Methylation
Diet & Lifestyle™
Whole being support for healthy methylation and epigenetic expression

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# Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AHYC</td>
<td>Adenosyl homocysteinase</td>
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<tr>
<td>AGE</td>
<td>Advanced glycation end-product</td>
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<td>AIP</td>
<td>Autoimmune pancreatitis</td>
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<tr>
<td>ALU</td>
<td>Arthrobacter luteus</td>
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<tr>
<td>ATP</td>
<td>Adenoise triphosphate</td>
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<tr>
<td>ADD</td>
<td>Attention deficit disorder</td>
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<tr>
<td>ADHD</td>
<td>Attention deficit hyperactivity disorder</td>
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<tr>
<td>Bcl-2</td>
<td>B-cell lymmpoma 2</td>
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<tr>
<td>BHMT</td>
<td>Betaine homocysteine methyltransferase</td>
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<tr>
<td>BH2</td>
<td>Dihydrobiopterin</td>
</tr>
<tr>
<td>BH4</td>
<td>Tetrahydrobiopterin</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BMPRII</td>
<td>Bone morphogenetic protein receptor 2</td>
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<tr>
<td>CBS</td>
<td>Cystathionine beta-synthase</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CIDP</td>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
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<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
</tr>
<tr>
<td>CoQ10</td>
<td>Ubiquinone or coenzyme Q10</td>
</tr>
<tr>
<td>CpG</td>
<td>C: Cytosine triphosphate deoxynucleotide p: phosphodeister, G: guanine triphosphate deoxynucleotide</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>DFE</td>
<td>Dietary folate equivalents</td>
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<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
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<tr>
<td>DHF</td>
<td>Dihydrofolate</td>
</tr>
<tr>
<td>DHFR</td>
<td>Dihydrofolate reductase</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DNMT</td>
<td>Deoxyribonucleic methyltransferase</td>
</tr>
<tr>
<td>EGCG</td>
<td>Epigallocatechin 3-gallate</td>
</tr>
<tr>
<td>Fli-1</td>
<td>Friend leukemia integration 1 transcription</td>
</tr>
<tr>
<td>FODMAPs</td>
<td>Fermentable Oligo –Di- Monosaccharides and Polyols</td>
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<tr>
<td>FR</td>
<td>Folate receptor</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>HPA axis</td>
<td>Hypothalamic-pituitary-adrenal axis</td>
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<tr>
<td>HVA</td>
<td>Homovanillate</td>
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<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>KLF5</td>
<td>Kruppel-like factor 5</td>
</tr>
<tr>
<td>L-Dopa</td>
<td>Levodopa or L-3,4-dihydroxyphenylalanine</td>
</tr>
<tr>
<td>MBP</td>
<td>Mega base pair</td>
</tr>
<tr>
<td>5-mC</td>
<td>5-methylcystosine</td>
</tr>
<tr>
<td>5-hmC</td>
<td>5-hydroxymethylcystosine</td>
</tr>
<tr>
<td>MAO</td>
<td>Monoamine oxidase</td>
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<tr>
<td>MAT</td>
<td>Methionine adenosyltransferase</td>
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<tr>
<td>MDL</td>
<td>Methylation Diet and Lifestyle</td>
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<tr>
<td>MS</td>
<td>Methionine synthase</td>
</tr>
<tr>
<td>MST1</td>
<td>Macrophage stimulating 1</td>
</tr>
<tr>
<td>MTFHR</td>
<td>Methylene tetrahydrofolate reductase</td>
</tr>
<tr>
<td>MTHF</td>
<td>Methyltetrahydrofolate</td>
</tr>
<tr>
<td>MTRR</td>
<td>Methyl tetrahydrofolate-homocysteine methyltransferase reductase</td>
</tr>
<tr>
<td>MTR</td>
<td>Methyl tetrahydrofolate-homocysteine methyltransferase</td>
</tr>
<tr>
<td>MTases</td>
<td>SAMe dependent methyltransferases</td>
</tr>
<tr>
<td>NK</td>
<td>Natural killer</td>
</tr>
<tr>
<td>NRF2</td>
<td>Nuclear factor erythroid 2 [NF-E2]-related factor 2</td>
</tr>
<tr>
<td>NFkB</td>
<td>Nuclear factor kappa-B</td>
</tr>
<tr>
<td>NHANES</td>
<td>National health and nutritional examination survey</td>
</tr>
<tr>
<td>NLRP3</td>
<td>Nod-like receptor protein 3</td>
</tr>
<tr>
<td>8-OHdG</td>
<td>8-hydroxy-2’-deoxyguanosine</td>
</tr>
<tr>
<td>PABA</td>
<td>Para-aminobenzoic acid</td>
</tr>
<tr>
<td>POP</td>
<td>Persistent organic pollutants</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>REST</td>
<td>RE1-silencing transcription factor</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
</tr>
<tr>
<td>SAH</td>
<td>S-adenosyl homocysteine</td>
</tr>
<tr>
<td>SAHH</td>
<td>S-adenosyl homocysteine hydrolase</td>
</tr>
<tr>
<td>SAMe</td>
<td>S-adenosyl methionine</td>
</tr>
<tr>
<td>SIBO</td>
<td>Small intestine bacterial overgrowth</td>
</tr>
<tr>
<td>SAHH</td>
<td>S-adenosyl-L-homocysteine hydrolase</td>
</tr>
<tr>
<td>TET</td>
<td>Ten-eleven translocation</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>UMFA</td>
<td>Unmetabolized folic acid, sometimes referred to as folic acid, synthetic folate or oxidized folate</td>
</tr>
<tr>
<td>VMA</td>
<td>Vanilmandelic acid</td>
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2  **Preface: The Need For Conservative Yet Effective Methylation Support**

*From the desk of Dr. Kara Fitzgerald, ND*

With the mapping of the human genome in 2001, the era of Systems Medicine has burst forth. At about 24,000 genes, the code for our lives was smaller than expected (you’ve no doubt heard the humorous comparison: “less than a grape, but more than a chicken”). Significant attention is now being paid to the regulatory aspects of the genome, and research on the heritable epigenome in particular is galloping ahead. At this writing, a PubMed search on “methylation”—a cornerstone epigenetic and metabolic process—yields more than 85,000 hits. Many genetic methylation research abstracts are summarized with the preface statement, “For the first time ever, we’ve shown that…”

With rapidly emerging understandings, and ready access to genetic testing, it is indeed a wildly exciting time to be practicing Functional Medicine, the clinical application of Systems Medicine. Many of our patients now arrive at our offices with some knowledge of their genetics, and most often with regard to their single nucleotide polymorphisms (SNPs) relating to methylation. Many assumptions are made around the phenotypic expression of these single nucleotide variations. Last week, a new patient sat before me, stating with grim determinism that her heterozygous mutation in MTHFR A1298C SNP made it impossible for her body to detoxify efficiently.

To those of us looking for biochemical “lesions” in methylation enzymes using a combination of genetic testing and the currently available metabolic biomarkers they appear to be common... Sometimes correcting identified imbalances can be highly clinically significant, other times (arguably more often than not) shifting biochemical methylation activity with high-dose methyl donors such as folate and B12 doesn’t appear to have a huge, immediate clinical outcome. But we know that methylation is incredibly fundamental and operates in many “behind the scenes” activities not limited to detoxification, neurotransmitter production and of course the all-important black box of epigenetic regulation. We’ve seen the powerful impacts of folic acid fortification in the reduction of neural tube defects, where augmenting methylation activity is a piece of the folic acid success story.

The spark of inspiration behind creating the Methylation Diet and Lifestyle (MDL) program was wanting to “do right by my patients” by embracing both the importance of healthy methylation balance while recognizing the limitations of our current understanding. What we don’t know in the biological sciences always far outweighs what we do know, and this is especially true in our understanding of methylation. Imbalanced methylation of the epigenome (comprising both hyper- and hypomethylation primarily of gene promoter regions) is an
emerging area of investigation implicated in many disease processes, ranging from aging and allergies to neurodegenerative processes and cancer. Regulation of the epigenome is a highly complex process; we cannot state with certainty what the impact is of high-dose, long term methylation interventions.

Thus, for the vast majority of our patients we need to consider whether high-dose, long-term supplementation really is the right approach. There is a dearth of research in this area, with the exception of folic acid, where, as we discuss below, reasonable concerns exist. There are also those patients who do not tolerate methyl donor supplementation, suspected to be chiefly due to either poor clearance of epinephrine and other biogenic amines, or “ramped up” detoxification activity.

While homage to Dr. Bruce Ames and his remarkable work around increasing enzyme kinetics using high dose cofactor supplementation is due, and understanding that this approach may indeed be appropriate for methylation in the short-term, our emerging understanding on the epigenome suggests that more “up-stream” and nuanced interventions are in order when possible. Food-based folates, for instance, have only been shown to be protective. Numerous additional phytochemicals, not directly tied to methylation, appear to favorably modulate global epigenetic and biochemical methylation activity. And reducing methyl donor depletion by minimizing toxic exposures, nourishing the microbiome, augmenting the stress response and far more, is safe and impactful. By removing the obstacles and drains on methylation while providing broad spectrum nutrient ingredients for balanced activity, we are allowing physiological wisdom to manage the process.

The Methylation Diet and Lifestyle would not have been brought into being in my clinical practice or in this eBook without the years of frank discussions I’ve had with leading expert Michael Stone, MD on current research and patient care approaches¹. Likewise with my Journal Club comrades, where each month for over the last three years we meet and “tussle with” new, often complex concepts in the biological sciences. A heart-felt “shout out” goes to my nutritionist extraordinaire, Romilly Hodges, who has worked tirelessly with me to capture the bulk of our thoughts in the below text.

This eBook serves as a guide to understand the current methylation issues and challenges facing practitioners, the potential concerns with supplementation alone, how to assess methylation

¹ Drs. Leslie and Michael Stone, along with their daughter, nutritionist Emily Rydbom, are doing remarkable work in the field of methylation assessment and support during preconception, pregnancy and the postnatal period at their clinic in Ashland, Oregon. Find them at www.ashlandmd.com and www.growbabyhealth.com.
status, and how to incorporate an MDL program into your protocols. Not only are there easy-to-apply menus, recipes and nutrient guidelines but important lifestyle factors are reviewed as well.

How should we determine when to use the MDL? Well, it may be the optimal way to offer methylation support right off the bat, especially for those who cannot tolerate supplementation. It is also a sensible and safe long-term strategy for most patients who have achieved balance through a short-term course of higher-dose methyl donors. Importantly, the full MDL program also supports detoxification, stress reduction, microbiome and hormone balance, and can be readily modified to incorporate other programs that we routinely prescribe such as elimination diets, grain and lectin-free plans, low FODMAP diets and general gut restoration programs. Highly restricted plans, such as the calorie restricted ketogenic diet, sometimes used in cancer and epilepsy, can incorporate aspects of the methylation diet with additional nutraceutical support. Virtually any dietary program can work with the MDL as a foundation.

Acknowledgements

We would like to acknowledge P. Michael Stone, MD, MS, Institute for Functional Medicine, for his groundbreaking work in the area of methylation.

We would also like to thank Lara Zakaria MS for her contributions to the menus, recipes and figures, and Brigid Krane (www.brigidkrane.com) for the cover and logo design.
3  INTRODUCTION

It has become increasingly common for functional medicine practitioners to recommend high-dose supplementation with methyl donors, such as 5-methyltetrahydrofolate (5-MTHF) and methylcobalamin, in certain patients. For example in those with genetic polymorphisms that may impair the functionality of relevant enzymes, most commonly methylenetetrahydrofolate reductase (MTHFR), or in those with out-of-range methylation-related biomarkers such as in hyperhomocysteinemia. Deficiency in methyl donors is a fairly frequent finding in laboratory analyses, depending on your population, and can relate directly to clinical symptoms; for example B12 deficiency-associated neuropathy, which is relatively common. Some practitioners may even look to supporting methylation as a means to improve inherited or environmentally acquired epigenetic programming.

Of course, improving global methylation status and averting the pathways of disease and dysfunction associated with a potential deficit in methylation activity is a commendable goal. However, as with other biochemical processes, methylation activity exists ideally in a state of active balance, or homeodynamics. Imbalance in these mechanisms can lead to dysfunction and disease. So while we can be confident that ensuring the adequacy of available methyl donors for use in the body is important, we have to question whether “pushing” reaction rates using supraphysiological doses is always safe. Rather than bluntly forcing reactions forward, perhaps our ultimate goal should instead be enabling the body to do the right thing at the right time.

There are a number of potential issues with long-term high-dose methyl-donor supplementation:

**The impact of genetic alterations is unclear.** Aside from the altered activity of MTHFR C677T and A1298C single nucleotide polymorphisms (SNPs) which has indeed been studied to some degree, the discovery of other SNPs remains a qualitative rather than quantitative indicator of enzyme functionality. The overall effect of these SNPs on methylation depends on the activity of many enzymes working together in the context of one’s internal and external environment. This fact underlies the many variable results found in genome-wide association studies. As a result, it isn’t readily possible at this time to determine exactly how much of an impact any one of those alterations, even MTHFR C677T, has on overall methylation status [1].

