help prevent Osteoporosis[1041]
- Help prevent macular degeneration[1044]
- Help prevent neural tube defects (NTDs), a type of birth defect[1041/2]
- Lower homocysteine levels, and therefore potentially lowering the risk of heart disease[1036/41/42]
- Help prevent megaloblastic anaemia
- Protect the myelin sheath around nerves
- Support healthy cell division in the mucosal lining of the digestive tract and in the bone marrow
- Support liver detoxification through the methylation pathway

Symptoms and side effects of vitamin $B_{12}$ deficiency include:

- Poor mental health[1036/41/42/44]
- Fatigue and lack of energy[1036/42/44]
- Increased inflammation[1041]
- Shortness of breath[1036]
- Headaches[1045]
- Foggy headed/difficulty concentrating[1044]
- Red inflamed tongue (Glossitis)[1044]
- Pins and needles in the hands and feet (Paraesthesia)[1041]
- Muscle cramps[1044]
- Gastrointestinal issues[1045]
- Erectile dysfunction[1044]
- Anaemia[1036/41/42/44]

- Jaundice[1045]
- Other neurological issues such as multiple sclerosis, demyelinating polyneuropathy [1044]

Prolonged deficiency increases the chance of other issues developing, such as heart failure due to anaemia or hyperhomocystineaemia, disabling neurological defects such as Subacute Combined Degeneration of the Spinal Cord (degeneration of the spinal column) or the development of autoimmune disorders such as rheumatoid arthritis, type 1 diabetes or Hashimoto's disease.[1045] Severe vitamin $B_{12}$ (or folate) deficiency can also lead to Megaloblastic anaemia. [1036/41]

## Toxicity

In general, there is no tolerable upper intake level (UL) set for vitamin $B_{12}$.[1079] The UL is the maximum daily dose of a nutrient that is not likely to cause adverse side effects. Vitamin $B_{12}$ is generally considered safe in high doses as it is a water-soluble vitamin, and any excess is excreted in your urine.

High doses for the purpose of treating vitamin $B_{12}$ deficiency are considered safe.

## The Absorption of Vitamin $B_{12}$

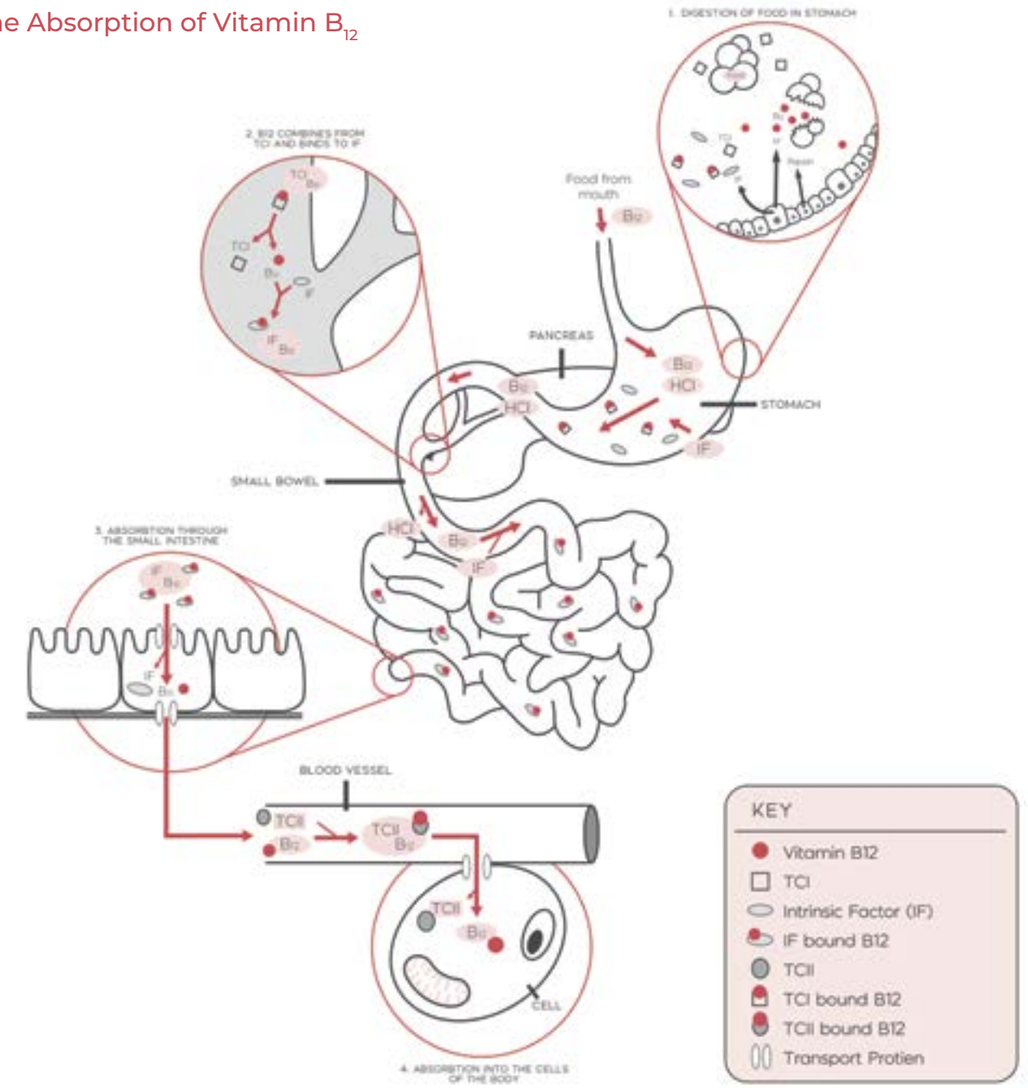
The way in which vitamin $B_{12}$ is absorbed into the body is unique. Unlike other B vitamins which are easily absorbed from the small intestine, vitamin $B_{12}$ requires the help of various transport proteins to deliver it safely to the cells.[1036]

