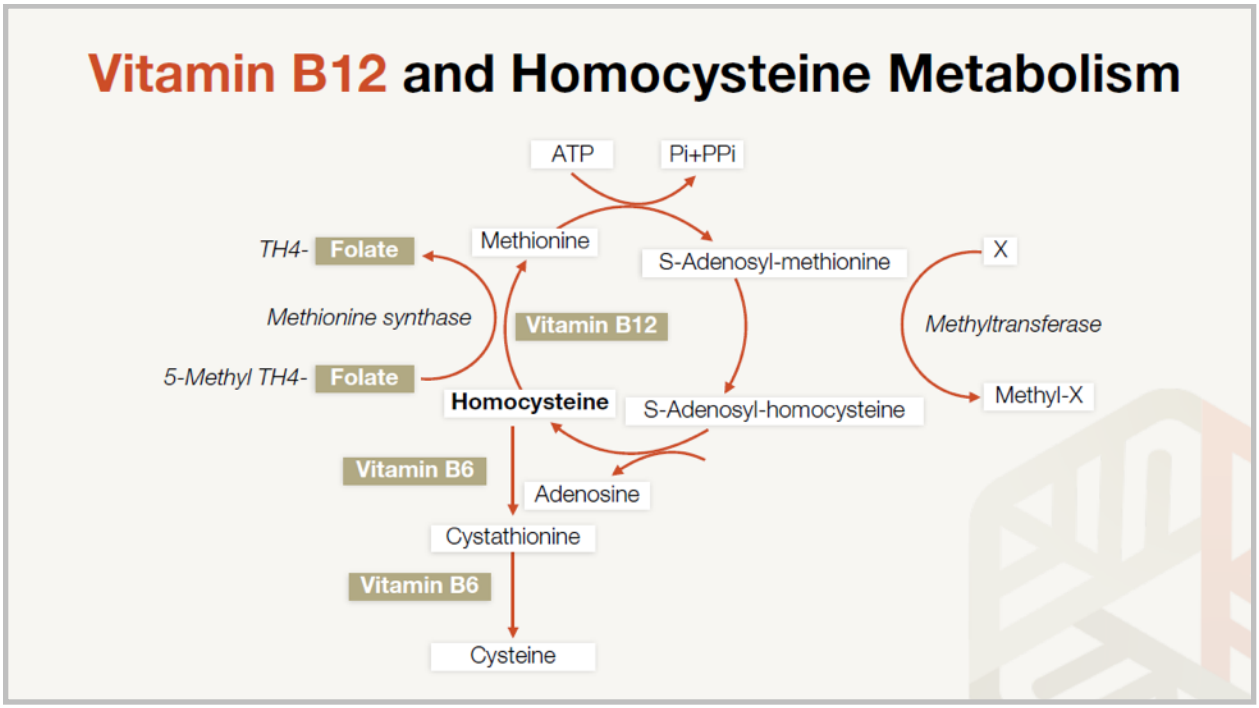
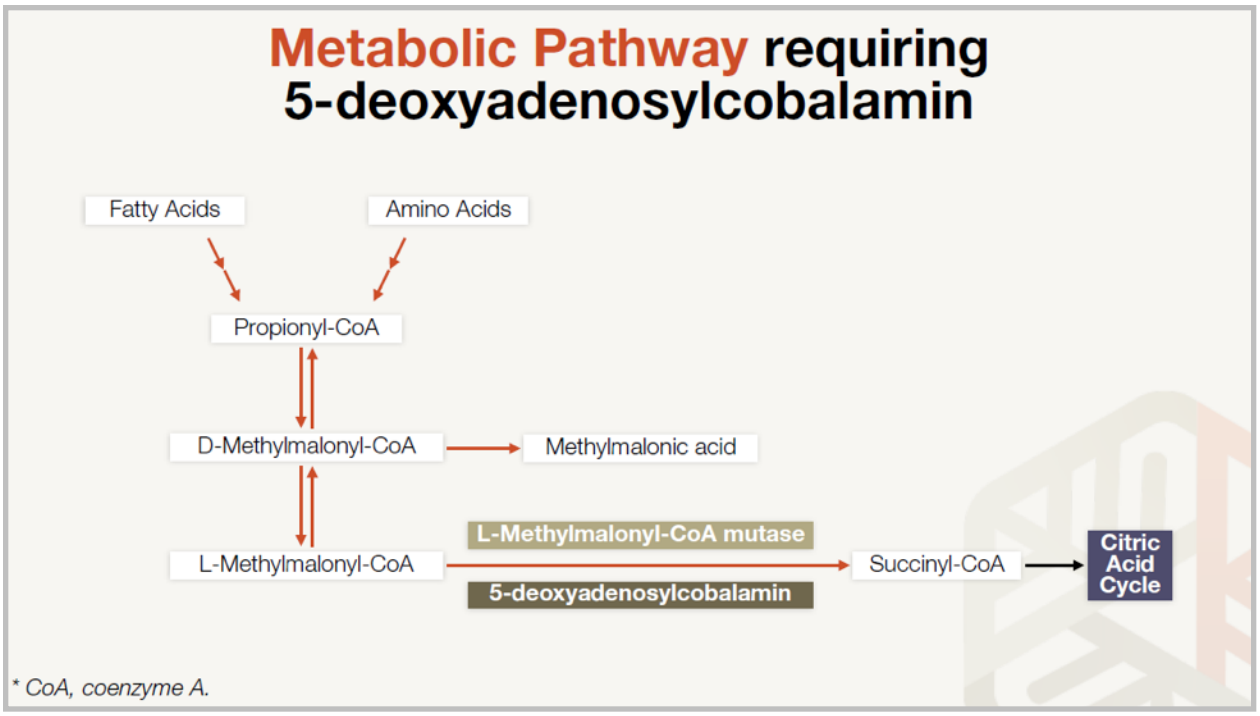
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

