S-Adenosyl-L-Methionine (SAMe)

SAMe is a substance found all over the body that is used in the methylation pathway.

This pathway is a complex circuit that leads to products that affect our DNA, our energy and our mood.

As a supplier of a methyl group and organic sulphur, SAM-e drives complex metabolic reactions that control **cell growth and lifecycle, inflammation, brain chemistry**, and more [3, 4].

SAM-e prevents uncontrolled cell division, which is the main feature of cancer cells.

It also inhibits MMP, an enzyme involved in cancer progression and inflammation [5].

The brain needs SAM-e to make serotonin, dopamine, and noradrenaline, which support mood, motivation, and overall mental health [6, 7, 8].

It combats oxidative stress and protects the cells by boosting the production of a master antioxidant, glutathione [9, 10, 11].

All these natural products have been well researched and shown to upregulate immunity while protecting the body against viruses and other microbes.

SAM-e has been shown to relieve depression, anxiety, brain fog, and pain including arthritic and fibromyalgia pain, improve memory, mood and sociability, and support liver health.

About Methylation and The Methyl Group

Methylation is a biochemical reaction in our body that is involved in many important bodily processes. It occurs more than one billion times per second in our cells. Although it occurs in all the cells of the body, 85% of methylation takes place in the liver.

Methylation involves the removal of a methyl group from one substance, and the addition of the methyl group to another substance. This happens repetitively in various chemical reactions.

A methyl group is one carbon atom attached to 3 hydrogen atoms “CH3". A carbon can bind to 4 other atoms. This means a methyl group has one unbound area. This area can attach and detach from other molecules. This process of attachment of a methyl group is called methylation. The methyl group can be transferred onto amino acids, proteins, enzymes, and DNA in every cell, and all the tissues in all the organs of the body. This process is catalyzed by a variety of enzymes in the body.

Where Do Methyl Groups Come From

They can come from ingestion of food or supplements. The supplement SAM or SAM-e is a methyl group donor. You can also ingest nutrients that are essential to

activate the amino acid methionine into SAM or recycle methione back to SAM once it donates its methyl group.

The body makes methyl groups and recycles them. S-Adenosyl Methionine (SAM) commonly donates a methyl group for reactions. The methyl group on methionine is used for adding methyl groups to numerous kinds of molecules, but only after methionine has been activated.

Methionine's methyl group is activated by by ATP or adenosine triphosphate when adenosine is added to the sulphur of methionine to form S-Adenosyl Methionine (SAM). Once the methyl group from SAM has been donated, S-adenosyl-homocysteine can continue through what is called the methionine cycle to be recycled into an activated SAM again.

Substrates

We talk about methyl groups being donated to a substrate. Substrates that methyl groups are donated to include nuerotransmitters/hormones, immune cells, DNA and RNA.

Enzymes

The enzymes needed for methylation are N-, and S- methyl-transferases. The co-substrate used is the S-adenosylmethionine (SAM).

Let's look at why we need methylation.

Basic Methylation Functions

Methylation is involved in most reactions that take place in our body. As I mentioned above it takes place billions of times per second in our cells and happens more in the liver than any other organ. Where we use the most methyl groups is in the production of creatine and phosphotidylcholine.

An easy way to understand how methylation can affect us is to examine coffee. Coffee has a lot of methyl groups. Think about how coffee affects you, and you will know one way of how methyl groups can affect you personally. Some folks must have their coffee in the AM to wake up, be able to wipe away some brain fog, be able to focus, articulate their thoughts, etc.

Methylation is involved in most of our body processes. Methylation will help our immune system protect us, help us focus our attention, support nerve transmission, help us detox, and keep our energy flowing. Methylation can turn genes on, and off in our body, which can be delightful or lead to problems. For some specific details read on...