This process starts with $B_{12}$ binding to a glycoprotein knows as transcobalamin I which is produced by the salivary glands and protects the $B_{12}$ from the acidic environment in the stomach. Once in the stomach the $B_{12}$ is released from its dietary protein by hydrochloric acid and the enzyme, pepsin, passing safely through to the less acidic environment of the small intestine. Here, the transcobalamin I is digested by pancreatic enzymes and the vitamin $B_{12}$ binds to another transport protein called Intrinsic Factor, which is produced by the cells in the stomach lining.

Once safely inside the cells of the small intestine, the vitamin $B_{12}$ binds to the protein holotranscobalamin II or Holo-TC and it is now that the $B_{12}$ becomes "active". It then passes into the liver where it can be stored and released into the bloodstream where it is delivered to the various tissues in the body. [1036]



## The Absorption of Vitamin $B_{12}$

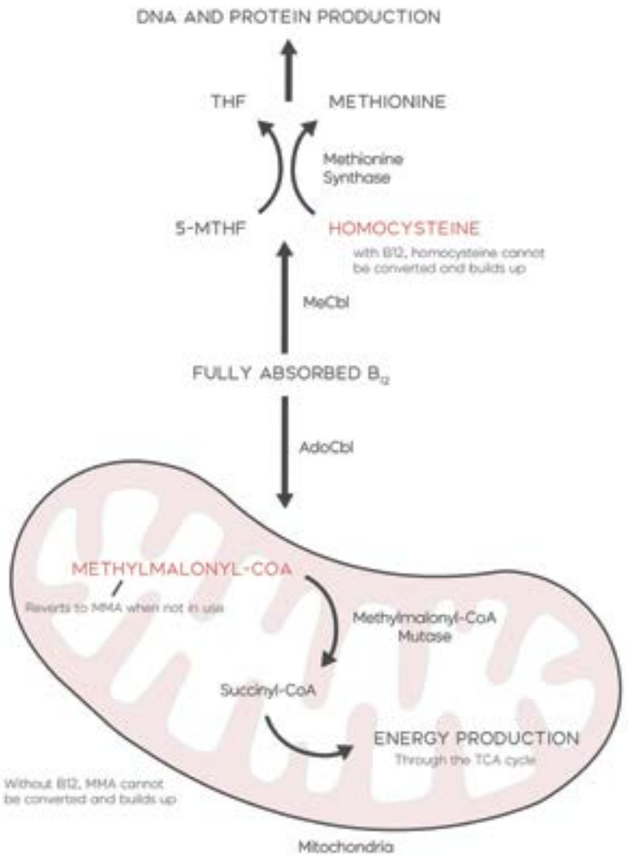


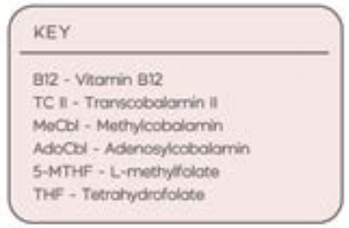

*Absorption of vitamin $B_{12}$*

Factors that have an effect on $B_{12}$ absorption include stomach pH, acid and pepsin levels in the stomach, secretions from the pancreas and liver processes such as bile production.[1042]