B12 Deficiency - Part One

Hey, everybody. In this presentation, we're going to discuss how to diagnose and treat B12 deficiency from a functional perspective. Vitamin B12 works together with folate in the synthesis of DNA and red blood cells. It's also involved in the production of the myelin sheath around the nerves and the conduction of nerve impulses. You can think of the brain and the nervous system as essentially a big tangle of wires, and myelin is the insulation that protects those wires and helps them to conduct messages.



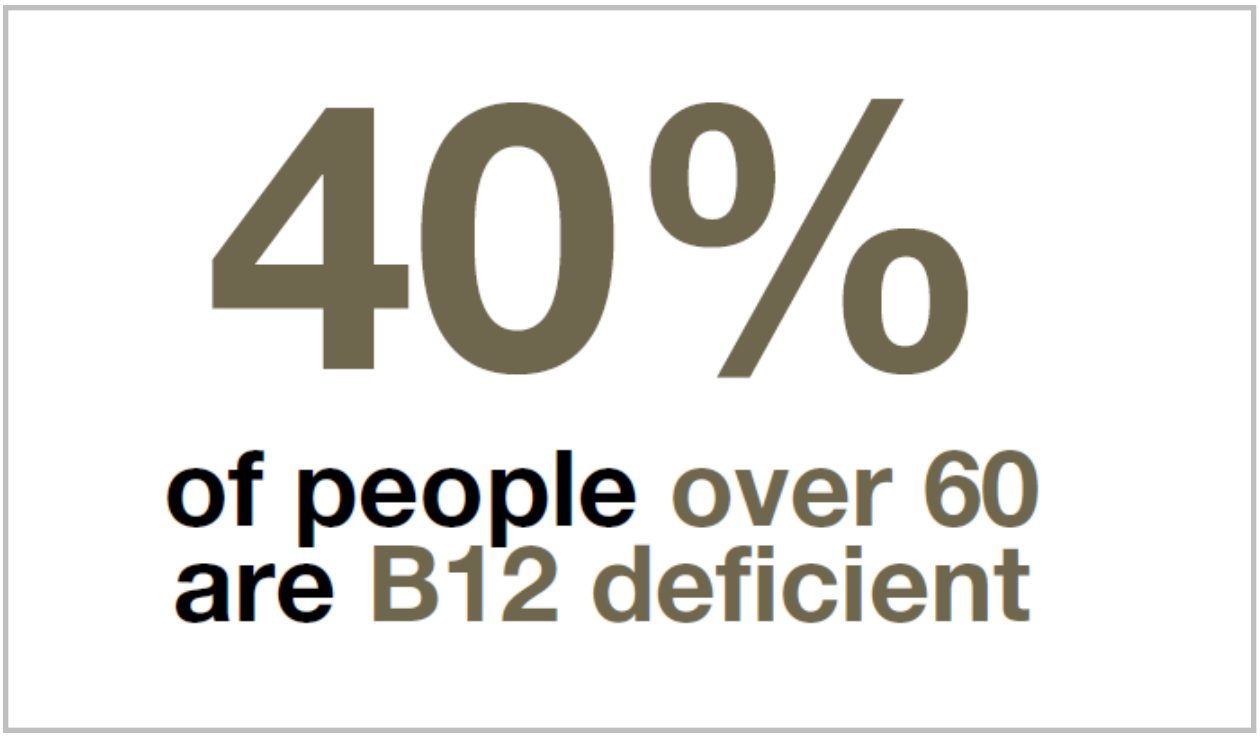
Methylcobalamin is a cofactor for methionine synthase. This enzyme is required for the synthesis of the amino acid methionine from homocysteine in the methylation cycle. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including the methylation of a number of sites within DNA, RNA, and proteins.