Some Important Processes That Need Methylation

- Production of energy (ATP via Krebs cycle, CoQ10, carnitine, creatine)
- DNA synthesis, and histone Synthesis (Thymine aka 5-methyluracil), repair & expression of DNA (turning genes on and off), RNA synthesis, regulating protein function,
- Modification of toxins and chemicals. Processing of both endogenous and xenobiotic compounds for removal from the body (biotransformation via Phase II liver clearing)

- Glutathione production which is very important in biotranformation/detoxification
- Ability to methylate modulates neurotransmitter function. Need it to build neurotransmitters such as dopamine, and epinephrine as well as degradation, or catabolism/breakdown of these neurotransmitters.
- Making and processing hormones
- Building immune cells (T cells, NK cells)
- Building and maintaining cell membranes (phosphatidylcholine). This is via utilization of phosphatidylcholine derived from phosphatidylethanolamine in the presence of functioning PEMT enzyme.
- Building myelin which is a protective insulation on nerves. and to inactivate histamine.

How You Are Affected by Methylation

- Mutations in the methyl transferase genes cause serious, sometimes lethal, defects. It is known that environmental conditions affect methylation, and that methylation degrades with age. Several of the diseases of old age, including diabetes and Alzheimer's, are known to be associated with aberrant patterns of methylation.
- In people with decreased activity in the methionine cycle there is a shortage of activated methyl groups in the body needed to execute many important bodily functions. Additionally, variants in methylation decrease protection from environmental, and infectious agents.
- These methylation variables can cause a wide range of conditions including thyroid dysfunction, early aging, diabetes, cardiovascular disease, neurological inflammation, neurotransmitter imbalances, chronic viral infection, atherosclerosis, cancer, schizophrenia, decreased repair of tissue damage, improper immune function, neural tube defects, Down's syndrome, Multiple Sclerosis, ADD, ADHD, Alzheimer's, autism, Huntington's disease, Parkinson's disease.
- Genetic variants in the methionine pathway, and methylation can cause susceptibility to health conditions. In addition, DNA methylation can cause epigenetic modification. Methylation is involved in how the genes respond to environmental triggers.
- Problems in the methylation pathway can reduce the body's ability to make the building blocks (purines and pyrimidines) needed for new DNA, and RNA synthesis. Some of the body's cells are more susceptible to these methylation issues such as the bone marrow which makes platelets, white blood cells, and red blood cells. Neural tissue is also more likely to be affected.
- Problems in methylation can affect the mitochondria in our cells. Mitochondria are the units that create energy in our cells and ultimately allow all the cells to function. Mitochondria need key nutrients/coenzymes dependent on methylation to be able to create energy. Their basic fuel is derived from glucose or fatty acids from triglycerides. However, they also need a variety of nutrients to function.

Aging and Methylation Effects

As we get older methylation does not work as well, and causes many diseases we associate with aging.

Scientific Data: Gene expression changes during development and maturation, and it is possible that this is accomplished through changing methylation patterns. Gene expression is known to change at advanced ages. These changes may be random, and haphazard, or programmed and determined. The current hypothesis is that altered patterns of methylation may be a cause of the disabilities and altered metabolism that come with age.

- DNA methylation declines with age, resulting in cellular dysregulation. In general, we lose more methylation activity than we gain over time. In research, DNA from older animals is less methylated than from young animals, though there are also some regions of the DNA where there is more methylation with age. In one human study (Bollati 2009), their results on an elderly population in Boston showed a gradual decrease through aging in repetitive element DNA methylation, particularly in Alu sequences. Both animals and people with less total methylation are prone to a variety of age-related disease. (Fraga, 2005).
- In the Fraga study, gene methylation patterns were compared in identical twins when they were very young, and when they were older. Methylation patterns were very similar in young twins but diverged markedly over time indicating a possible epigenetic alteration. Other evidence indicates that relatively small differences in epigenetic patterns can have a large impact on physiological traits. One hypothesis is that some of the body's loss of function with age has to do with the difference in the way that methylation changes over time.

Biotransformation/Detox Effects of Methylation

Taking a chemical from the environment, or from our body that could be harmful and transforming it into something that is less harmful that can be removed from the body or stored out of the way is called biotransformation, or detoxification. Methylation is involved in this process.

Scientific Data: This process involves conjugating (combining) methyl groups to the toxins prior to removal, as well as, supporting the production of glutathione and metalloproteins. Most of the methyl groups used for detoxification come from S-adenosylmethionine (SAM).

Methylation occurs when SAM (S-adenosine methionine) donates a methyl group, which is then attached to the molecule that is being detoxified. SAM then becomes S-adenosine homocysteine.