**The correct supplementation dose is as yet unknown, and may vary between individuals.** No studies have clarified yet what the right dosage or duration of methyl donor supplementation is needed to rebalance biochemical or epigenetic methylation status Some side effects of high-dose 5-methyltetrahydrofolate supplementation have been reported in clinical practice, including worsening of symptoms and anxiety. Consequently it may be safer in the long term to stay within physiologic levels [2].
**Hypermethylation states may occur and may also be detrimental:** The scientific literature contains many examples of region-specific DNA hypermethylation associated with adverse outcomes, including cancer, immune dysfunction and Downs Syndrome. Interestingly, both DNA hyper- and hypomethylation states can be identified in states of methyl donor deficiency and repletion. Certainly folic acid, in either deficiency or excess, has been associated with increased rates of cancer and immune hypersensitivity, but since the mechanism is not fully understood, should we not also be cautious with high levels of methylated folate? The mechanisms controlling DNA methylation and demethylation are incredibly complex, yet we know that pushing reaction rates through supraphysiological dosing of nutrient cofactors is possible [3]. The bottom line is that we don’t know what effect long-term, high-dose methyl-factor supplementation has on DNA methylation.

**Methylation status depends on many dietary and lifestyle inputs:** A complex interaction of dietary and lifestyle factors (including medications, stress, sleep, exercise and toxin exposure) plays a role in the methylation end-result. Singular interventions with high dose nutrient supplementation miss this intricate web of inputs and may lack long-term effectiveness, or may not achieve desired results.

Dietary and lifestyle interventions may be the best, and safest, long term option for most individuals with suspected methylation imbalances. This may be particularly true for certain vulnerable populations such as individuals with active cancers. Aging is known to be associated with diminished methylation activity, so there is a good rationale for using the MDL as an anti-aging tool. Careful methylation evaluation and treatment is essential during preconception, pregnancy and the postnatal period[^2]. A good evaluation coupled with the MDL program and appropriate nutraceutical support is a useful starting place.

A dietary and lifestyle approach can also be used as a long term follow-up plan to those requiring early high-dose nutraceutical support. Food sources of methylation nutrients can be abundant, and with proper planning, dietary modifications have been found to favorably influence methylation activity [4], [5].

In this eBook, you’ll find a comprehensive dietary and lifestyle approach to support methylation, aligned with a functional medicine approach and including important methylation nutrients, specific foods to include, foods to avoid, two 7-day menu plans (with calculated

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[^2]: Drs. Leslie and Michael Stone, along with their daughter, nutritionist Emily Rydbom, are doing remarkable work in the field of methylation assessment and support during preconception, pregnancy and the postnatal period at their clinic in Ashland, Oregon. Find them at [www.ashlandmd.com](http://www.ashlandmd.com) and [www.growbabyhealth.com](http://www.growbabyhealth.com).
levels of methylation nutrients), recipes and lifestyle factors. You’ll also learn the basic biochemistry of methylation, the many roles of methylation in the body, how to assess patient methylation status, the beneficial and potentially detrimental clinical impacts of supplemental methyl donor interventions, and the potential issues with too little, or too much methylation activity.
4 An Introduction to Methylation

4.1 The Biochemistry of Methylation

Methylation, also commonly termed “one-carbon metabolism,” is a biochemical process that involves the transfer of active methyl groups. Methyl groups consist of a hydrogen attached to three carbons (-CH₃) and can be formed in two ways:

1. By the addition of a hydrogen (“reduction”) to methylene (-CH₂-) groups, such as is facilitated by the enzyme methylenetetrahydrofolate reductase (MTHFR). The product of this reaction is 5-methylTHF.

2. By the transfer of a complete methyl group, such as is done by catechol-O-methyltransferase (COMT) or DNA methyltransferase (DNMT) enzymes [6]. Methyltransferase enzymes use methyl groups donated from the universal active methyl transfer compound S-adenosylmethionine (SAMe).

As it is utilized, SAMe is converted to S-adenosyl homocysteine (SAH), and then homocysteine (Figure 1). Homocysteine recycling to methionine can occur via one of two pathways. The dominant pathway, via methionine synthase conversion, requires the transfer of a methyl group from 5-methyltetrahydrofolate (5-mTHF). 5-mTHF is formed, irreversibly, by the enzyme methylenetetrahydrofolate reductase (MTHFR), perhaps the most widely-known of all enzymes in the folate metabolic pathways.

A lesser pathway for methionine biosynthesis from homocysteine is via betaine homocysteine methyltransferase in the liver and kidney. Homocysteine may also enter another biochemical pathway, especially during states of higher oxidative stress, which converts homocysteine to cystathionine and from there to taurine, glutathione or sulfate. The first step in transulfuration pathway is irreversible, however, glutathione recycling may spare homocysteine for SAMe production.

Dietary folate is found in foods primarily as pteropolyglutamates. In order to be absorbed, the polyglutamate form is hydrolyzed in the intestines to the monoglutamate form, tetrahydrofolate (THF).

Folic acid on the other hand, the most common synthetic form of the vitamin (and the form used in food fortification), must be reduced by the enzyme dihydrofolate reductase (DHFR) twice (i.e. it requires the addition of two hydrogens) in the liver before it can enter folate cycles as THF. Importantly, it is known that DHFR activity is low and variable [7]. Human liver DHFR activity is also 56 times slower per gram of tissue than in the rat, meaning that we should use caution when translating the pharmacokinetic studies of folic acid in animals [8].
Oftentimes, functional medicine practitioners will use other forms of supplemental folates including 5-mTHF and folinic acid (10-formyl THF) to avoid the potential DHFR blockage, and in the case of 5-mTHF with the intention to bypass polymorphism blockages at the MTHFR enzyme. Studies comparing the effects of 5-mTHF versus folic acid on folate status have found the natural, methylated form to be at least as effective at raising folate levels [9]. Folinic acid is sometimes used since it appears able to support cerebral folate levels in specific circumstances where autoantibodies to folate transport proteins at the blood brain barrier are present [10].

4.2 **Endogenous Methylation Uses**

The production of methyl donors is essential for a number of fundamental and critical biochemical pathways. An understanding of their known uses provides an irrefutable argument for the need to ensure effective methylation in the body.
Cell division, DNA and RNA synthesis. Folate metabolism is critical for DNA and RNA synthesis since it is involved in the biosynthesis of purine nucleotides and thymidylate [11]. Chronic methyl deficiency increases the potential for cytosine deamination to uracil, creating mismatch gene sites which increase the risk for DNA strand breaks, fragmentation, apoptosis and carcinogenesis [12].

Early CNS development. It has been known since the 1960s that folate deficiency is causatively associated with increased risk for neural tube defects [13]. The mechanism for this has yet to be fully elucidated, and although there are likely multiple genetic and environmental influences. Methylation imbalance is one suspected factor [11]. National folic acid food fortification programs have been successful at reducing the incidence of this condition in newborns [14].

Gene expression. DNA and histone methylation are major epigenetic mechanisms that regulate the expression of genes. The most common mechanism of DNA methylation is the attachment of a methyl group to cytosine bases in CpG dinucleotides by DNA methyltransferase (DNMT) enzymes [15]. Up to 80% of CpG dinucleotides are methylated in mammals under normal conditions. High levels of methylation in gene promoter regions typically lead to repression. Histone methylation can either promote or repress expression. Research suggests that aberrant promoter hypermethylation in DNA repair genes is linked to a variety of cancers [16], [17].

Post-transcription modification. Methylation of post-transcription RNA and microRNA appears to act in a regulatory function on microRNA translation and protein synthesis. Aberrant RNA methylation activity is starting to be understood to correlate with myriad disease states [18].

Immune cell differentiation. Methylation is involved in the maturation of immune cells such as T cells (including Th2 cytokine regulation) and natural killer cells [19].

Neurotransmitter biosynthesis and metabolism. Methylation via SAMe is a key step in the synthesis and metabolism of biogenic amine neurotransmitters, including dopamine, norepinephrine, epinephrine, and serotonin. It is also required in the pathway for acetylcholine biosynthesis. Methylation is also necessary for the regeneration of tetrahydrobiopterin, another important cofactor in these biosynthetic pathways.

Histamine clearance. One pathway for histamine metabolism is via histamine N-methyltransferase, requiring SAMe as methyl donor. Low SAMe or altered enzyme activity can lead to an increases accumulation of histamine and clinical symptoms [6].

Detoxification. Along with glucuronidation, sulfuration, and acetylation, methylation is a major pathway for biotransformation of xenobiotics within phase II detoxification. Poor methylation status can therefore impair the body’s ability to detoxify and can lead to toxicity-related dysfunction. Separately, DNA methylation also regulates Nrf2 signaling, referred to as
“the master regulator of antioxidant defense” a key mechanism that upregulates various phase II detoxification enzymes [20].

**Hormone biotransformation.** The methylation of estrogens via COMT is an important mechanism for their clearance and regulation. The interruption of this mechanism can be one factor in the increased risk for oxidative DNA damage from certain estrogen metabolites [21]. Methylation status is therefore an important consideration to support safe estrogen clearance and detoxification in patients presenting with estrogen dominance or with estrogen-receptor positive cancers.

**Cellular energy metabolism.** Through its role in the biosynthesis of CoQ10, carnitine and ATP, methylation plays a critical role in mitochondrial energy metabolism in every cell [6].

**Phospholipid synthesis.** SAMe is required for the biosynthesis of phosphatidylcholine, a major component of cellular membranes and acetylcholine precursor [22].

**Myelination of peripheral nerves.** Deficient concentrations of SAMe in cerebrospinal fluid have been shown to be causative in demyelination [23].

### 4.3 DNA Methylation Plasticity

Most DNA methylation is highly regulated, leading to little interindividual differences in epigenetic patterns [24]. However, DNA methylation imprints at regions termed “metastable epialleles” have been shown to occur stochastically, with significant interindividual differences, to be passed down to offspring during critical periods of fetal development, and preserved across multiple generations [24]–[26]. This genetic imprinting has been shown to be highly sensitive to environmental influences. For example, transient exposure to the fungicide vinclozolin and the pesticide methoxychlor can induce alterations in DNA methylation patterns that persist in future generations, despite the lack of continued exposure [26].

It has also been argued that factors that prevent efficient DNMT activity, either by deficiency of nutrients needed for SAMe biosynthesis or competition for SAMe or DNMT action, during these sensitive time periods might result in permanent deficits in CpG methylation [27]. Conversely, animal study has shown that maternal supplementation with methylation nutrients (folic acid, vitamin B12, choline and betaine) during these periods can have a significant, restorative impact on offspring DNA methylation [24].

Even at other times during life, the preservation of DNA methylation during mitosis in proliferative tissues may be undermined by nutritional deficiencies affecting methyl donor status [27] or by inhibition of DNMT activity [28]. In fact, gradual DNA de-methylation occurs over time, especially between ages 34 to 68, and is assumed to be associated with the normal aging process [29].
Human investigations support the assertion that non age-associated alterations in DNA methylation are possible outside of the fetal developmental windows. In a study published in the Lancet, researchers determined that hyperhomocysteinemia (between 16 and 100 μmol/L plasma or serum) was significantly correlated with DNA hypomethylation in humans (the population studied aged between 39-68 years) [30]. They theorized this occurred due to the increase in S-adenosyl homocysteine (SAH), which is a potent competitive inhibitor of SAMe-dependent methyltransferases (including DNMTs). Induced folate deficiency in the population studied further worsened hyperhomocysteinemia, and folate treatment (15 mg/d 5-mTHF for 8 weeks) decreased plasma total homocysteine and decreased DNA hypomethylation [30].

More evidence that DNA methylation is modifiable outside the critical development windows comes from animal studies, with indications that dietary interventions may help to restore methylation status where it has been previously lost in early-life programming. For example, methionine supplementation in adult rodent offspring has been shown to reverse DNA methylation changes in the hippocampal glucocorticoid receptor, as well as the adrenal and behavioral responses to stress, caused by negative maternal behaviors in early life [31]. And dietary betaine supplementation in vivo has been shown to induce promoter hypermethylation on specific genes in porcine liver [32]. Even though the evidence is still limited, and more research is needed to form strong conclusions, a number of other in vitro, animal and human studies demonstrate alterations in DNA methylation status that are driven by nutrient availability, including folate, choline, vitamin B12, and vitamin B6. Intriguingly, and perhaps most telling, the outcomes of many of these studies suggest that multiple factors such as lifestyle, environmental exposures and food-based modulators of epigenetic imprints, not just nutrients, shape the overall impact on DNA methylation outcomes [28], [33], [34].
5 THE CLINICAL PROBLEM

5.1 METHYLATION DEFICITS

The risk of folate deficiency and impaired folate metabolism has been most clearly illustrated by the association with neural tube defects. Without a doubt, the mandatory folic acid programs implemented by the majority of developed countries in the last two decades have had a tremendous, positive impact on the incidence of these conditions [35]. This clear benefit cannot be dismissed, despite the emerging concerns over the use of synthetic folic acid forms.