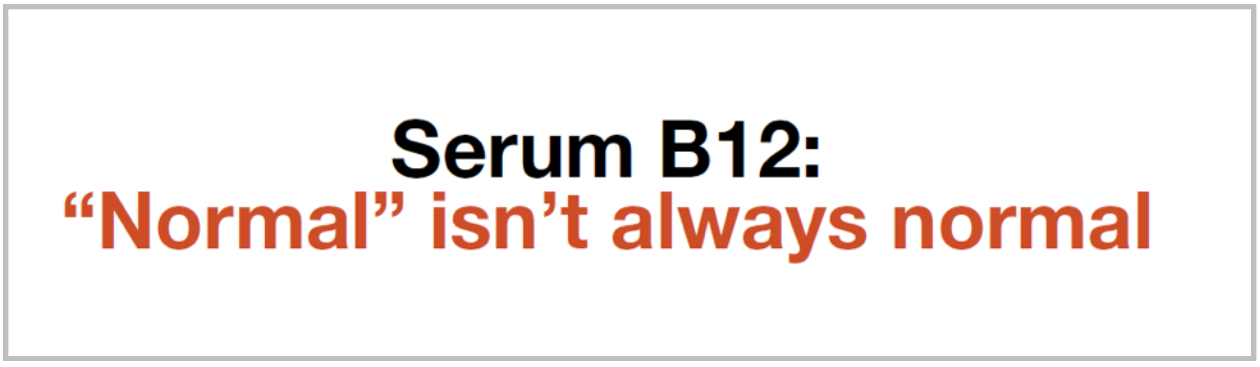
B12 also plays a role in energy production. 5-deoxyadenosylcobalamin is required by the enzyme that catalyzes the conversion of L-methylmalonyl coenzyme A to succinyl coenzyme A, which then enters the citric acid cycle. Succinyl-CoA helps to produce energy from lipids and proteins and is also required for the synthesis of hemoglobin.

New research suggests that B12 may play a role in nitric oxide production. One study showed that supplementing with adenosylcobalamin modulated the immune response by downregulating inflammatory processes mediated by iNOS. This may explain why B12 supplementation has been shown to reduce the severity of autoimmune conditions such as rheumatoid arthritis and eczema.

B12 deficiency is much more common than the conventional medicine establishment and general public realize. Data from the Tufts University Framingham Offspring Study suggests that 40 percent of people between the ages of 26 and 83 have plasma B12 levels in the low-normal range, a range at which many experience neurological symptoms. Nine percent had outright deficiency, and 16 percent exhibited near deficiency. Most surprising to the researchers was the fact that low B12 levels were as common in younger people as they were in the elderly.