Cancer Prevention

Hypermethylation as well as hypomethylation is associated with a large number of human cancers. Normalization of methylation is important in cancer prevention and is being researched for cancer treatment. Reduced DNA methylation results in genetic instability, aberrant gene expression, and increased cancer. Hypermethylation can also be associated with human cancers.

Folate deficiency has been implicated in the aetiology of lung, cervical, breast and brain cancer. Convincing evidence links folate deficiency with colorectal cancer incidence. Colorectal cancer incidence is inversely associated with both dietary folate intake and blood cell folate concentrations. Supplementation of folate to prevent colon cancer has had varied results and may have something to do with folic acid (synthetic form) being used in the research rather than folate. More research is needed.

Cell Membranes & Membrane Fluidity

Every cell in your body depends on methylation for its outside wall to be able to maintain strength and flexibility. Without methylation the cells membrane can not function well.

Scientific Data: Methylation is needed to build and maintain cell membranes. Methylation is necessary in making phosphatidylcholine that is used in making the cell membrane.

Our cell membranes need to have fluidity. The membrane fluidity allows it to be mobile as it protects the cell from negative outside influences or decides to let needed nutrients inside. This fluidity is dependent on the phospholipid membrane that incorporates phosphatidylcholine.

Creatine

Overtraining is an issue. Creatine needs SAM for its methyl group. The more muscle mass you have, the more creatine you need, and the more SAM you need to make it. Creatine, and phosphotidylcholine use up the majority of SAM in body. Creatine is about 70% of SAM use.

DNA & RNA

Methylation is a part of RNA, DNA creation, activation, silencing and repair. Methyl groups are important in control of gene expression. Genes can be turned on and off through DNA modification. Methyl groups (as well as some other molecules) can attach to the DNA sequence which will prevent or promote expression of the genes nearby.

They help turn your genes on (express the gene) and off (silences the gene). I have seen some people refer to this in relation to a charm bracelet and I think that analogy is helpful. Think of your DNA as the chains of a charm bracelet, and the methyl groups are the charms that can be added to the bracelet.

The very charm bracelet itself is dependent on proper methylation to create the proper DNA to build the bracelet. (This can be affected in utero.) The charms on the bracelet are the methyl groups. You can add charms (methyl groups) to the charm bracelet, or you can remove charms (methyl groups) from the charm bracelet.

We can think of DNA variants as changes in the bracelet chains as well as changes in the ability to make the appropriate number of charms and add or remove those charms.

Methyl groups can combine with other compounds that instigate reactions that will activate a gene or an enzyme. When there is a lack of methyl groups you do not get the necessary activity of the gene or enzyme. Sometimes lack of a methyl group could mean that a gene is turned on also.

Abnormal methylation changes play a role in diseases, such as cancer or fragile X syndrome, and may also occur as a function of aging or because of environmental influences.

Genetics And Epigenetics

So, we have seen above that methylation can control gene activity. In addition, various genetic mutations or what is also called variations, can affect methylation. A common genetic variation is the inability to create active folate from dietary folate. 40% of the population has this genetic variation that limits partially or completely the ability to process dietary folate into active folate due to a single nucleotide polymorphism (SNP) variation. This variation will decrease the activity of the methylation cycle which can affect DNA replication which can create an unhealthy cycle.

Genetics are useful, but epigenetics are generally as important and may even be more important than the genetics themselves. Lifestyle and diet make all the difference in the world. Eating appropriately, living in a non-toxic, non-stressful environment are key ingredients to adequate methylation. Genetics becomes more important when you come from a family that tends to die early or have a lot of chronic illness. Genetics becomes more important in pregnancy and in aging also.

Scientific Data on Folate and DNA Stability

Currently, it is believed that folate deficiency affects DNA stability principally through two potential pathways. 5,10-Methylenetetrahydrofolate donates a methyl group to uracil, converting it to thymine, which is used for DNA synthesis and repair. If folate is limited, imbalances in the DNA precursor pool occur, and uracil may be mis incorporated into DNA. Subsequent misincorporation and repair may lead to double strand breaks, chromosomal damage, and cancer.