Minute amounts of vitamin $B_{12}$ can be absorbed through the gut membrane, estimated at approximately 1-2%. In people with pernicious anaemia (lacking intrinsic factor) this is the only way to absorb vitamin $B_{12}$ from ingestion. This requires them to supplement with mega doses of $B_{12}$ or receive intra muscular injections to obtain adequate amounts of vitamin $B_{12}$ to maintain healthy levels.[1036]

## The Role of Vitamin $B_{12}$ in the Body

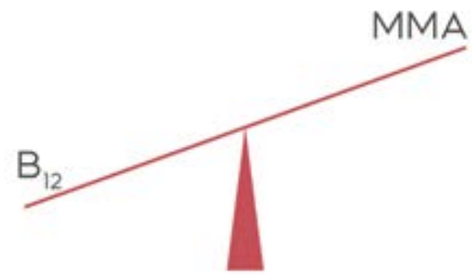



Vitamin $B_{12}$ has two biologically active forms; adenosylcobalamin and methylcobalamin both of which have different roles within the human body.

- Adenosylcobalamin (AdoCbl) is stored in the liver and its main site of action is in the mitochondria, the powerhouse of the cell. It is a cofactor, a helper molecule, for a selection of enzymes that are involved in energy production and carbohydrate, protein, and fat metabolism. Its key role is as a cofactor for succinyl-CoA from L-methylmalonyl-CoA as part of a biological process called the tricarboxylic acid cycle (TCA), also known as the citric acid cycle or the Krebs Cycle, which creates energy for the body.[1080]
- Adenosylcobalamin is also a cofactor for the production of myelin. The myelin sheath is a is a protective layer that's found on nerve cells, acting as an insulator, allowing electrical impulses to travel efficiently, and maintaining the strength of the impulse. Adenosylcobalamin deficiency can cause demyelination, damage to the myelin sheath, which can slow or even stop nerve impulses.[1036/41] Therefore, vitamin $B_{12}$ deficiency can lead to demyelination and raised MMA levels resulting in neurological disorders.[1036]

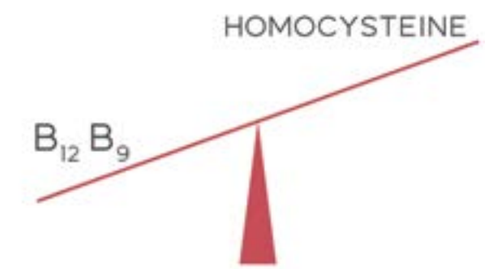
Methylmalonic acid (MMA) is a chemical that is created during the TCA. Without sufficient levels of active vitamin $B_{12,}$ the conversion of L-methylmalonyl-CoA to Succinyl-CoA is impaired and levels of




methylmalonic acid (MMA) rise.[1041] Elevated levels of MMA may damage nerve cells[1036] and some of the symptoms of vitamin $B_{12}$ deficiency may arise.

- Methylcobalamin (MeCbl) functions directly within the cells and is used as a coenzyme for the conversion of homocysteine to methionine. As well as breaking down the amino acid homocysteine, elevated levels of which are associated with cardiovascular disease, this conversion has implications in other pathways including the reactivation of folic acid, without which the folic acid cannot be fully affective, leading to anaemia, impaired cell replication, and damage to the nervous system. It is also involved in producing the precursor of a compound called SAM, which plays a crucial role in detoxification, the synthesis of neurotransmitters and gene regulation, and a shortage of which can lead to neurological disorders.[1040/1041/1063]

Declining levels of active vitamin $B_{12}$ may result in elevated levels of homocysteine. However, vitamins $B_9$ (folate) and $B_6$ work synergistically with vitamin $B_{12}$ to break down homocysteine. Therefore, testing for elevated homocysteine should not be used in isolation to assess active vitamin $B_{12}$ deficiency.