Beyond neural tube defects, deficits in folate and methylation status have also (and more recently) been associated with ADD/ADHD, addiction, allergies, Alzheimer’s Disease, anxiety, asthma, atherosclerosis, autism spectrum disorder, behavioral changes, bipolar disorder, cancers, chemical sensitivity, chronic fatigue, cleft palate, diabetes, dementia, depression, Downs syndrome, essential hypertension, fertility issues, fibromyalgia, insomnia, multiple sclerosis, neuropathy, Parkinson’s Disease, schizophrenia, and thyroid disease [6], [36]–[38]. Clearly methylation is a critical aspect of physiology, with wide-ranging application, and demands our clinical attention.

It is recognized that an individual may become deficient in methylation activity in multiple ways, including via nutrient deficiency, competition for methyl donor utilization, methylation inhibitors and genotype:

NUTRIENT DEFICIENCY

The depletion of cellular pools of methyl donors due to nutrient depletion can interfere with both metabolic and DNA methylation activity [39]. There are many nutrients involved in methylation pathways, which we will cover in more detail below. However, the most commonly-recognized of these are folate (a B vitamin) and vitamin B12. There are various factors that can impact the status of these, and other, nutrients in the body.

According to NHANES data, mean US adult dietary intake of food-fortified folic acid and natural food folates range from 454 to 652 mcg DFE per day, of which 190 mcg/d is estimated to come from folic acid fortification [40]. This is compared with a target RDA of 400 mcg/d DFE. Population means for erythrocyte folate levels also fall within so-called sufficient levels, however certain groups are identified as being at higher risk for deficiency. These include women of childbearing age and non-Hispanic black women. In our clinic we also routinely see low levels of dietary folate intake (ranging from 200-350 mcg/d DFE) in incoming patients who have removed sources of fortified foods from their diet, such as gluten-containing grains and processed breakfast cereals. While it is clearly advantageous to avoid processed and refined foods, and avoid provoking food sensitivities where they exist, care must be taken to increase natural sources of folate to achieve optimal intake levels.
Mean intake for vitamin B12, is estimated at 3.4 mcg/d, higher than the 2.4 mcg/d RDA for most adults [40]. However, we know that certain population groups are more vulnerable for functional deficiency. As we age, we have a reduced ability to produce the gastric hydrochloric acid and intrinsic factor necessary for B12 assimilation. This can be compounded by the presence of autoimmune pernicious anemia that further limits gastric secretions [22].

Many patients that seek out a functional medicine practitioner also have conditions that can negatively impact nutrient absorption and the functional status of nutrients in the body, including dysbiosis, small intestine bacterial overgrowth, altered transit time, Crohn’s disease, food allergies or sensitivities, impaired thyroid function and more. These should all be assessed and factored in to the overall nutrient need of the individual.

Ironically, while a move away from processed food-based diets is a clearly essential for optimizing health, fortification is no longer the ‘catch all’ that it is in the processed food world. Improperly-implemented whole-food diets still have the potential to be imbalanced. Care must be taken to include foods that together provide all necessary nutrients, including methylation nutrients, and it seems wise to also check functional nutrient status through laboratory evaluations especially in the context of genetic SNPs and/or clinical symptoms.

**COMPETITION FOR METHYL DONORS**

High demand from any single area of methylation activity outlined above, such as high catecholamine turnover, detoxification states, histamine clearance, or circulating estrogens, can drain the pool of available methyl donors.

For example, in states of high physiological and psychological stress, SAMe utilization for catecholamine biosynthesis and degradation is increased and can impact the availability of SAMe for other uses. Similarly, in individuals with active, ongoing reactivity to antigens, high histamine turnover can place significant demands on methyl donor levels.

L-Dopa medication is a common therapy in patients with Parkinson’s disease. L-Dopa metabolism occurs via COMT with SAMe as a cofactor that donates its methyl group, and its use is associated with reduced plasma folate and elevated homocysteine [41]. It is not without irony that L-Dopa may therefore compromise the very methylation detoxification capacity that can remove the heavy metals and other toxins that can be significant, causative contributors to the condition.

**METHYLATION INHIBITORS**

S-adenosyl homocysteine (SAH) is a powerful competitive inhibitor of SAMe-dependent methyltransferases (including DNMT), and is often increased with hyperhomocysteinemia [30]. The conversion of SAH to homocysteine is catalyzed by S-adenosyl homocysteine hydrolase, is fully-reversible, and favors biosynthesis rather than hydrolysis [30]. Therefore, an accumulation
of homocysteine can inhibit hydrolysis and promote formation of SAH, thereby inhibiting SAMe-dependent methylation activity.

**GENOTYPE**
Even though the MTHFR SNP may have landed methylation ‘on the map,’ there are many enzymes and their corresponding genes that play a role in overall methylation status and clinical outcomes. A number of practitioners already incorporate genotyping into their patient assessment. In addition, patients are able to order genetic profiling on their own, and are starting to bring that data to their health practitioners for evaluation and advice.

**Frequency and effects of MTHFR polymorphisms**
The most common MTHFR polymorphisms are C677T and A1298C. The frequency of homozygote 677TT variants is highly variable according to ethnicity and geography. The highest frequency (>20 percent) is reported in US Hispanics, Colombians and Amerindians in Brazil. The frequency among White populations in Europe, North America and Australia is 8–20 percent. The lowest frequency (<2 percent) is found in Black populations. The frequency of homozygote 1298CC genotypes in White populations in North America and Europe is reported to be 7-12 percent. Lower frequencies are reported in Hispanics (4-5 percent) and Asian (1-4 percent) populations. [42]. Clear data are lacking as to the dispersion of heterozygote genotypes, as well as compound genotypes, among population groups.

Of potential clinical relevance, it appears that the incidence of C667T polymorphisms may be increasing: Population studies from Spain, for example, report an increasing frequency of the C677T genotype in the post folic acid-fortification era. This is speculated to be due to the decreased levels of spontaneous abortions that are more likely when the polymorphism is present in conjunction with low folate status [43].

We know that these genetic polymorphisms alter enzyme capacity and stability. Homozygous 667TT variants have been found to have a 70-75% loss of enzyme activity [44], [45]. Heterozygotes appear to lose 33-35% of enzyme activity [44], [45]. Homozygous 1298CC genotypes appear to have a 39% reduction in enzyme activity, and heterozygotes a 17% reduction [45]. Compound heterozygotes for both 667CT and 1298AC may also lose as much as 52% of enzyme activity [45].

In turn, research also shows that this change in enzyme capacity does have an effect on blood folate concentrations and homocysteine levels. A recent systematic review and meta-analysis reports a 16% decrease in erythrocyte folate levels for homozygous 677TT genotypes when compared with their wildtype 677CC counterparts [46], and an 8% decrease for heterozygous 677CT genotypes. Note that red blood cell folate measurements include all the different folate vitamers, so we cannot separate out the effect of these genotypes on 5-mTHF, the active form needed for homocysteine metabolism.
AGING
Aging is associated with altered DNA methylation, specifically global hypomethylation but with hypermethylation at normally unmethylated CpG regions, which may lead to the suppression of specific genes or genomic instability [28], [29]. Preserving methylation status via nutrient and lifestyle support may be considered a reasonable strategy to slow the age-related decline in methylation status.

5.2 FOLIC ACID CONCERNS
Fortification and regular folic acid supplementation are now strongly suspected to carry risks, despite their clear benefits in preventing neural tube defects, especially at levels above the recommended intake of 400 mcg/d of dietary folate equivalent units (DFEs).

Folic acid is a purely synthetic compound that in itself has no known cofactor role. To be used in methylation pathways, it must be first converted to tetrahydrofolate (THF) by being twice-cycled through the enzyme dihydrofolate reductase (DHFR). One suspected cause of adverse folic acid effects is elevated unmetabolized folic acid (UMFA) due to the inefficiency of this mechanism and distinctly limited capacity of liver DHFR, now proposed to be the major site of folic acid metabolism [8]. One-time doses of about 260 mcg folic acid, or even multiple 100 mcg doses throughout the day have been shown to lead to detectable UMFA in serum [7].

Populations who regularly consume fortified foods such as ready-to-eat cereals as well as fortified grains can have a folic acid exposure up to the Tolerable Upper Limit of 1.0 mg/d, and with the use of multivitamin supplements, it is not uncommon for intake to rise beyond that [8], [43], [47], [48].

Another essential consideration is that folic acid from supplements is much more readily absorbed than folate from foods. In fact, one DFE is equivalent to 1 mcg of dietary folate but only 0.6 mcg folic acid from supplements (taken with food) or fortified foods [49]. Therefore 400 mcg of folic acid from a supplement should actually be considered as 667 mcg DFE.

Several studies link higher levels of folic acid intake with adverse health outcomes. This has led to speculation that dihydrofolate (DHF), an intermediate metabolite in the conversion of folic acid to tetrahydrofolate, and UMFA, may have deleterious effects.

Reported effects of DHF: DHF has been shown to inhibit thymidylate synthase and purine synthesis enzymes, which has the potential to impair DNA synthesis [43]. DHF also appears to inhibit the MTHFR enzyme, creating a “pseudo MTHFR deficiency,” which can ironically lead to a decrease in methionine synthesis and homocysteine clearance [43], [50]. Perhaps this is why a recent trial of high-dose (5 mg/d) folic acid supplementation in infertile men showed an unexpected reduction in sperm DNA methylation, an effect that was most pronounced in patients homozygous for the MTHFR C667T polymorphism [51].
**Reported effects of UMFA:** Various studies have also reported a connection between folic acid fortification and supplementation and colorectal cancer [52]–[55]. One of the proposed mechanisms is that UMFA may actually metabolize via photo-catalysis to DNA-toxic products [55]. A recent study that investigated the potential connection between levels of prediagnostic UMFA and subsequent colorectal cancer diagnosis found a small positive association in men and individuals with MTHFR C677T genotype (both heterozygous and homozygous) with the highest levels of plasma UMFA as compared to those with no observable plasma UMFA. However, a small inverse association was found with women in the study [56]. Higher UMFA was also found to be associated with anemia in US seniors who consumed alcohol, and reduced NK cell cytotoxicity in otherwise healthy postmenopausal women [56].

Recent research looking at folate receptors in epithelial cancers found a high frequency of receptor FR-alpha which preferentially uptakes UMFA. It is believed that FR-alpha promotes tumor progression and reduces apoptosis through increased expression of anti-apoptotic protein Bcl-2, among other mechanisms. Folic acid exposure to tumor cells in-vitro was shown to enhance this process [57], [58].

### 5.3 Methyl Donor Intolerance

Functional medicine practitioners who have been using high-dose methyl donor supplementation in their patients with indicated methylation deficits, will likely have encountered individuals who do not feel well on such a protocol. Clinical experience indicates that a worsening of symptoms, or the appearance of neurological symptoms, or both are possible outcomes, such that the individual is unable to tolerate the intervention despite a clear need for methylation support. Neurological symptoms may include heightened anxiety, irritability, brain fog, or depressed mood.

The mechanism behind these clinical responses is not well understood and there is a need for research to validate and help clarify the frequency and mechanisms of these effects. It has been theorized that impaired metabolism of catecholamines via COMT and MAOA may play a role (Case 1.0). Increased SAH is also thought to be a potential mediator of adverse effects.
Case 1.0: Methyl donor intolerance with COMT polymorphism

31-year-old female with long-term panic disorder and recent onset of agoraphobia. Genetic testing revealed homozygous for COMT and MTHFR single nucleotide polymorphisms (SNPs). Vanilmandelic acid (VMA) and homovanillate (HVA) urinary organic acids were low and low-normal, respectively, indicating poor clearance of norepinephrine and epinephrine. These catecholamines are catabolized via COMT methylation, and their poor clearance may contribute to heightened anxiety symptoms. Her homocysteine levels, on the other hand were normal, suggesting that either the MTHFR SNP was still functional enough to sustain SAMe levels, or that increased oxidative stress was confounding the normal homocysteine finding, by increasing transulfuration of homocysteine for glutathione formation.

Supplementation with high-dose methylated folate and betaine was initiated, but soon after the patient reported an exacerbation of symptoms. This could have been due to the increased production of SAMe from the combined effects of the supplementation. SAMe levels in the brain govern the rate of epinephrine biosynthesis from norepinephrine via methylation, so increased SAMe availability could have been driving increased epinephrine synthesis. This combined with the decreased clearance due to the COMT SNP could have been the underlying reason for increased symptomatology. Replacing methylated folate with unmethylated folic acid, and discontinuation of betaine resulted in significant symptom improvement, including resolution of the agoraphobia.