Moreover, folate effects gene expression by regulating cellular S-adenosylmethionine (SAM) levels. 5-Methyltetrahydrofolate serves as methyl donor in the remethylating of homocysteine to methionine, which in turn is converted to SAM. SAM methylates specific cytosines in DNA, and this regulates gene transcription. Because of folate deficiency, cellular SAM is depleted, which in turn induces DNA hypomethylation and potentially induces proto-oncogene expression leading to cancer. There is convincing evidence that folate modulates both DNA synthesis and repair and DNA hypomethylation with altered gene expression in vitro.

Energy production

Cells produce energy in the mitochondria which is often called the cellular powerhouse. Mitochondria produce energy to run the body. This energy is called adenosine tri phosphate (ATP). The methylation cycle products are a part of what empowers the mitochondria. Carnitine and CoQ10 which are both dependent on the methylation cycle are needed for mitochondria to function properly. Without energy you get tired, and you experience muscle pain and generalized inflammation along with other symptoms.

Exercise and Methylation

- Chronic moderate exercise appears to attenuate the age-dependent decrease in ASC gene methylation.
- High intensity exercise has been shown to result in reduced DNA methylation in skeletal muscle.

Caffeine could induce the same changes in DNA methylation as exercise. Calcium is stored in compartments in each muscle cell, and when it gets released this signal the muscle cell to contract. Bathing a muscle cell in caffeine will cause it to release its stored calcium, effectively causing muscle contraction. The researchers bathed the cells in caffeine to cause contraction and trick the muscles cells into thinking they were exercised. This resulted in a decrease in methyl groups on the same genes as before, causing increased expression of genes that support sugar and fat metabolism.

This in vitro research doesn't mean that we can all drink coffee, or other caffeine drinks/foods as a substitute for exercise and get the same results. Even if we could, the amount of caffeine used to bathe the cells in these experiments is equivalent to 50-100 cups of coffee!

People with type II diabetes have more methyl groups on the metabolic genes compared to people without type II diabetes, and this worsens their metabolic response to sugar, and fats because their genes are turned off. The researchers hypothesize that exercise may be a way to remove the methyl groups, and restore the proteins and enzymes to help control metabolism of sugar and reduce the symptoms seen in type II diabetic patients.

Gut Health

The gut houses about 3 lbs of friendly gut bacteria that is very important to our assimilation of nutrients needed for methylation. A large share of our immune system is in the gut. These microbes and the immune system can have a big effect on neurotransmitter status.

Hormones

Oestrogen is methylated to be broken down and removed. Without methylation it can rise to excess levels.

Heavy Metals

Arsenic

Found in some well water, chicken as well as rice can have high levels of arsenic. Arsenic negatively affects SAM (primary methyl donor) as well as glutathione. Need both to get arsenic out of the body.

Immune Function

The immune system needs methylation to function properly. Methylation decreases with age, thereby affecting our immune system. It appears that impaired methylation can create an inflammatory state and is a factor in autoimmune conditions.

Scientific Data: Problems in methylation can affect the immune system. As mentioned above, you may have trouble making the building blocks that are needed for new DNA synthesis. If you cannot make new DNA, then you cannot make new T cells and as a result you may lack immune system regulatory cells. T cells are involved in protecting us from viral and parasitic infections as well as controlling B cells which produce antibodies.

When the methylation pathway is not working well, the immune system will have an increased tendency to make B cells, which may result in an autoimmune disorder. Methyl cycle supplementation has been used in treatment of autoimmune disorders when related to underactive methylation.

Methylation is also involved in building natural killer (NK) cells.

As we age, methylation decreases. This can cause a decrease in T cells and NK cells which can change immune system function.

Methylation plays a role in the ability of the immune system to recognize antigens (foreign bodies) that it needs to respond to. Research has shown that methylation is decreased in humans with auto immune conditions. DNA methylation levels and patterns in mature T cells can result in T-cell autoreactivity in vitro and autoimmunity in vivo.

Research with DNA methylation in T cells has shown abnormal DNA methylation plays a role in idiopathic human lupus. Methylation may also affect the balance of TH1/TH2 (Helper cells in immune system). Methylation impairment may lead to alteration of TH1/TH2 and create an inflammatory state.