High levels of homocysteine are associated with increased risk of cardiovascular diseases such as thrombosis or coronary artery disease, as well as other diseases such as Alzheimer's and osteoporosis[1041] and is known to be a cause of depression.[1063]

## Vitamin $B_9$

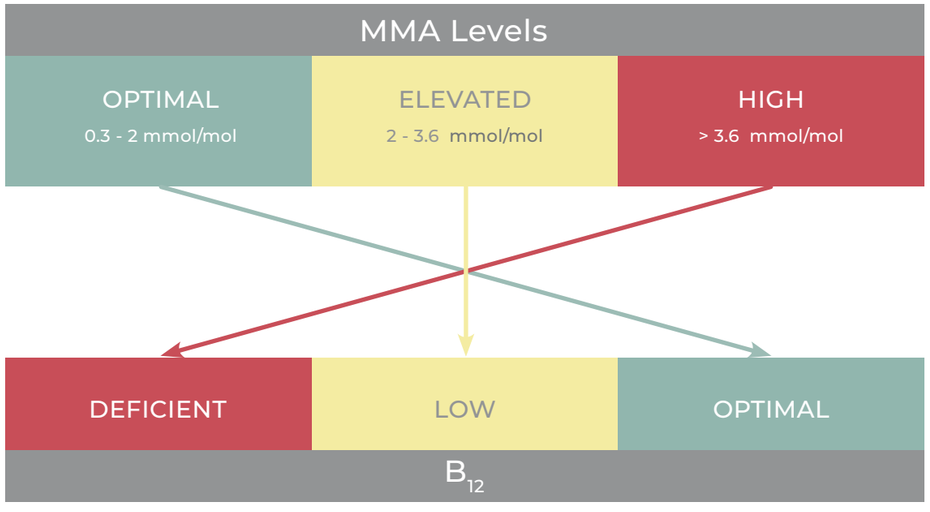
Vitamin $B_{12}$ and Vitamin $B_9$, which is also known as folate, are interconnected. Folate is another essential B vitamin, meaning your body cannot produce it and you need to get it from your diet. Like vitamin $B_{12}$ it plays key roles in the synthesis of DNA and due to its similar metabolic pathways deficiency of folate also leads to an increase of homocysteine. The two vitamins complement each other so well that one can be used to reduce the symptoms of a deficiency of the other. [1041]

## Vitamins $B_6$

Like Vitamin $B_{12}$ and folate, low levels of vitamin $B_6$ can raise homocysteine. However, having an isolated vitamin $B_6$ deficiency is rare and usually occurs with a deficiency of other B vitamins, particularly folate and $B_{12}$.

## Testing Vitamin $B_{12}$ levels

1. Methylmalonic acid (MMA). Measuring MMA is considered the most sensitive test for measuring your $B_{12}$ levels, this is because only vitamin $B_{12}$ that has been fully absorbed into the body can lower MMA. The absorption of $B_{12}$ is a multistage biological process needing the help of several other chemicals and therefore measuring MMA in either urine or blood is often called a functional $B_{12}$ test, as this test can highlight if there are any absorption issues.




*References ranges displayed above are for a urine test*



MMA is therefore more likely to detect $B_{12}$ deficiencies as well as $B_{12}$ low levels.

Whilst MMA can also be elevated if kidney function is impaired or in the case of hypovolemia (where there is a decreased volume of blood circulating around the body), the higher your MMA, the lower your vitamin $B_{12}$.

## Other ways to test for $B_{12}$

1. Serum $B_{12}$ – Serum Vitamin $B_{12}$ is the amount of vitamin $B_{12}$ in your blood. Serum $B_{12}$ is not considered a particularly accurate method of determining your $B_{12}$ levels. This is due to the fact it doesn't account for your vitamin $B_{12}$'s metabolism/absorption past this point.[1036]

2. Active $B_{12}$ (Holo-TC) – Active $B_{12}$ is the measurement of vitamin $B_{12}$ bound to Holo-TC. Measuring this provides an accurate measurement of a person's $B_{12}$ levels, accounting for metabolism and absorption. Whilst Active $B_{12}$ and MMA are both considered good markers, MMA is considered better at detecting subclinical (low but not deficient level) vitamin $B_{12}$ deficiencies.[1036]

3. Homocysteine – Like MMA, homocysteine can be tested for functional $B_{12}$ levels, similarly, rising as $B_{12}$ levels deplete. However, homocysteine levels also raise with low levels of folate ($B_9$), or although rare in isolation, low levels of $B_6$. Genetic mutations to the gene known as MTHFR, which has an impact on the conversion and utilisation of $B_6$, $B_9$ and $B_{12}$, which can lead to high homocysteine levels.