Case adapted with permission from Lord & Bralley, 2012, Case Illustration 11.1 p. 594.
5.4 **Methylation Gone Awry**

5.4.1 **Potential concerns about folic acid AND methyl-folate supplementation.**

Some of the risks of folic acid or other folate derivatives, including commonly used alternatives such as 5-mTHF and folinic acid, are widely accepted, and not generally disputed. These are:

- High intake may mask a B12 deficiency. B12 deficiency is normally indicated by megaloblastic anemia, but in when folate levels are high enough cell division will continue in bone marrow, and this will mask the anemia. Unaddressed B12 deficiencies can lead to irreversible neurological damage and cognitive impairment [43],[55].

- Supplemental folate or folic acid may also reduce the efficacy of certain antifolate drugs such as methotrexate, anticancer, antimalarial and antibacterial medications.

These issues are typically addressed by simultaneous, balanced B12 supplementation and risk-benefit analysis, respectively, and although important are not the main focus of our discussion here. What is worth our serious exploration is this: whether or not the adverse effects of folic acid supplementation, or aberrant DNA methylation activity seen in certain disease states, are a result of pushing methylation activity too far. Certainly epidemiological data suggest an inverse association between folate status and risk of disease, however this is not uniformly the case, and some intervention trials have suggested that excessive methylation factors may in some cases be harmful. To investigate this perhaps uncomfortable and controversial possibility, we take a closer look at the literature.

**UNEXPLAINED ADVERSE EFFECTS MAY BE DUE TO ABERRANT METHYLATION WHICH IS NOT NECESSARILY RESOLVED WITH 5-MTHF**

Firstly, there are more associations between folic acid supplementation and adverse outcomes that are not explained by UMFA or DHF (nor yet by any other mechanism), and for which we cannot rule out the possibility of aberrant or excessive methylation as a contributing/underlying factor:

**IMMUNE DYSREGULATION AND DYSFUNCTION**

Epigenetics are known to play a role in the development of allergic disease. For example, epigenetic changes including DNA hyper- and hypomethylation is associated with childhood IgE-mediated food allergy [59]. Although not all studies agree about the outcomes and specific mechanisms, there are findings linking the intake of methyl donor compounds with disease outcomes that should prompt concern and deeper investigation.

Some research has linked folic acid intake during pregnancy with an increased risk for allergic disease in offspring [60]. Higher levels of maternal folic acid supplementation (>500 mcg/d vs <200 mcg/d) have been associated with an 85% increased risk for allergic eczema, for example [61]. In animals, maternal supplementation with a combination of folic acid, vitamin B12,
choline, L-methionine, zinc and betaine during pregnancy enhances the development of many features of allergic airway disease including airway hyperreactivity and higher concentrations of serum IgE [62]. Similar maternal supplementation with non-dietary methyl donors, including synthetic folic acid, has been shown to increase offspring susceptibility to inflammatory bowel disease [63]. Another study, not of maternal intake, found that intakes of folic acid above 600 mcg/d (from food and supplements) was associated with impaired Natural Killer cell activity [43].

**BLOOD SUGAR DYSREGULATION**
Maternal folic acid supplementation at 500 mcg/d has also been associated with increased incidence of insulin resistance in children at 6 years of age, an effect apparently exacerbated by low maternal vitamin B12 status [64], [65].

**PRENATAL DEVELOPMENT DYSFUNCTION**
High folic acid intake is associated with embryonic loss and growth delay and increased incidence of ventricular septal heart defects [66].

**COMORBIDITY AND MORTALITY IN DIABETIC ADULTS**
In a retrospective study of 526 diabetic adults, high levels of RBC folate (determined to be primarily driven by folic acid intake) were associated with an increased risk for cardiovascular and cerebrovascular disease [67]. In addition, the hazard ratio for dying within 15 years in those with the highest levels of RBC folate was 2.10 (95% CI = 1.37 – 3.20), compared with a baseline (1.00) of those with the lowest levels of RBC folate.

If these unexplained associations between increased methylation factors and disease are caused via alterations in *methylation activity*, the possibility exists that alternative forms of folate supplementation can also alter methylation activity in ways that could generate the same risks. Unfortunately we simply don’t know enough to rule this out.
“It’s fashionable now to use large doses of methylating agents. But in that study of Prozac, using 15-50 mg of folic acid in depression, you have to realize that we have no idea what that is doing to the function of all the other genes. So if you need to use it for someone who has, say a mood disorder, use it, but follow the indices and use it for as short a period as possible.

I used methylated folate to treat a woman with depression. It happened to cure her endometriosis, too, because endometriosis, in part, is a genetic methylation defect. So there are places for these things, but don’t overdo it. Don’t overdo it.”

Robert Hedaya, MD, DLFAPA. Clinical Professor of Psychiatry, Georgetown University School of Medicine. Faculty, Institute of Functional Medicine
Changing folate status in humans has been demonstrated to alter DNA methylation [43]. In fact, one of the outcomes that functional practitioners often assume when they turn to folate supplements in under-methylating patients is the “restoration” of DNA methylation activity. Unfortunately, studies about the effect of folate and methylation status on the DNA “methylome” are conflicting and inconclusive, leaving us to attempt to derive sound clinical judgment in the absence of hard evidence. We do know that supraphysiological levels of substrates or cofactors can sometimes serve to override other regulatory or physiological limits, and push the rates of reactions forward [3]. We cannot rule out, therefore, that pushing levels of folate and SAMe methyl donors might increase DNA methylation beyond healthy levels.

According to Smith (2015), “It is now known that if there is too little methylation present, a gene that causes disease may be expressed. Conversely, with too much methylation, a gene that inhibits disease might be aberrantly suppressed.” If this is indeed true, we can assume there is absolutely potential for harm. Once again, let’s explore what the literature says about excessive DNA methylation and disease, specifically cancer, autoimmune conditions, immune hypersensitivity and Downs Syndrome:

**CANCER**

Aberrant DNA methylation has been put forward as a possible contributing cause to cancers [6], [43]. In cancer cell lines, both loci-specific DNA hyper- and hypo-methylation has been shown to occur, indicating that both states can be characteristic of tumorigenesis [68]. Global DNA hypermethylation is also apparent in various cancer cell lines, as shown in Figure 2.

The association between folic acid supplement use and colorectal cancer is one of the most studied folic acid-cancer correlations, and we should note that a recent systematic review and meta-analysis found inconsistent and inconclusive evidence for the effects of folic acid on colorectal cancer risk [69]. However, looking at broad associations may miss important details about the type, dose and effect of supplementation, and the folate, methylation and disease status of the individual, some of which we can glean from individual studies. For example, specific DNA site methylation in patients with stage II and III colon cancer has been significantly associated with increased risk of disease recurrence as well as being an independent predictor of poor overall survival (hazard ratio 2.9, 95% CI 1.5-5.8, P=0.002) and disease-free survival (hazard ratio 4.0, 95% CI 1.6-10.2, P=0.003) [52]. In another study, a randomized, controlled trial investigating the potential benefits of folic acid supplementation (1 mg/d) for the prevention of colorectal adenomas, researchers found that not only did folic acid fail to reduce recurrence risk, but that the risks for recurrent colorectal adenoma and noncolorectal cancers, especially prostate cancer, actually increased [70].

The influence of folic acid intake on breast cancer has also been explored and is considered controversial. For example, in one observational study, dietary supplementation with folic acid
greater or equal to 400 mcg/d was associated with a 20% increase in breast cancer risk compared with those reporting no supplement intake [71]. In contrast, food-sourced folate has a protective effect on cancer risk according to a 2014 Cochrane systematic review [72], and a recently published retrospective analysis of data from 367,993 women indicated that higher food folate intake is associated with a lower risk of sex-hormone receptor-negative breast cancer in premenopausal women [73].

The connection between folate status and cancer has also been investigated. In an investigation of women with breast cancer (n=204) compared with controls (n=408), individuals with the highest tertile of plasma folate (median 17 nmol/L) had the highest likelihood of ERβ(-) breast cancer (odds ratio 2.67, CI 1.44–4.92, P=0.001) [74]. Some of the same authors had previously found an increased risk in breast cancer specifically when the MTHFR C667T polymorphism was combined with high plasma folate levels [75], which may be concerning since patients who know they have this polymorphism are among the most likely to take supplemental folates.
In another case-control study of over 300 individuals, it appeared that high levels of serum folate acted as a promoter of the progression of existing benign tumors (polyps) to colorectal cancer, but also as an inhibitor of carcinogenesis in healthy controls [76], leading researchers to propose that serum folate can actually have dual roles in the onset and progression of cancer. In addition, recent cell studies point to potential dysregulation of one-carbon metabolism in cancer cells, specifically methionine uptake transporters have been found to be overexpressed, and the serine-glycine biosynthesis pathway is enhanced [77]. These offer perhaps some explanation for the potentially harmful effect of folic acid or even other forms of folate where there is a prior history of cancer.

We can’t know from these studies what folate derivative (see Figure 1) plays the biggest role in these observed findings, since serum folate measures various folate vitamers, but we do know that serum folate is largely made up of 5-MTHF (86.7%), with UMFA typically making up a much smaller amount (4.0%) [7]. Whether the potency of the smaller amount of UMFA is enough to cause the progression of pre-cancerous lesions, or whether high levels of 5-MTHF are also implicated, is not possible to discern; leaving the practitioner having to make a clinical judgment about what intervention to choose which will present least risk to the patient.

AUTOIMMUNITY
Systemic sclerosis is a poorly-understood autoimmune condition, characterized by endothelial injury, immune abnormalities and fibrosis. It is increasingly thought to originate from epigenetic dysfunction in immune cells that influence immune cell activation and proliferation [78]. Alterations in various epigenetic mechanisms are implicated in the pathogenesis of the disease. Hypermethylation of certain genes, Fli-1, KLF5 and BMPRII, reduce their anti-fibrotic effects. Conversely, the overexpression of immune cells CD40L, CD70 and CD11a is also involved, and is associated with hypomethylation of their corresponding genes.

The pathogenesis of other autoimmune conditions may also be influenced via methylation. IgG4-related autoimmune pancreatitis (AIP) and other autoimmune-like phenotypes are associated with MST1 (a serine/threonine kinase) deficiency in humans, which leads to T-cell immunodeficiency and hypergammaglobulinemia with autoantibody production. IgG4-related AIP patients who also exhibit extrapancreatic lesions demonstrate a significant increase in the frequency of methylation of MST1 and reduced protein productions, suggesting that this gene is regulated, at least in part, via methylation [79] and may contribute to the underlying disease onset and progression. Aberrant methylation patterns, both hypo- and hyper have also been observed in rheumatoid arthritis and autoimmune thyroid diseases. [80].

ALLERGY
In revisiting immune dysfunction we also find that researchers have hypothesized that environmental exposures that increased DNA methylation may also increase the risk for allergic
disease by suppressing Th1 and T regulatory cell differentiation that would otherwise inhibit the differentiation of allergy-promoting Th2 cells [60]. In a study of elderly men (n=704), minor increases (0.31%) in methylation at gene Alu repeat sequences have been significantly associated with incidence of prior sensitization to at least one allergen, raising the possibility that even small changes in epigenetic regulators might have significant clinical effects [60]. Even more compellingly, general hypermethylation at specific CpG sites has been proposed to be useful for differentiating clinically non-reactive versus clinically reactive food-allergic phenotypes, in a manner that appears to be even more predictive than serum IgE and skin prick testing [81].

**DOWNS SYNDROME**

In Downs Syndrome, early-life downregulation of the TET family genes involved in DNA demethylation, and downregulation of REST transcription factor expression and subsequent methylation of REST-vacant sites, have been proposed as potential pathways leading to the global DNA hypermethylation associated with the condition (Figure 3) [82].

*Figure 3: Epigenetic mechanisms in the development of Down Syndrome (DS) phenotypes, adapted from [83]*

![Epigenetic mechanisms in the development of Down Syndrome (DS) phenotypes](image-url)
5.5 **Reason to Tread Carefully**

While the effects of methylated folate or folic acid cannot be conclusively determined from the studies and reviews discussed above, what is overwhelmingly apparent is that there are enough unknowns to justify concern. Research is ongoing and it is not yet clear how aggressive 5-MTHF, or other methylation supplementation, affects health or the process of disease. At the very least these data suggest that we proceed with caution and focus on supporting the body’s own healthy mechanisms for methylation balance rather than attempting to override them.

The reality is that metabolic and DNA methylation are incredibly complex, the latter both in its own regulation and its regulation of gene expression with the added dimension of tissue-, site-, and gene-specific nuances. Epigenomic regulation is also intricately dependent on *many* environmental inputs, including both nutrients and lifestyle factors, which together make up the detailed mosaic of methylation activity regulation.

