KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Impaired Methylation - Part Two

B12 intake recommendations

Source	Amount (mcg)
Current RDA	2.4
Studies on minimizing chromosomal damage and improving DNA repair	7
Average daily intake of hunter-gatherers	17.6

We've discussed B12 intake in the B12-deficiency presentation. The current RDA for B12 is 2.4 mcg per day. This is for healthy adults, under age 50, with normal absorption. The average intake in the U.S. is 3.4 mcg per day. However, as we discussed, for adults over 50 or those with impaired absorption, anyone with GI issues, the RDA increases to 150 to 200 mcg per day. In these populations, less than 1 percent of orally consumed B12 may be absorbed, and given the prevalence of GI issues, the RDA of 2.4 mcg per day is very likely inadequate even in people under 50. In my experience, as I shared with you, B12 deficiency is likely much more common than believed, even among omnivores.

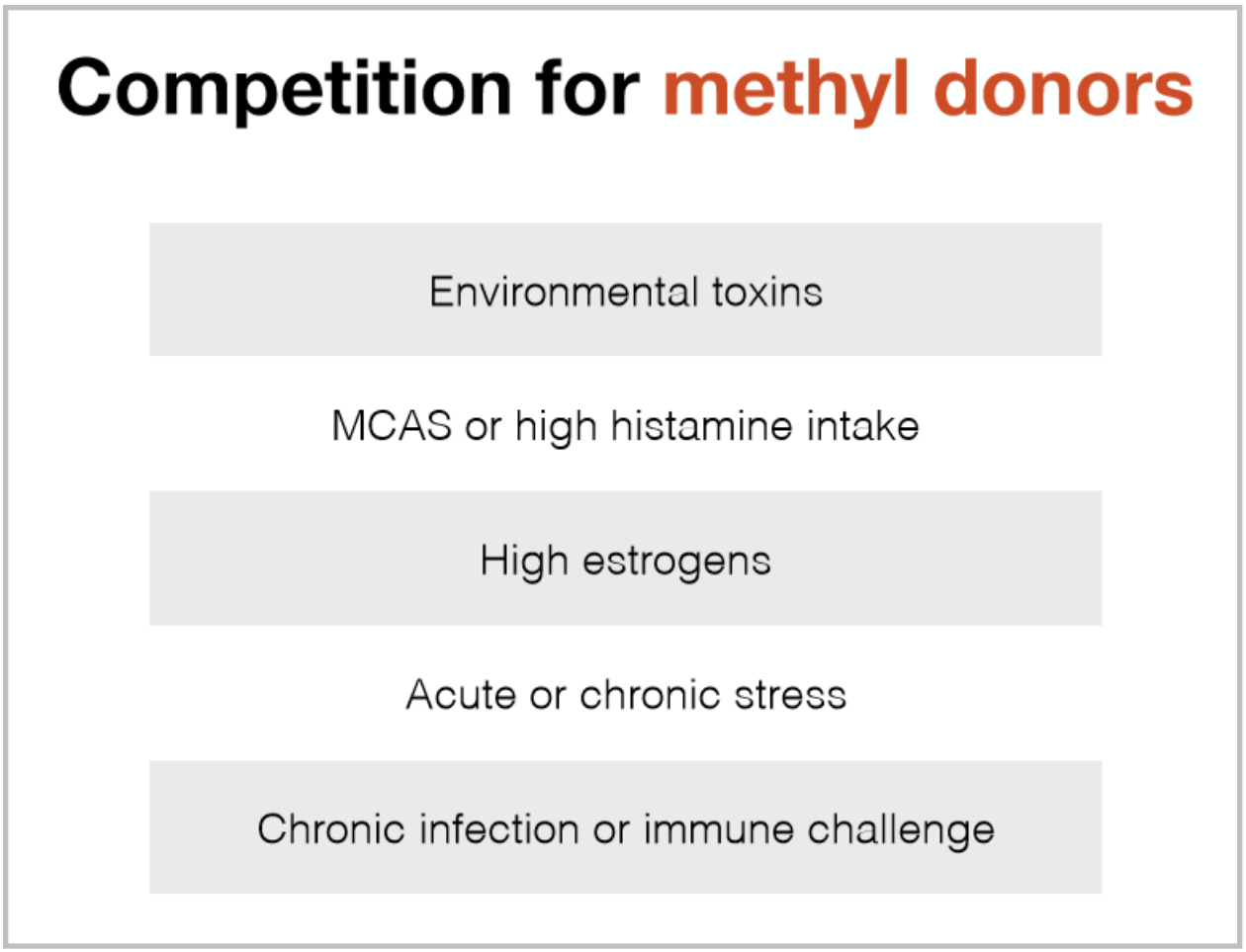
Studies that looked at optimal B12 levels based on minimizing chromosomal damage and improving DNA repair, as you recall from the B12 presentation, suggest an RDA of 7 mcg per day in people without absorption issues. Loren Cordain's research suggests that the average daily intake of B12 in hunter-gatherers was 17.6 mcg per day, which is significantly higher even than the 7 mcg per day threshold. If we use this higher number as the recommended daily intake for healthy people under 50 years of age with no absorption issues, that number for people over 50 or with absorption issues would be tenfold higher—1,700 mcg per day—which is almost impossible to achieve without supplementation, and it suggests that many elderly people or people with absorption issues might do better taking a B12 supplement. This is supported by research showing that patients with no overt signs of B12 deficiency as defined by serum cobalamin, which as you know isn't particularly reliable, experienced remarkable improvements after high-dose B12

supplementation. There is no tolerable upper intake level for B12, and no toxicity threshold has been found. Therefore, advising higher intakes is safer than advising lower intakes.