4. MCV (Mean Corpuscular Volume) test – MCV is a test that measures the average size of your red blood cells. As a person becomes deficient in vitamin $B_{12}$ or folate, their red blood cells increase in size eventually leading to megaloblastic anaemia. Whilst this test can identify that a deficiency may be present, it will not provide an accurate estimation of the severity or differentiate between vitamin $B_{12}$ and folate.[1036/41]

## Clinical Deficiency vs Subclinical Deficiency

Traditionally when people talk about a deficiency they have been talking about clinical deficiency. This is a deficiency that has progressed to noticeable symptoms and negative side effects.

Subclinical deficiency, however, is at an earlier stage with no obvious symptoms, and the ones that may be present are non-specific to the nutrient e.g. fatigue. Catching a deficiency at the subclinical stage allows a person to address the issue and potentially prevent the development of a clinical deficiency.

In the case of our urinary $B_{12}$ test, a deficient result is a clinical deficiency, and the low results is a subclinical deficiency.

## Where to get vitamin $B_{12}$?

Vitamin $B_{12}$ is produced from certain strains of bacteria since animals and plants are unable to produce it. For the average adult we recommend (based on EU guidelines) consuming 4 µg a day of vitamin $B_{12}$.[1046]

### 1 Diet

Vitamin $B_{12}$ is usually obtained from animal-based sources where the synthesised $B_{12}$ is transferred and accumulated in the tissues of animals. Red meat and fish/shellfish are known

for their high amounts of vitamin $B_{12}$. Other meats, dairy products, eggs, clams and liver are also good sources.

Sources of vitamin $B_{12}$ for vegetarians and especially vegans are much more limited. Whilst most plant based foods have none present, some mushrooms and seaweed/algae contain some amounts of vitamin $B_{12}$.[1053] For example, Nori, a type of seaweed/algae commonly used in sushi, is considered a good source of vitamin $B_{12}$ for vegetarians/vegans.[1071] There are also some foods fortified with vitamin $B_{12}$, these include some breakfast cereals, milk alternatives and nutritional yeast.

Certain fermented foods are also known to be natural sources of vitamin $B_{12}$ but amounts can vary quite significantly from product to product, ranging from virtually none to huge quantities depending on the fermentation process.[1071]

Below is a selection of food with their average vitamin $B_{12}$ content. By seeing their amounts per portion, you can see the effect these foods have on your $B_{12}$ levels.[2037] Please note that this does not show any of the other nutritional values the food may provide.

| Food | Vitamin B12 per Portion (µg) | %NRV | Portion Size | Source Type |
|---|---|---|---|---|
| Kombucha (black tea)[1070] | 0 - >240 | 0 - > 10,000 | 100 mL | Fermented product |
| Lamb liver | 76.5 | 3,188 | 85g | Meat |
| Beef Liver | 70.7 | 2,944 | 85g | Meat |
| Clams | 17 | 708 | 85g | Seafood |
| Nutritional yeast (fortified) | 8.3 - 24 | 346 – 1,000 | 60 mL | Fortified food |
| Sardines (canned) | 6.7 | 279 | 1 tin (75g) | Seafood |
| Nori (seaweed) [1071] | 3.1 | 129 | 4g | Algae |
| Sauerkraut/kimchi[1071] | 0 - 3 | 0 - 125 | 30g | Fermented product |
| Salmon | 2.6 | 108 | 85g | Seafood |
| Tuna (canned) | 2.5 | 104 | 85g | Seafood |
| Beef (minced) 15% fat | 2.4 | 100 | 85g | Meat |
| Shiitake mushroom (dried)[1071] | 1.7 | 70 | 30g | Mushroom |
| Milk 2% | 1.3 | 54 | 250 mL | Dairy |
| Plain fat free yoghurt | 1.0 | 43 | 170g | Dairy |
| Breakfast cereals (fortified) | 0.6 | 25 | 30g | Fortified food |
| Cheddar cheese | 0.5 | 19 | 43g | Dairy |
| Egg | 0.5 | 19 | 1 large egg | Animal product |
| Turkey (breast) | 0.3 | 14 | 85g | Meat |
| Tempeh | 0.1 | 3 | 125 mL | Fermented product |

## 2 Supplements

It can be difficult for some people to regularly consume adequate amounts of vitamin $B_{12}$ from the diet alone, particularly for vegetarians or vegans. Fortunately, vitamin $B_{12}$ is easily accessible in the form of food supplements.