A safer way to support methylation activity, especially over the longer term, may be through food-based nutrients that provide the substrates and cofactors necessary for methylation pathways, as well as food and lifestyle practices that have been shown to promote favorable methylation activity and epigenetic imprints.
6 ASSESSMENT OF METHYLATION STATUS

While there are various assessments that can be used clinically to evaluate methylation status, there is no single assessment tool that accurately reflects the complexity of methylation activity in the body. Current laboratory assessments can provide insight into methylation-related genetic polymorphisms, nutrient status, methylation-related neurotransmitters and neurotransmitter metabolites, amino acids, hormones and metabolites, oxidative stress and detoxification load, all of which can provide inputs into the picture of methylation status in any one individual. Some measures, such as DNA methylation status, are not yet available to practitioners and are generally limited to research studies. As DNA methylation assessment does become available, care will be required on interpretation of data, as conflicting outcome has been demonstrated in research based on different methodologies employed and tissue methylation sites investigated. Furthermore, while technologies and research are rapidly advancing, patterns of DNA methylation in humans across tissues, age, populations, disease or environmental conditions (including dietary influence) are only just being characterized [84].

It is important that we not overemphasize any one single indicator, and be mindful of the limitations of our interpretation as well as confounding factors. Plasma homocysteine, for instance, can decrease as methylation activity improves, however it can also decrease when oxidative stress levels are high, independently of methylation improvements. And as we’ve discussed, only a few SNPs have known, quantifiable changes in enzymatic function, and even then the overall effect on methylation is unknown. The practitioner must therefore rely on multiple laboratory indicators in the context of clinical presentation to build an overall picture of methylation health.

In this section we review methylation assessment options available to practitioners. A summary checklist of these can be found in Appendix A.

6.1 GENETIC PROFILING

Genetic profiling can provide some indication of potential methylation status and disease risks. Some gene SNPs lean towards heightened methylation activity (e.g. CBS), and others may increase a tendency towards reduced methylation activity (e.g. MTHFR, BNMT, MTR, MTRR, AHCY). However, the interpretation of overall effects of gene SNPs is complicated by other polymorphisms and environmental inputs.

For example, it is known that the MTHFR C677T polymorphism is associated with an increased risk of autism spectrum disorder (odds ratio = 1.42, 95% CI 1.09-1.85), but that this risk can be mitigated by sufficient periconceptional folate or folic acid intake [85]. But if a maternal MTHFR C677T polymorphism is combined with a CBS polymorphism, a lack of prenatal
supplementation with B vitamins and a fetal COMT polymorphism, the odds ratio for autism spectrum disorder rises dramatically to 7.2 (CI = 2.3–22.4; P=0.05) [86].

This kind of clarity of disease risk related to genotype is unfortunately rare, since research into the combined effects of gene SNPs is still very much in its infancy. In many situations the practitioner will need to use careful clinical judgment to guide their interventions.

The methylation-related genes presented in Table 1 are frequently evaluated for SNPs.

Table 1: Genes related to methylation metabolism. Note that many SNPs do not result in clinically significant changes to enzymatic function. However, understanding the biochemical role of the enzyme coded for by the mutated gene can provide insight into biomarkers to test for and supportive interventions to consider.

<table>
<thead>
<tr>
<th>Gene Acronym</th>
<th>Gene Full Name</th>
<th>Enzyme &amp; Role</th>
<th>Possible SNP Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHCY</td>
<td>Adenosyl homocysteinase</td>
<td>Encodes for the enzyme S-adenosyl homocysteine hydrolase (SAHH), which converts S-adenosyl homocysteine (SAH, the metabolic product of SAMe methylation reactions) to homocysteine. SAH is potently inhibitory to methyltransferases.</td>
<td>Reduced enzyme activity. Hypermethioninemia, s-adenosylhomocysteinemia and impaired methyltransferase activity.</td>
</tr>
<tr>
<td>BHMT</td>
<td>Betaine-homocysteine methyltransferase</td>
<td>Catalyzes an alternative route for the conversion of homocysteine to methionine in the liver.</td>
<td>Reduced enzyme activity. Reduced conversion of homocysteine to methionine. Theoretically associated with hyperhomocysteinemia.</td>
</tr>
<tr>
<td>CBS</td>
<td>Cystathionine-β-synthase</td>
<td>Converts homocysteine to cystathionine via transulfuration. This is an alternative pathway to methionine resynthesis and the only route for homocysteine elimination.</td>
<td>Activity may be increased or decreased, depending on mutation. Downstream products potentially impacted include sulfate, taurine, glutathione and ammonia. Upstream compounds possibly impacted include homocysteine and homocystine.</td>
</tr>
<tr>
<td>Gene</td>
<td>Enzyme/Protein</td>
<td>Function</td>
<td>Notes</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>CBS</td>
<td></td>
<td>CBS is overexpressed in patients with Down Syndrome resulting in hypohomocysteinemia.</td>
<td></td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
<td>COMT enzymes metabolize the catecholamine neurotransmitters dopamine, norepinephrine and epinephrine, as well as the catecholestrogens (produced from estradiol). Note that there are two different forms of the COMT enzyme, soluble (associated with estrogen metabolism in the liver, kidneys and GI tract) and membrane bound (associated with brain neurotransmitter metabolism).</td>
<td>The most studied COMT SNP is Val158Met, associated with up to a 35-50% reduced activity as compared to wild type COMT [87]. Reduced clearance of catecholamines: dopamine, epinephrine, norepinephrine. Accumulation of catecholestrogens.</td>
</tr>
<tr>
<td>MAO-A</td>
<td>Monoamine oxidase enzymes A and B</td>
<td>MAO-A is primarily involved in the catabolism of serotonin, norepinephrine and dopamine. MAO-B primarily catabolizes dopamine, phenylethylamine (PEA), and N-Methylhistamine. Both MAO-A and B catabolize trace amines including tryptamine and tyramine.</td>
<td>MAO-A and MAO-B mutations may be associated with reduced clearance of dopamine, serotonin, epinephrine, norepinephrine, N-Methylhistamine and trace amines [88].</td>
</tr>
<tr>
<td>MAO-B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAT1A</td>
<td>Methionine adenosyltransferase I, alpha</td>
<td>Encodes for MAT which forms SAMe from methionine. Alcohol inactivates liver MAT [89].</td>
<td>Results in reduced enzyme activity. May result in decreased SAMe and compromised methylation activity; increased homocysteine</td>
</tr>
<tr>
<td>Gene</td>
<td>Protein Name</td>
<td>Function</td>
<td>Effects</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Methylene tetrahydrofolate reductase</td>
<td>Converts 5,10-methylene THF irreversibly to 5-methyl THF which is the active form used in the conversion of homocysteine to methionine for subsequent SAMe formation.</td>
<td>May cause reduced enzyme activity. Most studied SNPs are C677T and A1298C. May result in low SAMe, elevated homocysteine and reduced methyltransferase activity.</td>
</tr>
<tr>
<td>MTR</td>
<td>5-methyltetrahydrofolate-homocysteine methyltransferase</td>
<td>Encodes for the enzyme methionine synthase (MS) which catalyzes the final step in methionine biosynthesis. MS converts homocysteine to methionine by transferring a methyl group from methylcobalamin to homocysteine to form methionine. The methyl group is obtained from 5-mTHF, transforming it into THF.</td>
<td>May result in reduced enzyme activity. Low THF, increased homocysteine, decreased SAMe, increased reactive oxygen species.</td>
</tr>
<tr>
<td>MTRR</td>
<td>5-methyltetrahydrofolate-homocysteine methyltransferase reductase</td>
<td>Encodes for the enzyme methionine synthase reductase which re-methylates cobalamin using 5-mTHF for use by methionine synthase.</td>
<td>Decreased methionine synthase activity, increased homocysteine and reactive oxygen species, decreased SAMe.</td>
</tr>
</tbody>
</table>

Source: adapted from [6], [22]
6.2 **NUTRIENT STATUS**

Folate and vitamin B12 are perhaps the most well-known nutrients that play a direct role in methylation activity, however there are multiple other nutrients involved with methylation enzymes and pathways, either as substrates or cofactors (Figure 4).

*Figure 4: Nutrients that support methylation pathways*

There are various methods for the assessment of nutrient status (Table 2), including laboratory analytes and physical exam findings. Dietary intake assessment, via analysis of diet diaries, also provides a view of nutrient intake and can be a useful tool for evaluating nutrient inputs and as a basis for adjustment of nutrient intake. In our practice we routinely use nutrient intake analyses in conjunction with laboratory and physical functional status assessments.
Table 2: Roles and assessment of nutrients involved in methylation activity.

Laboratory tests are listed in order of preferred specimen. Note that physical exam findings are generally not specific and confirmatory testing is recommended, especially with regard to identifying causes of cardiac arrhythmias.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Role</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>Precursor to SAMe</td>
<td>Plasma</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Spares homocysteine to enter the methylation pathway and can act as a precursor for methionine and SAMe</td>
<td>Plasma</td>
</tr>
<tr>
<td>Taurine</td>
<td>Spares homocysteine to enter the methylation pathway to create SAMe</td>
<td>Plasma</td>
</tr>
<tr>
<td>DHA</td>
<td>Upregulates MTHFR expression, downregulates MAT expression, reduces homocysteine [90]</td>
<td>RBC or plasma Physical exam: xeroderma, dermatitis, keratosis pilaris, sensory neuropathy, poor wound healing</td>
</tr>
<tr>
<td>Zinc</td>
<td>Cofactor for betaine-homocysteine S-methyltransferase (BHMT) which converts homocysteine to methionine</td>
<td>RBC, plasma, hair Physical exam: loss of taste/smell, delayed wound healing, oral candidiasis, nail changes include leukonychia, koilonychia, Beau’s lines, onychorrhexis</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Cofactor for conversion of methionine to SAMe. Magnesium is required for any ATP and/or B6 dependent enzyme</td>
<td>RBC, whole blood, plasma, serum, urine. Magnesium deficiency can cause refractory hypernatremia, hypokalemia and hypocalcemia Physical exam: muscle spasms including blepharospasm, tremor, cardiac arrhythmias. Nail changes include onychorrhexis.</td>
</tr>
<tr>
<td>Nutrient</td>
<td>Cofactor(s)</td>
<td>Laboratory Tests</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Potassium</td>
<td>Cofactor for MAT enzyme</td>
<td>RBC, serum (obtain both for best assessment)</td>
</tr>
<tr>
<td>Riboflavin (B2)</td>
<td>Cofactor for MTHFR and MTRR enzymes.</td>
<td>Urine alpha-keto acids, plasma</td>
</tr>
<tr>
<td>Niacin (B3)</td>
<td>Cofactor for MTHFR and MTRR enzymes.</td>
<td>Serum, urine lactate &amp; pyruvate, alpha keto acids, picolinate</td>
</tr>
<tr>
<td>Pyridoxine (B6)</td>
<td>Required for formation of 5,10-methylene THF, the form of folate that is the substrate for MTHFR. Cofactor for cystathionine beta synthase (CBS)</td>
<td>Urine xanthurenate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine kynurenate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma homocysteine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma B6</td>
</tr>
</tbody>
</table>
Note that B6-dependent enzymes always requires magnesium.

<table>
<thead>
<tr>
<th>Folate</th>
<th>Source of folate derivatives for MTHFR and methionine synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine formiminoglutamate</td>
</tr>
<tr>
<td></td>
<td>Plasma homocysteine</td>
</tr>
<tr>
<td></td>
<td>RBC folate*</td>
</tr>
<tr>
<td></td>
<td>Macrocytosis/macrocytic anemia (with B12)</td>
</tr>
<tr>
<td></td>
<td>Whole blood neutrophil hypersegmentation</td>
</tr>
<tr>
<td></td>
<td>Serum folate</td>
</tr>
<tr>
<td></td>
<td>Physical exam: angular chelitis, cheilosis, candidiasis, glossitis, recurrent apthae, stomatitis, periodontal disease; sensory neuropathy. Nail changes caused by general B vitamin deficiency include beading, onychorrhexis, koilonychia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamin B12</th>
<th>Cofactor for MTR as methylcobalamin. B12 is remethylated via MTRR (5-mTFH provides the methyl group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine or serum methylmalonate</td>
</tr>
<tr>
<td></td>
<td>Plasma homocysteine</td>
</tr>
<tr>
<td></td>
<td>Serum vitamin B12</td>
</tr>
<tr>
<td></td>
<td>Macrocytosis/macrocytic anemia (with folate)</td>
</tr>
<tr>
<td></td>
<td>Physical exam: Angular chelitis, cheilosis, glossitis, macroglossia, recurrent apthae, stomatitis, periodontal disease; sensory neuropathy, hyperpigmentation, vitiligo, atopic dermatitis. Nail changes caused by general B vitamin deficiency include beading, onychorrhexis, koilonychia</td>
</tr>
</tbody>
</table>
deficiency include beading, onychorrhexis, koilonychia

Betaine (trimethylglycine)  Cofactor for BHMT; activator for CBS enzyme  Not typically measured

Choline  Can convert to betaine in the body. Spares tetrahydrofolate.  Plasma

Sulfur  Spares homocysteine for conversion to SAMe, especially in presence of oxidative stress (see below)  Sulfur-containing amino acids in amino acid profiles: methionine, cysteine/cystine, homocysteine/homocystine, cystathionine, taurine.