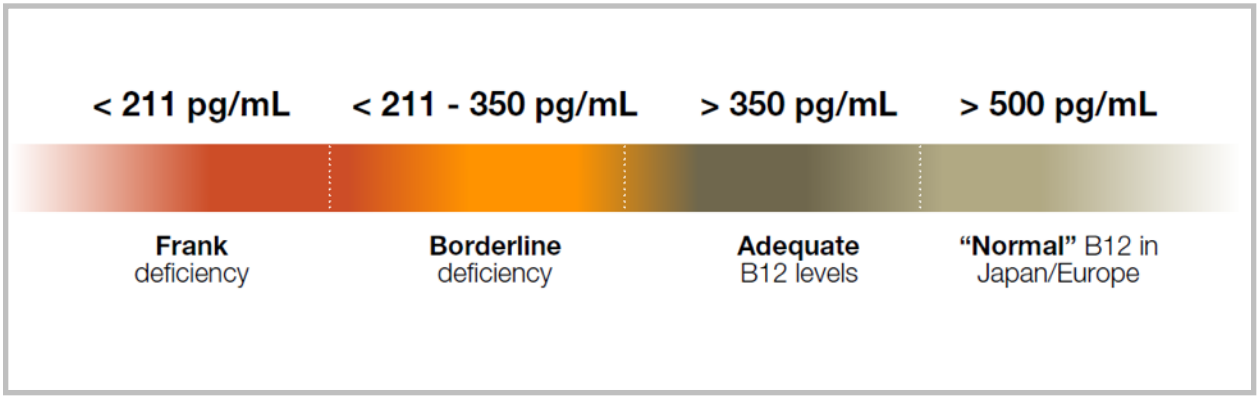


B12 deficiency has been estimated to affect about 40 percent of people over 60 years of age. It can mimic the signs and symptoms of diseases that are commonly associated with aging such as Alzheimer's, dementia, cognitive disorders, multiple sclerosis, Parkinson's, and other neurological problems; mental illnesses such as depression and anxiety; cardiovascular disease; cancer; and low libido. It's entirely possible that at least some of the symptoms we attribute to "normal" aging such as memory loss, cognitive decline, and decreased mobility are at least in part caused by B12 deficiency.

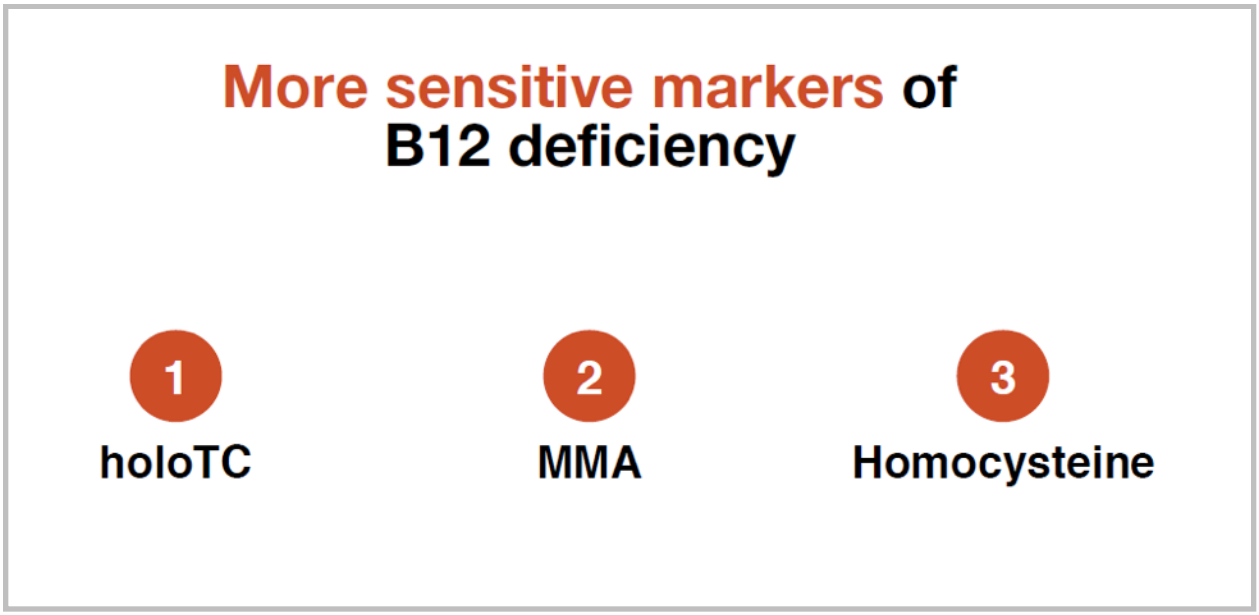


B12 deficiency is often missed for two reasons. First, it's not routinely tested by most physicians. Second, the conventional serum B12 test that most doctors run only picks up a small fraction of people who are actually B12 deficient. This test measures the total amount of B12 in the blood and does not rule out functional B12 deficiency, which means low levels of active B12. The low end of

the laboratory reference range for serum B12 is too low. Many people who are B12 deficient have so-called normal levels of B12.