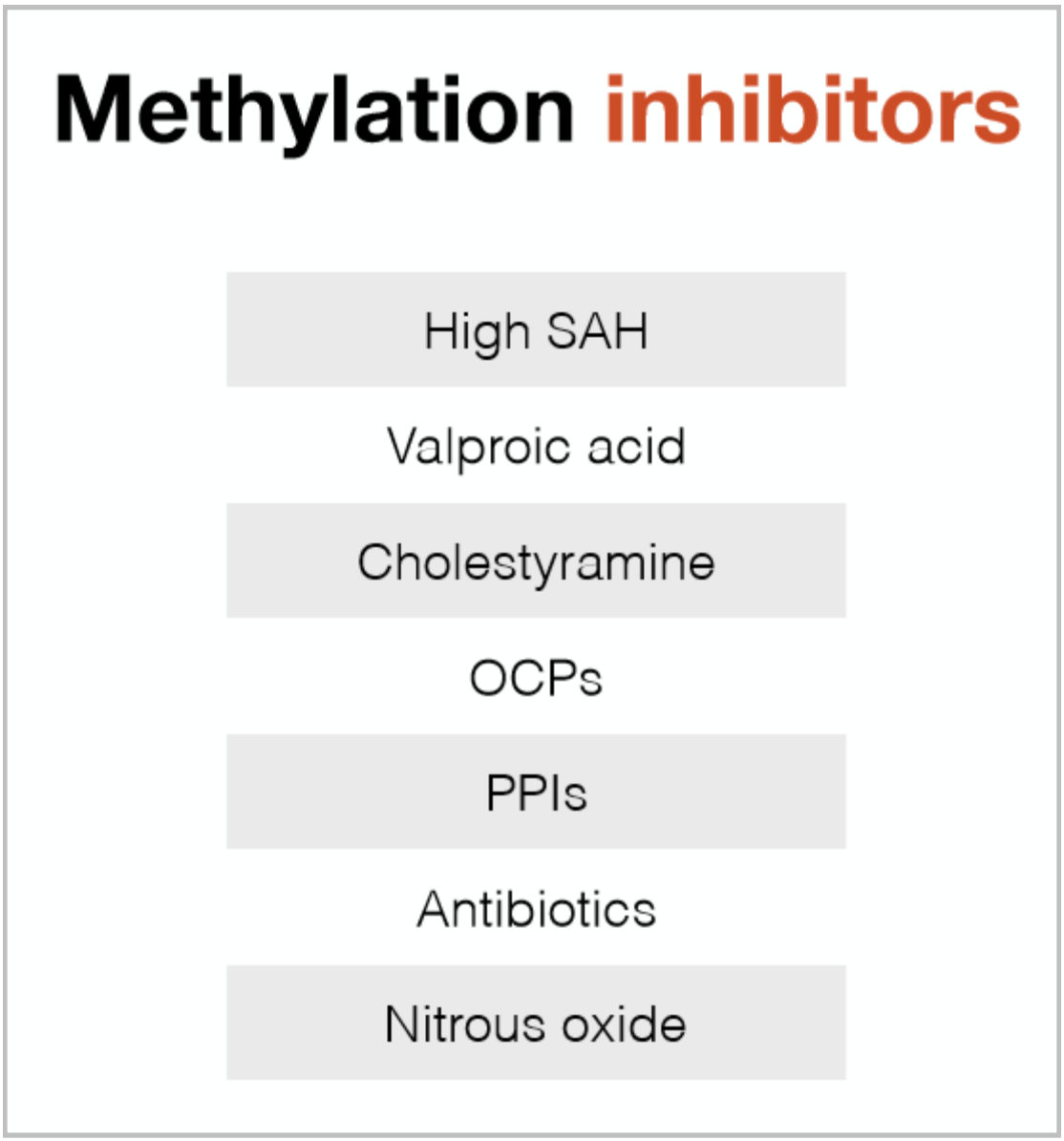
Highest dietary sources of B12

Food	Amount (mcg per 100g)
Clam	99
Lamb liver	90
Beef liver	83
Duck liver	54
Oyster	35
Pork liver	26
Caviar	20
Mackerel	19
Herring	19
Mussel	12
Crab	11
Sardine	9
Salmon	6

Here are the highest dietary sources of B12. Again, this is from the previous presentation, but I just put it here for convenience. If the patient is not eating organ meats or fish, it's quite possible they are not getting enough B12. As you can see here, shellfish and liver again top the list by far, clams at 99 mcg per 100 g serving. Really every significant source of B12 on here, from the 99 mcg for clam all the way down to 6 mcg for salmon, are either organ meats or fish. Especially if the patient is over 50 or having GI issues, and they are not eating these foods regularly, they may not be getting enough B12.