Urine sulfate  Physical exam: Sulfur deficiency can result in broad changes to keratin-rich tissues, including nails, skin and hair

Source: adapted from [6], [22]

* The CDC has identified an optimal red blood cell folate range (>906 nmol/L) for the prevention of neural tube defects [91].

### 6.3 Methylation Metabolites

A number of additional laboratory-assessed metabolites are also used in the assessment of methylation status (Table 3).

**Table 3: Additional metabolites used in the assessment of methylation status**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Significance</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine</td>
<td>Elevated homocysteine can indicate low formation of SAMe for methylation reactions</td>
<td>Plasma</td>
</tr>
<tr>
<td><strong>SAMe</strong></td>
<td>Low SAMe can indicate deficiency of methyl donors for methylation reactions</td>
<td>Plasma</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>SAH</strong></td>
<td>Elevated SAH can indicate poor conversion of homocysteine to methionine and inhibition of DNA methylation</td>
<td>Plasma</td>
</tr>
<tr>
<td><strong>SAMe:SAH ratio</strong></td>
<td>Considered a ‘methylation index’, a low ratio is often interpreted as an indicator of poor methylation status. Other factors may also lower this ratio, however, such as increased oxidative stress</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cystathionine</strong></td>
<td>High cystathionine can indicate early-stage elevated oxidative stress which can inform the interpretation of homocysteine results</td>
<td>Plasma</td>
</tr>
</tbody>
</table>

Additional methylation-related substrates, amino acids and amino acid derivative compounds may also be suggestive of methylation status. Care is advised in interpretation. These include:

- Compounds that interact with the folate cycle: glycine, serine, threonine, sarcosine, phosphoserine, ethanolamine, phosphoethanolamine, phenylalanine, tyrosine, tetrahydrobiopterin (BH4) products neopterin/biopterin.
- Compounds produced via SAMe-dependent methyltransferases: vanilmandilate (metabolite of epinephrine and norepinephrine), homovanillate (metabolite of dopamine), melatonin and creatinine.
- Substrates metabolized via SAMe methylation: histamine, estrogens.

Resources for laboratory interpretation:

- Metametrix Handbook (downloadable from Genova.net).
- Laboratories offering evaluation panels often have interpretive guides and training options.
6.4 **Nutrient Assimilation Capability**

Nutrient status is dependent on various factors. While optimal nutrient status starts with food ingestion, there is a process of digestion, absorption, transport, utilization and metabolism of each nutrient that must work in concert to deliver the required effect. Two of the most common and addressable issues in that chain are digestion and absorption.

To that end, practitioners using a MDL program may also evaluate and correct gastric function, pancreatic function, intestinal dysbiosis, intestinal permeability, food sensitivities, and malabsorption issues, all of which can have an impact on the absorption of nutrients necessary for methylation function.

6.5 **Inflammation**

Inflammation, and its associated increase in cytokine production, can interfere with methylation in various ways. DNA methylation is affected by inflammation-related signaling molecules. Cytokines, chemokines, free radicals, prostaglandins, growth factors and matrix metalloproteinases are among the molecules produced during inflammation, and these induce epigenetic changes including DNA methylation [92]. IL-1β for example, suppresses p53 expression [93], creating a more favorable environment for tumorigenesis. NFκB, a central transcription factor activated by inflammation, regulates the expression of more than 400 genes. It is also a direct regulator of NKκB-dependent histone demethylase which in turn regulates the fate and transdifferentiation of tumor cells [93]. IL-6, another potent inflammatory signaling molecule, regulates the activity of DNMTs, microRNAs and histone methyltransferases, and is able to alter the epigenetics of p53 tumor suppressor genes in a way that reduces their expression [93], [94]. TNF-alpha induces increases in mitotically-preserved and region-specific DNA methylation in a manner that appears to associate with impaired cellular differentiation and renewal [95].

*In vitro* evidence suggests that inflammation may also drive the production of methyl radicals which induce DNA methylation of the normally unmethylated tumor suppressor genes, leading to gene silencing and carcinogenesis [96].

Inflammation can also contribute to a metabolic milieu that drains methylation resources, for instance via dysregulation of glucose homeostasis. Pro-inflammatory molecules interfere with insulin signaling in peripheral tissues [97] and reducing inflammatory mediators improves insulin signaling [98]. Insulin dysfunction and hyperglycemia promote increased oxidative stress which drives increased utilization of glutathione and depleted homocysteine, methionine and SAMe. Further, disordered DNA methylation patterns influencing metabolism and inflammation were identified in adipose tissue from subjects with type 2 diabetes [99].
Table 4: Factors in the assessment of excess inflammation

<table>
<thead>
<tr>
<th>Category</th>
<th>Inflammatory Factor</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometrics</td>
<td>Weight</td>
<td>Overweight and obesity, especially excess abdominal adipose tissue, is associated with increased levels of inflammation</td>
</tr>
<tr>
<td></td>
<td>Body-mass index</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Waist circumference</td>
<td></td>
</tr>
<tr>
<td>Standard laboratory inflammation indicators</td>
<td>CRP</td>
<td>Laboratory markers that are routinely used in the assessment of inflammatory status</td>
</tr>
<tr>
<td></td>
<td>Ferritin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythrocyte Sedimentation Rate</td>
<td></td>
</tr>
<tr>
<td>Microbial assessment</td>
<td>Dysbiosis</td>
<td>Disturbances in bacterial populations residing in the gastrointestinal tract can generate pro-inflammatory compounds that can enter circulation</td>
</tr>
<tr>
<td></td>
<td>Small intestine bacterial overgrowth (SIBO)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Periodontitis</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Various, e.g. active autoimmunity, co-infection</td>
<td>Active autoimmunity or infection can increase systemic inflammation</td>
</tr>
</tbody>
</table>

6.6 OXIDATIVE STRESS

Oxidative stress is closely related to inflammation. States of high, or chronic, oxidative stress can negatively impact methylation metabolism via two mechanisms. Firstly, oxidative stress increases the demand for glutathione synthesis, which pulls homocysteine towards transulfuration pathways, at the expense of methylation pathways and SAMe formation [39]. Secondly, oxidative stress and increased hydroxyl radical formation can damage DNA and impair the ability of DNA methyltransferase enzymes to appropriately methylate DNA; this can lead to global DNA hypomethylation and specific areas of hypermethylation [4].

DNA guanine nucleotides can be major sites of DNA oxidative damage, and are frequently used as a biomarker of DNA-level oxidative stress (8OHdG). Normally, guanine acts as a
hydrogen bond acceptor in the formation of methyl binding protein (MBP)-DNA complexes. However, oxidation of guanine significantly diminishes MBP binding when adjacent to the 5-methyl cytosine nucleotide. In addition, 5-methylcytosine (5-mC) is also susceptible to oxidation (hydroxylation), forming 5-hydroxymethylcytosine (5-hmC), in the presence of environmental stimuli such as oxidative stress. This can interfere with DNA-protein interaction and inhibits the binding affinity to MBPs, leading to potentially heritable epigenetic alterations. [4]

Most-commonly used methods to detect DNA methylation do not differentiate between 5-mC and 5-hmC, which may prove to be an important distinction, especially in the brain where most DNA hydroxymethylation appears to present [100]. There is evidence that acute psychological stress can increase DNA hydroxymethylation in the hippocampal glucocorticoid receptor gene and that this epigenetic change predisposes to neuropsychiatric and neurodegenerative disorders [100]. Aging is also associated with increases in 5-hmC in the brain, and may be prevented by caloric restriction and antioxidant upregulation [101].

Table 5: Common analytes in the assessment of oxidative stress

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-OHdG</td>
<td>A marker for DNA damage induced by oxidative stress</td>
</tr>
<tr>
<td>Alpha-hydroxybutyrate</td>
<td>A marker for glutathione status</td>
</tr>
<tr>
<td>Pyroglutamate (5-oxoproline)</td>
<td>A marker for glutathione loss and decreased antioxidant capacity</td>
</tr>
<tr>
<td>F2-isoprostanes</td>
<td>Product of free radical activity on arachidonic acid</td>
</tr>
<tr>
<td>Lipid peroxides</td>
<td>Product of free radical activity on lipids</td>
</tr>
</tbody>
</table>

Source: [22]
7 THE METHYLATION DIET AND LIFESTYLE

We prescribe the full MDL or portions of the program to all of our patients. We are pleased to report that thus far our patients have responded well, both in terms of palatability and “do-ability” of the diet as well as clinically. For example: a 57-year-old male presenting with diffuse myalgia and arthralgia and a history of toxic mold exposure, who complained of years-long methyl donor intolerance, had a baseline homocysteine of 15.7. After one month of the MDL program, his follow-up homocysteine is 11.8, which appears associated with a modest reduction in pain. No other changes to his plan were made.

Functional medicine practitioners may utilize The MDL program in various ways:

- As a stand-alone intervention for long-term support
- Alongside folate and other nutrient supplementation to support effectiveness
- As an alternative intervention for individuals who do not tolerate methyl donor supplementation

In this section, we review the foundational interventions that are relevant to the MDL program. Readers may also find a summary checklist of these interventions in Appendix B.
7.1 **FOOD-BASED NUTRIENTS**

*Recommendation: As possible, use nutrients from foods for methylation support and for addressing significant genetic SNPs*

It is reasonable to conclude that supporting methylation status through non-fortified whole foods is a lower-risk and effective intervention, as long as adequate status of the relevant nutrients can be maintained.

When compared side-by-side in a 16-week human placebo-controlled trial, an increase of 200 mcg/d folate from folate-rich foods (from a baseline average of 292 mcg/d) showed the same ability (no statistical significance between effects) to increase plasma and erythrocyte folate levels, and lower homocysteine compared with an equal amount of supplemental folic acid or 5-mTHF (as Metafolin®) [102]. Dietary folate, along with other lifestyle factors, has also been shown to have a significant, favorable effect on DNA methylation [4], [25]. There is no upper limit set for folate intake sourced from non-fortified foods, and at this time of writing we know of no studies showing adverse effects from sourcing folates and other methylation nutrients from foods.

The question of what level of nutrient intake is sufficient to optimize methylation status has no definitive answer, and will inevitably vary from individual to individual based on their genetic fingerprint and environmental factors. A Cochrane systematic review, published in 2014, found that food-sourced folate had a protective effect on cancer risk (specifically breast cancer) within the range of 153 – 400 mcg/d [72], suggesting that high dosing is not necessarily advantageous for the general population. However, it may be reasonable to assume that certain populations, often those whose health concerns lead them to seek out Functional Medicine, may have genetic or environmental disturbances that merit higher nutrient intakes.