Inflammation

Poor methylation and inflammation are found hand in hand. They feed off each other. If you have one, you have the other.

Scientific Data: Poor methylation produces inflammation and inflammation decreases the ability to methylate adequately. So, you can get a continuous feedback loop.

More inflammation tends to lower methylation. IL6 and TNF alpha are two biochemical markers that are high in inflammatory states. When these are high, they tend to lower methylation status.

When methylation is low, histamine levels tend to be high. Histamines are deactivated by receipt of a methyl groups. Histamines are released in response to antigens and are linked to inflammation.

Inadequate methylation is associated with autoimmune disorders.

Morphine Effect

S-adenosylmethionine (SAM) is the queen of methylators. Morphine, cow milk protein, and a wheat protein were all examined and found to decrease SAM significantly. This would significantly decrease methylation in the body. Cow milk protein lowered SAM, but human milk protein did not.

Scientific Data: Review of research - Epigenetic programming, including CpG methylation and histone modifications, occurring during early postnatal development

can influence the risk of disease in later life, and such programming may be changed by nutritional factors such as milk, and wheat, especially during the transition from a solely milk-based diet to one that includes other forms of nutrition. The hydrolytic digestion of casein (a major milk protein) and gliadin (a wheat-derived protein) releases peptides with opioid activity.

This study demonstrated that these food-derived proline-rich opioid peptides modulate cysteine uptake in cultured human neuronal, and gastrointestinal epithelial cells (cells lining gut) via activation of opioid receptors. Decreases in cysteine uptake were associated with changes in the intracellular antioxidant glutathione and the methyl donor S-adenosylmethionine.

Morphine and exorphin peptides caused progressive decreases in reduced glutathione/oxidized glutathione, reaching more than 3-fold at 24 h ($P<.01$, Fig. 2a). Morphine, bBCM7 (cow milk protein) and GM7 (wheat protein), but not hBCM7 (human milk protein), transiently decreased SAM/SAH, with a 2–3-fold reduction of SAM/SAH levels observed with morphine, bBCM7 and GM7 treatments at 24 h ($P<.01$).

Thus, the decrease in cysteine uptake caused by morphine, and opioid peptides translates into downstream changes affecting redox status, and methylation capacity in research with human neuroblastoma cells.

Myelination

Nerves carry their messages from one neuron to another or to other tissues in the body. Nerves can be compared to an electrical wire. Just as an electric wire is usually insulated to protect it and help it to carry the electricity from your electric box to your light bulb, the bodies nerves also need insulation to protect them. This insulation on nerves is called myelin, and myelination is the act of putting this insulation on the nerves.

Methylation is involved in proper myelination. Lack of proper myelination is associated with a variety of health conditions. Sometimes there are anti-myelin antibodies in the body. Inflammation is usually associated with antibodies against our own body and methylation inadequacy is associated with inflammation.

Nerve Health, Excitotoxins & Methylation

Excitotoxins are toxins that are created in the body, or that are from our environment. Excitotoxins are added to the food supply as flavour enhancements. They include such additives as monosodium glutamate, hydrolysed vegetable protein, and aspartame. Glutamate or glutamine is also found in some nutritional supplements.

Although excitotoxins are found naturally in the body such as glutamate, it is in very low concentrations. Excitotoxins found in food can over-excite the nerve cells. They become inflamed and may fire so fast they become exhausted or even die. People with a genetic variation that causes susceptibility to glutamate or other excitotoxins need to be aware of these additives and food supplements.

Body glutamate can rise when there is inadequate methylation. If the methylation pathway is not working fully, folate (a polyglutamate) is not used in the pathway properly, and it can break down into glutamate. The body deals with excess glutamate by increasing glutamate receptors which has been shown to correlate to

higher intelligence. So, although there can be neuron inflammation and even damage due to high glutamate, you may also see increased intellect.

Neurotransmitter function

S-adenosylmethionine (SAM) brings methyl groups to numerous chemical compounds in your body. It creates neurotransmitters such as dopamine, and norepi/epi as well as changing or degrading neurotransmitters. If we don't have enough SAM, or if SAM can't be recycled due to an inadequate methylation cycle, this can result in imbalances in our neurotransmitters. This impacts a wide range of behaviours, mood, ability to focus attention and sleep.