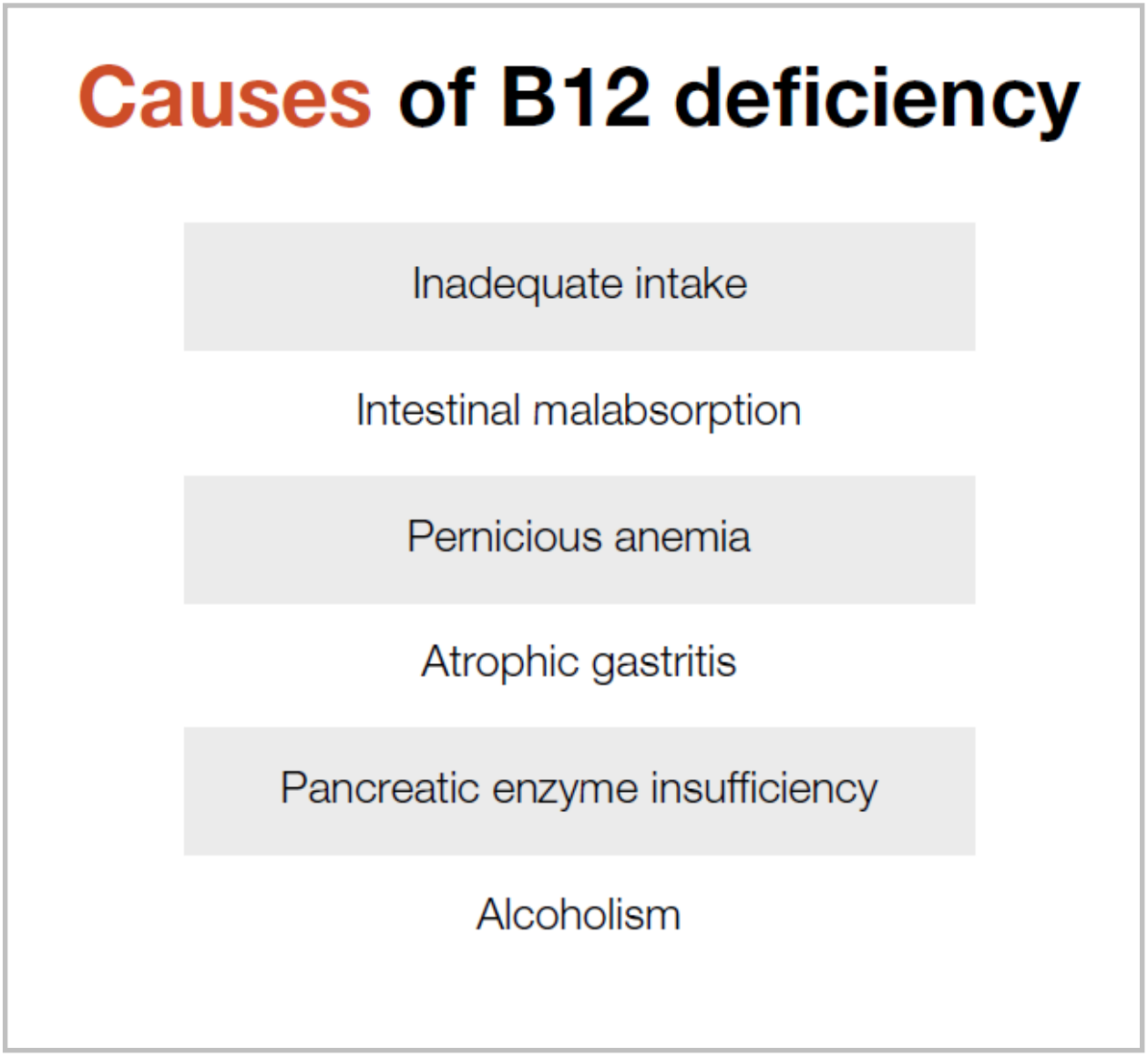
For example, the lab reference range goes down to 211 pg/mL in most cases, yet it's well established in the scientific literature that people with B12 levels between 200 and 350, levels that are mostly considered to be normal in the U.S., may exhibit clear B12 deficiency symptoms. In Japan and Europe, the lower limit for B12 is between 500 and 550, the level associated with psychological and behavioral manifestations such as cognitive decline, dementia, and memory loss. Some experts have speculated that the acceptance of higher levels of normal in Japan and the willingness to treat levels considered normal in the U.S. explain the low rates of Alzheimer's and dementia in that country.