There are various nutrients involved with methylation enzymes and pathways, either as substrates or cofactors, as shown in Figure 4. Table 6 lists out these nutrients of particular interest and their dietary sources. Some of these nutrients are already used as targeted supplements by many functional medicine practitioners, and are a central component of the MDL Food Plan and Menu Plans.
<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Rich Dietary Sources (Sourced from [103] unless otherwise noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>Egg, cod, whitefish, sesame seeds, spirulina, parmesan cheese, sunflower seeds, Brazil nuts, chicken, beef, lamb, salmon, buffalo, turkey, halibut, pork, anchovy, Romano cheese, game meats, gruyere cheese, goat cheese, goose, duck, snapper, tilapia, mackerel, haddock, lobster, pumpkin seeds, sardine, herring, bison, game meats.</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Egg, sesame, sunflower, beef (especially liver), cod, tofu, spirulina, soybeans, pork, whitefish, fish roe, butternuts, black walnuts, sunflower seeds, goose, duck, watermelon seeds, buffalo, lamb, chicken, oats, pumpkin seeds, quail, octopus, halibut, pistachio nuts, flaxseed, clams.</td>
</tr>
<tr>
<td>Taurine</td>
<td>Animal and fish protein, eggs and brewer’s yeast.</td>
</tr>
<tr>
<td>DHA 22:6(n-3)</td>
<td>Fish oil, cod liver oil, mackerel, salmon, fish roe, anchovy, whitefish, herring, trout, bass, tilefish, sardine, halibut, oysters, squid, flatfish, mussels, shrimp, crab, perch, scallops.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Oysters, pumpkin seeds, sesame seeds, chervil, beef, game meats, lamb, poppy seed, shiitake mushroom, cardamom, celery seed, crab, bison, turkey, pork, peanuts, pine nuts, cocoa, thyme, parsley, rice bran, basil, agar seaweed, cashews, lobster, mustard seed, dark rye.</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Seaweed (agar), herbs, spices, bran, pumpkin seeds, cocoa, flaxseed, Brazil nuts, sunflower seeds, sesame seeds, poppy seeds, almonds, cashews, buckwheat, amaranth, rye, molasses, walnuts, quinoa, great northern beans, mung beans, teff, tofu, chickpeas, oats, daikon radish, bulgur, lambsquarters, hazelnuts, leeks, black beans, kidney beans, horseradish.</td>
</tr>
<tr>
<td>Potassium</td>
<td>Dried herbs, daikon radishes, sun-dried tomatoes, turmeric, cocoa, chili powder, dried apricots, lima beans, oregano, white beans, shiitake mushrooms, kidney beans, pinto beans, great northern beans, lambsquarters, adzuki beans, mung beans, pistachio nuts, lentils, pumpkin seeds, sunflower seeds, yam,</td>
</tr>
<tr>
<td>Vitamin</td>
<td>Foods</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Riboflavin (B2)</strong></td>
<td>Lamb liver, spirulina, beef liver, egg, paprika, chives, coriander leaf (cilantro), spearmint, chicken liver, tarragon, shiitake mushrooms, parsley, almonds, fish roe, cayenne pepper, duck liver, goose liver, chili powder, soybeans, game meat, daikon radish, chervil, goat cheese, mackerel, brie cheese, sesame.</td>
</tr>
<tr>
<td><strong>Niacin (B3)</strong></td>
<td>Anchovy, beef liver, lamb liver, peanuts, chicken, chicken liver, shiitake mushrooms, sesame seeds, salmon, spirulina, pork, cilantro (coriander leaf), mackerel, parsley, beef, game meats, sun-dried tomatoes, tarragon, trout, lamb, chili powder, mustard seed, duck, cod, sunflower seeds.</td>
</tr>
<tr>
<td><strong>Pyridoxine</strong></td>
<td>Rice bran, paprika, chili powder, ancho peppers, sage, cayenne pepper, tarragon, basil, chives, turmeric, bay leaf, rosemary, dill, pistachio nuts, baker’s yeast, turkey liver, parsley, sunflower seeds, garlic, oregano, leeks, marjoram, curry powder, shiitake mushrooms, salmon, chervil, celery seed, chicken liver, cod, ginger, sesame seeds, palm heart, sunflower seeds, prunes, pork, brown rice, beef, game meats, molasses, chestnuts, octopus, goose, cornmeal, trout, daikon radishes, potatoes, cilantro (coriander leaf), fenugreek seed, amaranth, cloves, hazelnuts, black walnuts, soybean, thyme, lentils, peanuts, English walnuts, chickpeas (garbanzo beans), dried apricots.</td>
</tr>
<tr>
<td><strong>Folate</strong></td>
<td>Liver (duck, goose, turkey, chicken, beef), mung beans, chickpeas (garbanzo beans), spearmint, pinto beans, great northern beans, lentils, black beans, fava beans, kidney beans, soybeans, leeks, navy beans, rosemary, daikon radishes, split peas, basil, cilantro (coriander leaf), marjoram, oregano, sage, tarragon, thyme, peanuts, sunflower seeds, wakame seaweed, spinach, turnip greens, asparagus, mustard greens, quinoa, kelp seaweed, bay leaf, parsley, pinto beans, black eye peas, collard greens, shiitake mushrooms, parsley, dill, okra, egg, peanuts, artichokes.</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Clams, liver (lamb, beef, turkey, duck, goose, chicken), oysters, mussels, mackerel, whitefish, salmon, crab, cod, herring, trout, game meat, eggs, beef, chicken, goose, pork, lamb, snapper, lobster.</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Betaine (trimethylglycine)</td>
<td>Beets, lambsquarters, spinach, and quinoa. Liver, sunflower seeds, kamut, and rye are also good sources. [104]</td>
</tr>
<tr>
<td>Choline</td>
<td>Egg yolk and liver are excellent sources. Choline is also found in meats, especially beef, salmon, whitefish, trout, soybeans, lentils, cauliflower and flaxseeds [104], [105].</td>
</tr>
<tr>
<td>Sulfur</td>
<td>Egg, cabbage, Brussels sprouts, leeks, horseradish, ginger, mustard, fish, shellfish, lamb, beef, chicken, pork, duck, goose, turkey, lentils, peas, butter beans, barley, oatmeal, cress, haricot beans, Brazil nuts, almonds, peanuts, walnuts [106].</td>
</tr>
</tbody>
</table>
Depending on the genotype of the individual, nutrient needs can be further customized to support potential enzyme deficiencies. Individuals with specific SNPs may benefit from increased intake of cofactor nutrients utilized by the associated enzyme since it has been shown that high cofactor intake can push the rate of enzymatic reactions forward [3]. Table 7 lists frequently evaluated methylation-related genes and the nutrients that can be utilized to support activity.

Table 7: Methylation-related genes and nutrition to support SNPs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cofactor Nutrient Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR</td>
<td>Riboflavin, niacin</td>
</tr>
<tr>
<td>MTR</td>
<td>Vitamin B12, zinc</td>
</tr>
<tr>
<td>MTRR</td>
<td>Riboflavin, B12</td>
</tr>
<tr>
<td>MAT1A</td>
<td>Magnesium, potassium*</td>
</tr>
<tr>
<td>MAO</td>
<td>Riboflavin, iron</td>
</tr>
<tr>
<td>COMT</td>
<td>Magnesium</td>
</tr>
<tr>
<td>CBS</td>
<td>Vitamin B6, magnesium betaine</td>
</tr>
<tr>
<td>MTRR</td>
<td>Vitamin B12</td>
</tr>
<tr>
<td>BHMT</td>
<td>Betaine, choline</td>
</tr>
</tbody>
</table>

*Source: adapted from [6], [22]*

*While there are no known risks of dietary potassium intake, potassium supplementation should be physician supervised.*

### 7.2 SUPPORT FOR NUTRIENT ASSIMILATION

**Recommendation: Support optimal micronutrient assimilation with the Five-R gut repair protocol**

Where a need is indicated, either by laboratory testing or physical exam findings, the Five-R Protocol, outlined in Table 8, is an ideal way to improve nutrient assimilation and functional status. It can be done either alongside a short-term course of methylation supplementation (with subsequent transition to the MDL) or alongside the MDL from the start.
Table 8: Overview of the Five-R Protocol for Optimizing Gut Function

<table>
<thead>
<tr>
<th>Step</th>
<th>Target</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remove</td>
<td>Microbial overgrowth or pathogens, reactive or destructive foods</td>
<td>Herbal or pharmaceutical treatments to lower pathogenic load. Identify and remove offending foods (clean food sources, Elimination Diet). Review medications.</td>
</tr>
<tr>
<td>Replace</td>
<td>Digestive capacity</td>
<td>Support digestive function through oral digestive enzymes, acid, bile or factors that promote digestive secretions (e.g., bitters, cholagogues).</td>
</tr>
<tr>
<td>Re-inoculate</td>
<td>Microbiome health</td>
<td>Probiotics and prebiotics to favorably repopulate bacterial populations.</td>
</tr>
<tr>
<td>Repair</td>
<td>Mucosal lining and immune integrity</td>
<td>Targeted supplementation for mucosal and immune health.</td>
</tr>
<tr>
<td>Rebalance</td>
<td>Lifestyle</td>
<td>Stress reduction and stress management, sleep hygiene, exercise.</td>
</tr>
</tbody>
</table>

### 7.3 MICROBIOME

*Recommendation: Support balanced microbial populations and folate-producing species*

Early research findings suggest that the microbiome may play a role in regulating host DNA methylation activity, at least in their local environment. DNA methylation of intestinal epithelial cells is shown to be significantly dysregulated and reduced in germ-free mouse models when compared with conventional controls [107]. This study also showed that reestablishing commensal bacterial populations via fecal transplant correlates with significant
increases in CpG methylation. Gut microbes also produce butyrate, which potently inhibits histone deacetylase and also appears to affect DNA methylation [108], [109]. Researchers argue that these findings suggest a sophisticated, directive role for microbes in host epigenetic regulation, beyond simple facilitation [107].

Specific bacterial species may also exert different effects on DNA methylation. In one human pilot study, higher levels of the bacterial phylum Firmicutes (vs bacterial phylum Bacteroidetes) was associated with increased promoter methylation of 568 genes, and decreased promoter methylation of 245 genes (P=0.05). The genes affected were associated with cardiovascular disease, inflammation, metabolic pathways and cancer [110]. Previous studies in humans have identified various Firmicutes/Bacteroidetes ratios in obese individuals [111].

The gut microbiota also affects nutrient status, and in this role may also indirectly impair or support methylation activity. Most Lactobacillus species are in vitro consumers of folate with the exception of L. plantarum strains which can produce folate in the presence of para-aminobenzoic acid (PABA). Many Bifidobacteria species, especially strains of B. bifidum and B. infantis, are folate producers, along with B. breve, B. longum, B. adolescentis, and B. pseudocatenulatum [112]. Most of these species also produce folate in both its THF and 5mTHF forms, with B. adolescentis producing the highest levels of methylated folate [113]. In vivo, the administration of B. adolescentis (MB 227 and MB 239) and B. pseudocatenulatum (MB 116) raised serum folate levels in folate-deficient rats, and the co-administration of prebiotic fructans raised serum folate levels further still [114]. While human folate absorption occurs primarily in the small intestine, it also occurs in the colon [115]. Administration of B. longum to hemodialysis patients reduced serum homocysteine in a manner attributed to the increased supply of folate produced by this species in the gastrointestinal tract [116].

In addition, dysregulation of commensal populations or overgrowth of bacteria in the small intestine can hinder general nutrient absorption and appetite signaling with consequences for functional status of methylation substrates and cofactors [117]. And, as an example of the interconnectivity between the various inputs to methylation health, unfavorable microbial balance may underlie local and systemic inflammation [118], which, as we have reviewed, can also have effects on methylation activity.

### 7.4 Inflammation

*Recommendation: Adopt an anti-inflammatory diet and lifestyle*

Strategies to reduce inflammation are appropriate for methylation support (see Section 6.5. While a full exploration of all anti-inflammatory interventions is beyond the scope of this book, the following provide a summary of potential actions and are common approaches used in Functional Medicine:
• Regulate blood glucose: chronically elevated circulating glucose levels, and also acute, postprandial glucose spikes activate oxidative stress [119], indicating that both aspects of glucose control should be addressed.

• Healthy weight maintenance: Adipose tissue produces pro-inflammatory cytokines including TNF-alpha and IL-6 [120] and is associated with aberrant DNA methylation patterns [99]. A higher body-mass index (BMI) and especially central adiposity is a driver of chronic, systemic inflammation [121].

• Resolve microbially-driven inflammation: Excessive levels of bacteria or dysbiosis in the GI tract promote higher levels of local and systemic inflammation [122]. Bacterial pro-inflammatory compounds with systemic effects can derive from the small and large intestine, and also in the stomach, and oral cavity. Pro-inflammatory pathogenic bacterial species may also take up residence in internal tissues such as atherosclerotic plaque [123]. Helicobacter pylori, a potential pathogen in the stomach, is also associated with aberrant DNA methylation [124].

• Reduce exposure and sensitization to food antigens: food allergies and sensitivities have been shown to increase inflammation via innate immune activation [125].

• Adopt an anti-inflammatory diet: which avoids pro-inflammatory foods such as sugars, refined carbohydrates, conventionally-raised animal products, refined vegetable oils, hydrogenated fats, and includes phytonutrient-rich whole plant foods and omega-3 fatty acids.

• Support an anti-inflammatory lifestyle: Pro-inflammatory lifestyle factors such as stress [126] and sedentary behavior [127] can be mitigated by stress management techniques and physical activity. Lifestyle factors also exert effects on methylation activity that are independent of their potential actions on inflammation.

7.5 OXIDATIVE STRESS

Recommendation: Reduce sources of oxidative stress and support balanced antioxidant capacity

Sources of oxidative stress can be metabolic, dietary or environmental: excessive calories, excessive sugars/refined carbohydrates, too little or too much exercise, excessive alcohol consumption, tobacco smoke, air pollutants, fungal toxins, charbroiled foods (and other advanced glycation end products), ionizing radiation, chronic infections, poor sleep, and gut dysbiosis can all contribute to oxidative stress. Addressing oxidative stress involves reducing sources as well as support in the form of antioxidants as found in a high plant-food diet, herbs, spices, nuts, seeds and unrefined oils. Specific supplements such as N-acetylcysteine, alpha lipoic acid and coenzyme Q10 may also be useful where there is a specific need that cannot be met via diet alone.
7.6 DETOXIFICATION

Recommendation: Reduce exposure to environmental toxins and support biotransformation and elimination

Methylation is an important detoxification pathway, and so high exposure to environmental toxins such as heavy metals and chemicals can place excessive demand on methyl donors and limit their availability for other uses. Environmental toxins may also exert their effects on DNA methylation via other mechanisms such as endocrine disruption, oxidative stress and inflammation [128].