A common form of vitamin $B_{12}$ used for supplements (and for fortifying foods) is called cyanocobalamin. This is a synthetic/manufactured form of vitamin $B_{12}$ that converts into the natural forms once absorbed into the body. Supplements of the natural forms of vitamin $B_{12}$, methylcobalamin and adenosylcobalamin, are also available. As supplements are produced from bacteria, they are considered vegan.

| Our Recommendations[1046] | |
|---|---|
| 0 – 6 months | 0.4 µg |
| 7 months – 7 years | 1.5 µg |
| 7 – 10 years | 2.5 µg |
| 11 – 14 years | 3.5 µg |
| 15 + years | 4 µg |
| Pregnancy | 4.5 µg |
| Lactation | 5 µg |

## 3 Injections

Intramuscular injections (injections directly into the muscle) bypass the gut absorption process that occurs when consuming vitamin $B_{12}$ orally. Injections rapidly increase vitamin $B_{12}$ levels in those who are deficient and are an effective way of managing a person's vitamin $B_{12}$ levels in people with absorption issues. Vitamin $B_{12}$ is usually injected in a specialised form known as hydroxocobalamin as it is retained more easily by the body, however cyanocobalamin can also be used.[1036]

Injections of vitamin $B_{12}$ can be given to individuals with vitamin $B_{12}$ deficiency by medical practitioners such as doctors, nurses and pharmacists. A deficiency or absorption issue should be identified before any injections of $B_{12}$ are administered.
Whilst the most effective method of increasing vitamin $B_{12}$ quickly, some people do experience side effects such as:- [1050]

- Skin Irritation/Skin Conditions e.g. Acne[1048]
- Headaches
- Dizziness and Nausea
- Diarrhoea
- Fatigue
- Tingling sensation in the hands or feet

## Recommended Dosages

Whilst the UK recommendation for $B_{12}$ supplementation is up to 1.5ug, we recommend daily AI (adequate intake) doses of vitamin $B_{12}$ based on the EU Nutrient Reference Values,[1046] listed below. These are the amounts recommended to people to maintain adequate vitamin $B_{12}$ levels for healthy individuals with no known vitamin absorption/metabolism issues.[1046]

Age, BMI, sex, smoking, alcohol intake, dietary requirements, medical conditions, and medications may affect your levels and how much is required to maintain optimum levels.

People with a vitamin $B_{12}$ deficiency are usually given doses of 1,000 µg by way of injection or oral supplementation for 1-2 weeks to treat the initial deficiency state.[1036] We do not recommend supplementing at this level for people with adequate levels of vitamin $B_{12}$ with no history of

deficiency related issues. Please contact your health professional for further advice.

## Who is at risk of Vitamin $B_{12}$ deficiencies?

There are multiple reasons that a person may become deficient in Vitamin $B_{12}$: -

- Vegan or vegetarian – Vegetarians and especially vegans are at high risk of vitamin $B_{12}$ deficiency, as dietary vitamin $B_{12}$ is usually obtained from animal-based products and few plant sources contain vitamin $B_{12}$. Vegan sourced vitamin $B_{12}$ is largely limited to food that has been fortified and with supplementation. In the UK, at least 11% of vegans are deficient in vitamin $B_{12}$.[1054]

- Pregnancy/breastfeeding – Vitamin $B_{12}$ is a crucial nutrient for the development of a child, and when pregnant or breastfeeding the amount of vitamin $B_{12}$ is shared between the mother and the child. Inadequate intake of vitamin $B_{12}$ can quickly deplete the mother's stores of vitamin $B_{12}$. During the pregnancy this increases the chance of birth defects such as neural tube defects (NTDs).[1041] Children of deficient mothers are either born deficient or at a very high risk of becoming deficient.[1078]

- Hormonal birth control - Birth control has been found to decrease the body's ability to absorb vitamin $B_{12}$. However, whilst lower, the decrease isn't enough to push someone into a full deficiency by itself.[1081]

- Age – Absorbing vitamin $B_{12}$ becomes increasingly difficult with age, as it becomes more difficult for a person to digest food and the chance of other gut based issues increases.[1082] Older age is one of the leading causes of vitamin $B_{12}$ deficiency. In the UK, 5% of people aged 65-74 years are deficient, and over 10% for people aged 75 years and over.[1072] However, more recent studies have found that it could be much higher than this.