When methylation is inadequate a person cannot make the necessary components needed to generate neurotransmitters like serotonin, which regulates mood, emotion, and appetite, as well as problems converting serotonin to melatonin, which allows us to sleep at night.

Proper dopamine signalling requires that the dopamine receptor be able to move freely within the cell membrane. The dopamine receptor, located on the cell surface, is like a fishing pole that catches dopamine. Methylation supports receptor mobility by keeping the phospholipids in the cell membrane fluid. Membrane fluidity also aids proper signaling of the immune system and protects nerves from damage.

Stress Effect

Stress increases cortisol which increases methylation. Ongoing stress pushes methylation all the time, and means you need to produce more methyl donors. You need leafy greens to support the methylation cycle, and stress often induces people to eat more carbohydrates, and less leafy greens, which means you are using up methyl donors and not making enough of them.

Epinephrine, and norepinephrine are increased from stress, and need SAM (methyl group) to convert norepinephrine to epinephrine.

Thyroid Relationship

If one is hypothyroid, and thyroxine (T4) levels are low, combined with low riboflavin status, then the MTHFR enzyme will function more slowly even if there is no MTHFR mutation/defect. You need thyroxin (T4) to convert the b2 into the active Flavin Adenine Dinucleotide (FAD) needed to assist the enzyme MTHFR in making 5-mthf (as well as glutathione by the way and many other things.)

Specific Health Issues Related to Methylation Disorders

Methylation plays a role as primary or related role in all health disorders. Methylation is always taking place in all cells of your body.

- Addictive Behaviours
- Alcoholism
- Allergies
- Alzheimer's Disease
    - You see increased homocysteine in Alzheimer's Disease. Cerefolin (5methylfolate drug) is used to target the treatment of dementia in Alzheimer's patients at a 5.6 mg pill dose.
- Anxiety

- Aromatase Excess may be related to decreased methylation. Research has noted this correlation in breast adipose tissue. Need more research.
- Arthritis
- Atherosclerosis
- Attention deficit disorder
    - Ritalin is also a methyl donor and therefore helps children with low methylation status improve their attention span.
- Autism
- Bipolar Disorder
- Bowel dysfunction - Bowl dysfunction is related to the low T cells seen with methylation problems. This can lead to elevated B cells, leading to autoantibodies such as seen against gluten (wheat) and casein (milk). Additionally, when methylation is low and T cell production is low, then histamine levels tend to be high. Histamine is linked to inflammation and inflammation in the gut can cause "leaky gut".
- Cancer
- Reduced DNA methylation results in genetic instability, aberrant gene expression, and increased cancer — although high methionine intake may increase cancer in different ways than low methionine intake.
- Cardiovascular disease
- As we age, methylation decreases. This causes an increased level of homocysteine which is a risk factor for cardiovascular disease. Carnitine and CoQ10 are lacking with poor methylation, and they are needed for proper heart function.
- Decreased BH4 is seen with hypertension, atherosclerosis, and endothelial dysfunction.
- Cervical Dysplasia
- Chemical Sensitivity
- Chronic Fatigue Syndrome
- Chronic bacterial/viral infections
- Cleft Palette
- Congenital Heart Defects
- Decreased repair after tissue damage
- Depression
- Diabetes
- In a diabetic state there is increased expression of specific methyltransferases that utilize SAM derived methyl groups and produce homocysteine. Although the supply of methyl groups from the folate-dependent 1-carbon pool appears to be diminished under diabetic conditions, the increased production of homocysteine is compensated for by stimulation of folate independent re-methylation, and catabolism by trans-sulphuration, resulting in hypohomocysteinemia.
- You see decreased BH4 in diabetes.
- DNA Dysfunction
- The ability of Polychlorinated biphenyls (PCBs) to reduce DNA methylation in animals may also be reflected in humans.
- DNA Repair Impairment
- Down's syndrome
- Downs syndrome is linked to specific methylation mutations/variations in methionine synthase, methionine reductase and elevated homocysteine.