Another risk factor for impaired methylation is competition for methyl donors. One particular function of methylation may be in overdrive and sucking up available methyl donors at the expense of other functions of methylation. This can be caused by toxic burden. For example, the presence of heavy metals, mold, or other toxins that upregulate detox pathways; mast cell activation disorder or a high histamine diet, which increases demand for histamine and methyltransferase-dependent breakdown of histamine; high estrogen levels due to oral contraceptive use or other causes, increasing demand for estrogen clearance; acute or chronic stress causing high catecholamine turnover—dopamine, epinephrine, or norepinephrine—and increased demand for catecholamine synthesis; chronic infection or immune challenge causing increased demand for maturation of T cells and other immune cells. Again, all of these are common in the modern lifestyle, which increases demand for methylation and risk of methylation deficit, and it explains why environmental factors are more important than genetic factors.



Methylation inhibitors can also interfere with methylation-dependent functions in the body. Elevated homocysteine levels, which are most often caused by B12 and folate deficiency, will increase S-adenosylhomocysteine and impair methylation. Some drugs can interfere with methylation such as valproic acid or Depakote, which is a drug used to treat seizures, and it is a histone deacetylase inhibitor. Cholestyramine, a drug used to treat biotoxin illness, interferes with the absorption of folate, fat-soluble vitamins, and other nutrients required for methylation. Oral contraceptive pills deplete magnesium, B6, B2, and riboflavin, and increase estrogen levels, which has a dual effect of both impairing methylation and increasing the need for methylation. PPIs, acid-blocking drugs, reduce the absorption of folate and other methyl donors. Antibiotics deplete beneficial bacteria. Studies have shown that metabolites produced by beneficial bacteria serve as critical cofactors and allosteric regulators of epigenetic processes. Nitrous oxide, which some

patients take at the dentist, is a known oxidizer of cobalamin, and oxidation of cobalamin destroys it unless there are adequate nutrients available to restore the cobalamin back to its active state.

The last risk factor that I'd like to talk about for impaired methylation is genetics. Polymorphisms in methylation-related genes can lead to reduced capacity for methylation. Methylenetetrahydrofolate reductase, MTHFR, is the best known of these genes, but there are many other genes that affect methylation, including COMT, MTR, MTRR, and BHMT. The most common MTHFR polymorphisms are C677T and A1298C. The frequency of homozygosity for C677T is highly variable according to ethnicity and geography. The highest frequency over 20 percent homozygous is reported in U.S. Hispanics, Columbians, and Amerindians in Brazil. The frequency of homozygous C677T among white populations in Europe, North America, and Australia is anywhere between 8 and 20 percent. The lowest frequency, under 2 percent, is found in black populations. The frequency of homozygous A1298C genotypes in white populations in North America and Europe is reported to be between 7 and 12 percent, and lower frequencies are reported in Hispanics, 4 to 5 percent, and Asian populations, 1 to 4 percent.

Homozygous C677T: 70-75% loss of enzyme activity

Homozygous C677T variance has 70 to 75 percent loss of enzyme activity, while heterozygotes, people with only one polymorphism in MTHFR C677T, lose 33 to 35 percent of enzyme activity. Homozygous A1298C genotypes have a 39 percent reduction in enzyme activity, so pretty similar to heterozygotes for C677T. Heterozygotes for A1298C have a 17 percent reduction of enzyme activity. Compound heterozygotes who have one copy of C677T and one copy of A1298C may lose as much as 52 percent of enzyme activity.

A recent systematic review and meta-analysis reports a 16 percent decrease in red blood cell folate levels for homozygous C677T genotypes when compared with their wild type C677T counterparts and an 8 percent decrease for heterozygous C677T genotypes.

Note that there are many other genes that affect methylation. This is an extremely complex, active area of research that I'll cover in more detail in a future advanced course. Also, I believe that environmental causes are more significant for the reasons that we've discussed than genetic factors. Because I've done both genetic and functional methylation testing on many patients, I can tell you that sometimes there is a correspondence between genotype and functional methylation status, and at other times there is not.

Markers of impaired methylation

Marker	Value
Serum folate	Low
RBC folate	Low
Serum B12	Low
Serum MMA	High
Serum homocystine	High
Urine MMA	High
Urine FIGLU	High

Alright, let's talk about the markers that we're going to be going over for impaired methylation. The bolded markers on this slide are included in my functional blood chemistry case review panel, and then the plain text markers can be used as add-ons. Remember, MMA and FIGLU are inverse markers, so that means when they are high they are indicative of B12 deficiency. Homocysteine is also inverse, when it's high, it means that more B12 and folate are required to convert homocysteine back into methionine. So we have serum folate, red blood cell folate, serum B12, serum MMA, serum homocysteine, and then urine MMA, and urine FIGLU.