- Pernicious anaemia – Pernicious anaemia is an autoimmune disease that targets intrinsic factor and the cells that produce it. It can severely reduce the amount of intrinsic factor. The gut is then unable to absorb vitamin $B_{12}$ quickly leading a person to develop megaloblastic anaemia. A person with pernicious anaemia usually requires regular injections of vitamin $B_{12}$ and/or extremely large doses of vitamin $B_{12}$. People with a family history of pernicious anaemia or another autoimmune disease are more likely to develop it.[1055]

- Medical conditions - The following diseases are known to have an effect on vitamin $B_{12}$ levels:-[1036]
  Chronic Gastritis
  Atrophic Gastritis
  Bacteria Overgrowth (SIBO, H. pylori infection)
  Irritable bowel syndrome (IBS)
  Chronic acid reflux
  Crohn's Disease
  Ulcerative Colitis
  Other gastric diseases
  Pancreatic disorders
  Multiple Sclerosis
  Celiac Disease
  Kidney Diseases
  Liver Diseases (can disrupt the storage of vitamin $B_{12}$)
  Human immunodeficiency viruses (HIV)
  Aplastic Anaemia
  Certain Cancers - Multiple myeloma, myelodysplastic syndrome
  Rheumatoid Arthritis[1056]
  Psoriatic Arthritis[1056]
  Hashimoto's[1057]
  Graves[1057]
  Diabetes
  Graft versus host Disease (GvHD)[1041]
  Vitiligo[1064]

- Gastric surgery – Surgeries such as gastrostomies, gastric bypasses or gastric stapling reduce the amount of acid, pepsin and intrinsic factor required for the absorption of vitamin $B_{12}$.[1042]

- Parasitic infestation – Sometimes a vitamin $B_{12}$ deficiency can be caused by a parasitic infestation. Creatures such as the Fish Tapeworm will absorb the vitamin $B_{12}$ intended for the host.[1036]

- Medication – The following medication is known to reduce vitamin $B_{12}$ levels:-[1036]
  Metformin (Diabetes medication)
  Proton Pump Inhibitors (PPIs) - e.g. Omeprazole, Esomeprazole
  Antacids
  Nitrous oxide
  Colchicine
  Antibiotics – e.g. neomycin,
  L-Carnitine
  Sodium bicarbonate

- Smoking - Smoking is widely known to reduce the amount of vitamins your body absorbs, including vitamin $B_{12}$. The cyanides in cigarette smoke become detoxified when reacting with the active $B_{12,}$ turning it into inactive $B_{12}$ and lowering your active $B_{12}$ levels.[1066/7]

- Drinking – Alcohol is also known to reduce the absorption of B vitamins including $B_{12}$. Even moderate drinking can result in lower vitamin $B_{12}$ levels.[1068] Alcohol-based liver damage is also known to cause the liver to fail in an attempt to hold on to the vitamin $B_{12}$ stores it has, this can result in a very serious deficiency.[1069]

## Summary

Whilst estimates of $B_{12}$ deficiency vary, it is evident that this is a common issue globally and is impacted by many factors including age, diet and lifestyle. What is particularly concerning is that up to 40% of people in the UK have subclinical vitamin $B_{12}$ levels,.[1047] This hidden condition may be affecting the quality of life of many people without them knowing it's linked to a vitamin $B_{12}$ deficiency.

$B_{12}$ is an important and essential vitamin, meaning that your body cannot make it and it can only be obtained from your diet or by taking supplementation.

Having adequate $B_{12}$ levels is important for all individuals to function and is particularly important during pregnancy.

Taking vitamin $B_{12}$ supplementation or injections will only give you an energy boost if you have fatigue from low levels of $B_{12}$. If you have sufficient vitamin $B_{12}$ levels, supplementation or injections will bring no extra benefit.

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