In addition, as we'll see shortly, more sensitive markers for B12 deficiency are now available, including methylmalonic acid, or MMA, and holotranscobalamin-2, or holoTC, although this is not yet widely available clinically in the U.S. Other indirect markers such as homocysteine may be more

sensitive and accurate for detecting the early stages of B12 deficiency. Unfortunately, few clinicians are aware of them, and they are rarely used in clinical practice. You can't find what you're not looking for, so this is the real problem with B12.

This is a serious problem because B12 deficiency can take years to become clinically evident, and the effects can be irreversible. In some cases, such as screening for breast cancer with mammograms, the screening procedure itself isn't harmless and can lead to increased risk of harm due to overtreatment. However, overdiagnosis of B12 deficiency is completely innocuous because B12 is so safe to supplement with, whereas misdiagnosis is not because of the potentially irreversible neurological damage, which is completely preventable.



Causes of B12 deficiency include inadequate intake, which is common in vegetarians and vegans, as we'll see; intestinal malabsorption due to low stomach acid, celiac disease, Crohn's disease, or

other gastrointestinal conditions; pernicious anemia, which is an autoimmune condition resulting in the destruction of parietal cells that produce intrinsic factor or antibodies to intrinsic factor itself, and intrinsic factor is required to absorb B12, and this affects 2 percent of people over 60 years of age; atrophic gastritis, which is often caused by H. pylori infection in the elderly, which affects about 10 to 30 percent of people over 60 years of age—by the way, both pernicious anemia and atrophic gastritis can affect younger people as well; pancreatic enzyme insufficiency; and then alcoholism, which reduces the absorption of B12 in the terminal ileum.

Populations that are at risk for B12 deficiency include vegans and vegetarians. Early studies suggested that vegans and vegetarians had similar rates of B12 deficiency to omnivores. However, these studies relied on serum B12 levels, which are not sensitive indicators of B12 deficiency. Later studies that used either MMA or holoTC found much higher rates of deficiency in people following plant-based diets—68 percent for vegetarians and 83 percent for vegans, compared to just 5 percent for omnivores. That's a huge, game-changing difference, and it means that conventional testing is missing 61 percent of vegetarians and 31 percent of vegans who are B12 deficient.

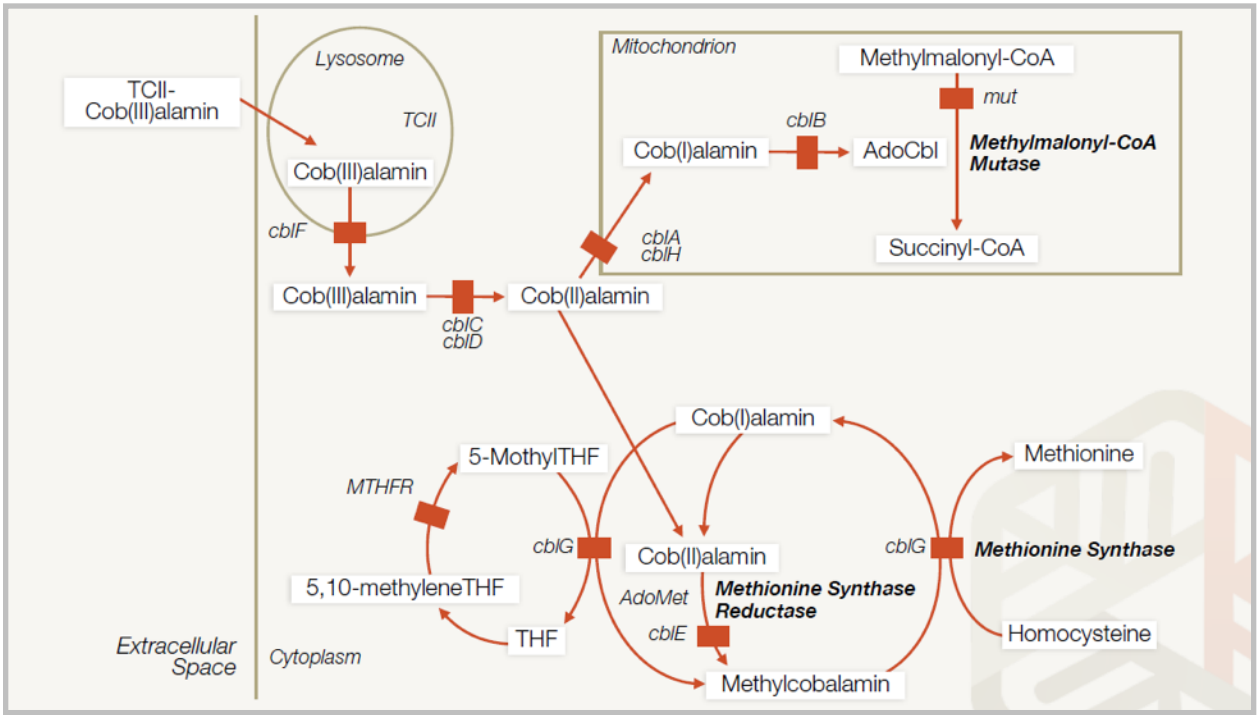
Vegans and vegetarians are at much higher risk because B12 is only found in animal products. B12 is the only vitamin that contains a trace element, cobalt, which is why it is called cobalamin. Cobalamin is produced in the gut of animals. It's the only vitamin we can't obtain from plants or sunlight. Plants don't need B12, so they don't store it. A common myth among vegetarians and vegans is that it is possible to get B12 from plant sources such as seaweed, fermented soy, spirulina, and brewer's yeast, but plant foods said to contain B12 actually contain B12 analogs called cobamides that block the intake of and can increase the need for true B12.