- Fibromyalgia
- Heavy metal toxicity
- Herpes
- Huntington's disease
- Immune Deficiency
- Infertility
- Insomnia
- Leaky gut: Involved in protecting the intestinal lining.
- Mitochondrial disease
- Multiple Sclerosis
- Neural tube defects
    - There is now common acceptance of the association with inadequate methylation being a risk factor for neural tube defects. Elevated homocysteine concentrations have been observed in mothers who have delivered children with an NTD but who have normal folate levels, which was taken as an indicator of dysfunction of folate metabolism. The strong homocysteine-lowering effect of folate supplementation indicates that this form of dysfunctional folate metabolism can be overcome by additional folate intake.
    - Mothers who are homozygous for the MTHFR 677C>T variant (677 TT) have a 60% increased risk of giving birth to an infant with an NTD, whereas homozygous offspring themselves have a 90% increased risk of being born with an NTD. Furthermore, we also found a 10% increased NTD risk in mothers and 30% increased risk of offspring who are heterozygous for the MTHFR 677C>T variant (677 CT).
    - The 677C>T polymorphism (which leads to substitution of Ala by Val at amino acid number 222) results in the loss of flavin adenine dinucleotide (FAD) from MTHFR. Folate binding to MTHFR prevents this loss. Riboflavin (vitamin B2), which is a precursor of FAD, lowers homocysteine concentrations in individuals with the 677 TT genotype, which indicates that, in addition to folate, it could be important to investigate riboflavin intake in relation to the prevention of NTDs. (Blom, 2006)
    - Additionally, the 677 TT genotype results in a global reduction in the methylation of DNA. (Friso,2002) This does not sound like good news.
    - The methionine synthase reductase (MTRR) 66A>G variant has emerged as a possible genetic risk factor for NTDs. Other potential candidates are the MTHFR 1298A>C, methylene-tetrahydrofolate dehydrogenase (MTHFD) 1958G>A and transcobalamin 776C>G variants. (Linden, 2006)
    - If a woman's MTHFR enzyme is missing, the final product it would usually produce can be given as a supplement. This would be 5-MTHF. Additionally, riboflavin (also known as vitamin B2), which is a precursor of FAD, lowers homocysteine concentrations in individuals with the 677TT genotype, which indicates that, in addition to folate, it could be important to investigate riboflavin intake in relation to the prevention of NTDs.
- Neuropathy
- The inhibition of methylation is a factor for the b12 or cobalamine deficiency-associated neuropathy.

- Neurological inflammation
- Excitotoxins such as monosodium glutamate, hydrolysed vegetable protein, and aspartame found in some food products can overexcite the nerve cells. They become inflamed and may fire so fast they become completely exhausted or may die.
    - One of these excitotoxins that is also made in the body called glutamate, can also rise when there is inadequate methylation. If the methylation pathway is not working fully, folate (a polyglutamate) is not used in the pathway properly and it can break down into glutamate.
- Neurotransmitter imbalances
    - You see decreased dopamine and serotonin with decreased BH4.
- Parkinson's disease
- Prenatal caffeine ingestion: Various research studies have shown that caffeine may be associated with various in utero changes resulting from alterations in DNA methylation. These in utero changes in DNA methylation are associated with risk for developing obesity, and cardiovascular disease, (Basurto-Islas, 2014) as well as intrauterine growth retardation (Ping, 2014)
- Psoriasis - Decreased methylation has been associated with Psoriasis.
- Renal failure - Increased homocysteine is seen in renal failure. Seems to be related to BHMT pathway which is the pathway that converts homocysteine to methionine without folate. It is also called the short pathway and is only in kidney and liver. The end product is methionine and DMG. You see excess DMG in renal failure along with the rise in homocysteine.
- Rett's syndrome
- Schizophrenia
- Seizures
- Sleep disorders: Insomnia can arise from the lack of melatonin. Methylation is necessary to make melatonin from serotonin. Serotonin is converted to melatonin by three steps involving a series of enzymes that add an acetyl, methyl and finally a hydroxyl group to the indole ring.
- Spina Bifida
- Stroke
- You see increased homocysteine in stoke patients.
- Systemic lupus erythematosus
- Thyroid Dysfunction

Adapted from the excellent website - https://youarethehealer.org