The elderly is another population at risk. H. pylori infection and chronic proton pump inhibitor use lead to low stomach acid, which decreases B12 absorption. Remember, B12 deficiency is thought to affect up to 40 percent of people over age 60.

It's not just the elderly who are at risk from PPI use. Anyone who regularly uses PPIs can be susceptible to this effect, and that now includes a lot of people under 60 years of age. Over 15 million prescriptions were filled for PPIs in 2013, and the FDA in its infinite wisdom recently made omeprazole, or Prilosec, available over the counter in 2000. This was soon followed by Prevacid becoming available over the counter. PPIs were only approved for short-term use of two weeks, but they are now taken for years or even decades. Numerous studies have shown side effects, risks, and complications, but this has not affected their use.

The next population at risk is those with digestive disorders that lead to malabsorption. This includes celiac disease, which blunts the intestinal villi and causes malabsorption of several nutrients, and Crohn's disease, which causes inflammation of the terminal ileum in many cases, and the terminal ileum is where the intrinsic factor B12 complex is absorbed.

Another population to consider B12 deficiency in is women with frequent or recurrent miscarriage or infertility. Both B12 and folate are required for making new cells. If either is deficient, that can lead to infertility, miscarriage, or birth defects.



Another population that may be susceptible to B12 deficiency is those with genetic polymorphisms affecting B12 assimilation and metabolism. These are thought to be responsible for a variety of clinical symptoms of B12 deficiency, even when B12 intake is adequate. The figure on this slide illustrates several genetic polymorphisms that can impair various steps in B12 assimilation and intracellular metabolism. Note that while we do know these polymorphisms exist and there is some research correlating certain SNPs with changes in B12 levels, I don't think the genetic testing is at the point where it affects clinical decision-making above and beyond what the functional B12 markers tell us. It doesn't really add to the clinical picture, so I don't recommend doing the testing right now.

Finally, the diabetes drug metformin has been shown to deplete B12 levels, so be aware of that if you have a patient who has been taking metformin for some time.

While kids are not at particular risk unless they fall into the other categories we've just talked about, the effects of B12 deficiency in kids can be particularly alarming. Studies have shown that kids raised until age six on a vegan diet are still B12 deficient even years after they started eating at least some animal products. In one study, the researchers found a significant association between cobalamin status and performance on tests measuring fluid intelligence, spatial ability, and short-term memory, with formerly vegan kids scoring lower than omnivorous kids in each case. The deficit in fluid intelligence is particularly troubling, the researchers said, because it involves

reasoning, the capacity to solve complex problems, abstract thinking ability, and the ability to learn. Any defect in this area may have far-reaching consequences for individual function.

Now, I recognize that there are many reasons why people choose to eat the way they do, and I respect people's right to make their own choices. I also know that, like all parents, vegetarians and vegans want the best for their children. This is why it's critical for those who abstain from animal products to understand that there are no plant sources of B12, and that all vegans and most vegetarians should supplement with it. This is especially important for vegetarian or vegan children or pregnant women whose need for B12 is even greater than adults.