Figure 5: Potential Mechanisms Linking Environmental Toxin Exposure with Epigenetic Effects, adapted from [128]
The following environmental toxins are among those that have been found to produce DNA methylation alterations:

- Pesticides [2]
- Fertilizer [2]
- Automobile fumes [2], [129]
- Bisphenol A [128], [130]
- Phthalates [130]
- Persistent Organic Pollutants (POPs) [128], [131]
- Jet fuel [130]
- Benzene [33]
- Mold toxins (aflatoxin, fumonisin) [132]
- Arsenic [128], [133], [134]
- Mercury [133], [134]
- Lead [134]
- Cadmium [128], [134]
- Nickel [128]

Heavy metals may be particularly problematic. Specific DNMT inhibition and reduced DNMT gene expression has been shown with lead exposure [134]. Cadmium appears to induce DNA hypomethylation via DNMT inhibition in the short term, but may actually have the opposite effect, that of hypermethylation, when chronic exposure is present [134]. In vitro research suggests that one mechanism involved in aberrant DNA hypermethylation is via the induction of toxin or inflammation-mediated methyl radicals (from oxidized methionine) that prompt the direct formation of DNA hypermethylation of tumor suppressor genes resulting in gene silencing and oncogenesis [96]. Oxidized methionine formation has been detected in smokers, inflammation and aging [96]. Inorganic arsenic is detoxified in the body by methylation, leading researchers to conclude that arsenic exposure may drain the endogenous pool of methyl donors [134].

Total exposure to toxins such as persistent organic pollutants (POPs) and heavy metals may have cumulative and long-lasting effects. Manikkam et al. (2012), investigating the DNA methylation effects of bisphenol A, phthalates, digoxin and jet fuel (as listed above) also found that the epigenetic alterations persisted across generations and appeared to induce early onset puberty four generations later in rodents [130].

Environmental toxins may also inhibit healthy methylation activity by interfering with other folate mechanisms. Fumonisins (a type of mold toxin), for example, have been found to inhibit the proper function of folate binding proteins (human folate receptor alpha) [132].

In light of our growing understanding of how toxins influence methylation, and other health aspects, reducing exposure where possible is essential. This may involve the assessment and remediation of exposures to mold, lead, and mercury amalgams, for example, minimizing the use of plastic food containers, avoiding high-mercury fish, and switching to nontoxic household...
and personal care products. The Environmental Working Group (www.ewg.org) provides an excellent resource for further understanding sources of toxin exposure, and independent product testing.

Supporting endogenous biotransformation via Phase I and Phase II detoxification pathways, as well as well-functioning elimination, is also essential. Short term use of supplement protocols for detoxification are often used in functional medicine, where an excessive toxic burden is indicated. Food and lifestyle also present an opportunity to support detoxification. The following are basic principles to follow for everyday detoxification support:

- Proper hydration
- Adequate fiber sources
- Low-toxin foods including organic, and antibiotic and hormone-free
- High intake of colorful plant foods, especially deep greens and berries
- Regular intake of cruciferous vegetables
- Adequate protein intake
- Maintain micronutrient intake

7.7 **STRESS MANAGEMENT**

*Recommendation: Manage stress exposure and response*

States of high psychological and physiological stress increase the production of the catecholamines epinephrine and norepinephrine, which require methylation for their biosynthesis, metabolism and excretion. High methylation activity in these pathways draws on the available pool of SAMe, and can lower the availability of this methyl donor for other reactions. Stress reduction and management is, therefore, an appropriate intervention for sparing methyl donors for other functions.

In addition to metabolic methylation, psychological stress can also alter DNA methylation via mechanisms distinct from competitive demand for methyl donors. And it is clear that, once again, there is a significant amount of complexity that governs the overall and site-specific effect, and that our current understanding is limited. Methylation of the promoter region of genes coding for the glucocorticoid receptor, a key modulator of the HPA axis and stress response, has been shown to be differentially altered in various stress states including early life stress, post-traumatic stress disorder, and chronic fatigue syndrome [135], [136].

**PRENATAL AND EARLY LIFE STRESS EFFECTS**

**Stress sensitivity:** We know that stress-mediated epigenetic ‘priming’ via methylation during critical developmental windows is associated with later onset of psychopathology. For instance, and as we reviewed earlier, low levels of maternal nurturing is associated with altered levels of
DNA methylation in the glucocorticoid receptor promoter, and increased expression of the receptor, suggesting that traumatic experiences, perhaps especially during vulnerable periods of development, might ‘prime’ an individual for a later, hyper-stress response [31]. Some authors have theorized that methylation changes that potentiate the effects of the stress response, may explain the connections between stress and diseases such as asthma [137].

**Metabolic risk:** Prenatal maternal stress, as evaluated after the January 1998 Quebec ice storm, correlates with increased central adiposity and BMI in offspring at age 13 ½, and these changes are thought to be, in part, mediated via DNA methylation [138].

**STRESS EFFECTS OUTSIDE THE PRENATAL AND PERINATAL TIME PERIODS**

**Stress sensitivity:** Traumatic childhood experiences, including maltreatment, and parental death or desertion, outside of the prenatal and perinatal developmental periods also appear to alter methylation of the glucocorticoid receptor gene promoter, corresponding with attenuated cortisol responsiveness [139].

**STRESS AND INFLAMMATION**

Acute and chronic stress also directly increase circulating inflammatory factors including IL-1β, CRP and IL-6, mediated via upregulation of the NLRP3 inflammasome [140], and this is may be a significant way in which stress mediates epigenetic alterations. The effects of inflammation on methylation activity are reviewed above.

### 7.8 Exercise

**Recommendation:** *Adopt a personalized, moderate exercise plan; caution with over-training*

Exercise alters metabolic methylation-related activity and biomarkers. According to a 2014 systematic review, daily activity is consistently associated with lower homocysteine levels in a dose-dependent manner [141]. And in animal models, exercise has been shown to prevent folate deficiency-induced hyperhomocysteinemia at least in part via increased BHMT expression (two-fold) in the kidney [142]. Acute exercise, however, is associated with a temporary (<24 hour) increase in plasma homocysteine, especially in untrained individuals, which is thought to be due to the increased catabolism of muscle proteins during exercise to make amino acids available for gluconeogenesis in the liver [141], [143]. This acute effect can be exacerbated by low folate and vitamin B12 status [144], making nutrient repletion important.

Exercise, especially regular and at moderate intensity, is an effective antidote to factors that can deplete methyl donor reserves or negatively alter methylation activity, namely psychological stress, oxidative stress and inflammation [145]. Aerobic exercise and resistance training are also associated with increased cellular glucose uptake and reduced blood glucose [146], which would also reduce oxidative stress caused by higher AGE-promoting glucose levels.
The enhanced production of reactive oxygen species and free radicals during acute exercise, as well as increased levels of pro-inflammatory cytokines, is well documented [140], [147], but long-term effects of these changes depends on the type of activity and duration of an active lifestyle. Some caution is warranted with high-intensity or anaerobic exercise which may have deleterious pro-oxidative effects, particularly in untrained individuals. Endurance exercise, for example, may produce circulating levels of IL-6 that are up to 120 times that of baseline, as well as localized increases in other predominantly pro-inflammatory cytokines [140]. And a 2013 systematic review, investigating the effect of exercise on levels of oxidative stress in the brain, found that regular, moderate, aerobic exercise increases the brain’s antioxidant capacity, but that high-intensity, anaerobic exercise could reduce the antioxidant response [148]. These discrepancies may be explained by a hormesis model of exercise (Figure 6), which argues that too little or too much exercise can produce negative effects [149]. Gradual build-up of exercise, via regular practice or training, can shift the hormesis curve to the right, meaning that exercise tolerance and benefits are highly personalized.

*Figure 6: Hormesis and Exercise* [149]. Used with permission.

Magnitude of Stress/Exercise

It has been argued in recent reviews that abundant dietary antioxidants provided by a diet rich in natural plant phytochemicals (vegetables, fruits, whole grains, legumes and beans, sprouts and seeds) are an effective way to meet the antioxidant requirements of physically active individuals and athletes [147], [149]. In fact, dietary intervention may well be a more effective...
strategy than antioxidant supplementation, since studies using supplementation show insufficient and mixed results, and some researchers even theorize that antioxidant supplementation may blunt the beneficial hormetic effects of exercise and delay muscle recovery [147], [149].

Both acute and chronic exercise do appear to induce changes in DNA methylation, according to a recent review of literature [150]. For example, in a retrospective study of 647 women, regular exercise throughout a lifetime appears to act to preserve the age-related depletion of global methylation status; physical activity (including sports, and also daily movement such as climbing stairs, housework, and yardwork) that was greater or equal to the median in three distinct life stages (childhood, adolescence, and adulthood), did have small, but significant, increases in global DNA methylation compared with those who did not meet that level of physical activity in all three life stages [151]. Women who practiced physical activity at or above the median in only one or two of those life stages also had increased DNA methylation, but statistical significance was lost. The median level of exercise was calculated as 9.8 hours per week in childhood, 5.9 hours per week in teenage years, and 12.5 hours per week in adulthood.

In a separate case-control study of 500 females, long-term tai-chi practitioners (at least one hour per week for 3 years or more) demonstrated a slowing of age-related DNA methylation losses, of between 5-70%, compared with controls [152]. During their research, the investigators determined that a significant difference in methylation between the two groups at a number of specific sites only occurred after 50-55 years of age, leading to their speculation that tai-chi may be of particular benefit in this age-group.

Although the mechanisms of the effects of exercise on DNA methylation are not yet well understood, theories speculate that this may be mediated by the inflammation-lowering effect of exercise, or via altered sex hormone levels that then in turn alter DNA methylation [150]. Mind-body exercises such as tai-chi may also be beneficial due to their effects on stress hormone levels and stress responsiveness.

### 7.9 **Nutraceutical Interactions**

*Recommendation: Understand the potential interactions with long term supraphysiological supplementation of niacin, selenium, and phosphatidylethanolamine*

As most of us have witnessed, nutraceutical supplements used in functional and integrative medicine, and nutrition practice, have powerful effects on physiology. Indeed, they are one of the primary tools that practitioners use to help their patients achieve optimal wellness. However, it behooves the practitioner to be aware of potential interactions, and in this context the ones that may negatively affect methylation.

Certain nutrients are metabolized in the body via methylation, specifically niacin, selenium and phosphatidylethanolamine (Table 9). Therefore high dose supplemental regimens of these
nutrients may drain the pool of available methyl donors and either create or worsen a methylation deficit. Niacin also limits pyridoxal kinase, which normally activates vitamin B6 [6], therefore high doses of this nutrient may impair vitamin B6 status.

<table>
<thead>
<tr>
<th>Caution with long term, high doses of these nutrients that are metabolized via methylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
</tr>
<tr>
<td>Selenium</td>
</tr>
<tr>
<td>Phosphatidylethanolamine</td>
</tr>
</tbody>
</table>

### 7.10 Medication Interactions

**Recommendation:** Caution with medications that alter the status of methylation nutrients

A number of medications are known to impede methylation activity in distinct and specific ways. Some medications may impair nutrient absorption, some inhibit enzyme function, and others deplete SAMe (Table 11). An understanding and judicious use of these is imperative to optimally preserve methylation function.

**Table 10: Select medications that can inhibit methylation nutrients and pathways [6]**

<table>
<thead>
<tr>
<th>Medication(s)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12</td>
<td></td>
</tr>
<tr>
<td>Antacids and proton pump inhibitors</td>
<td>B12 insufficiency</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Alters B12 and folate absorption</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Alters B12 and folate absorption</td>
</tr>
<tr>
<td>Metformin</td>
<td>B12 malabsorption</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Inactivates methionine synthase</td>
</tr>
<tr>
<td>B6</td>
<td>Depletes SAMe and limits pyridoxal kinase which normally activates B6</td>
</tr>
<tr>
<td>----</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Niacin</td>
<td>Limits pyridoxal kinase</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Limits pyridoxal kinase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Folate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Folate antagonist</td>
</tr>
<tr>
<td>Carbamezepine</td>
<td>Folate antagonist</td>
</tr>
<tr>
<td>Antimalarials, pyrimethamine, proguanil</td>
<td>Inhibit DHFR</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Inhibits DHFR</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Inhibits DHFR</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Inhibits DHFR</td>
</tr>
<tr>
<td>5-fluorouracil (5-FU)</td>
<td>Inhibits thymidylate synthase</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Increases folate requirements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Homocysteine clearance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin A</td>
<td>Decreases renal function, increasing homocysteine, increasing requirement for conversion to methionine</td>
</tr>
</tbody>
</table>
8 THE METHYLATION DIET FOOD PLAN

A vital step in supporting methylation with food is to utilize a “Food Plan” that encompasses the different nutrient requirements and limits or avoid factors that can negatively impact methylation.

A Methylation Diet Food Plan should be nutritionally replete, anti-inflammatory, low-glycemic, antioxidant rich, and supportive of detoxification processes. A balanced diet of vegetables, fruits, legumes, nuts, seeds, complete proteins, and whole grains provides plentiful methylation nutrients. Methylation “superfoods” including beets, spinach, sea vegetables, daikon radish, shiitake mushrooms, salmon, fish roe, whitefish, oysters, eggs, pumpkin seeds, sesame seeds and sunflower seeds provide high levels of methylation-specific nutrients. Organ meats such as liver are also valuable, dense sources of relevant nutrients, especially the vitamins B2, B3, B6, folate, choline and betaine.

Foods as DNA Methylation Modulators?

Food bioactive components can affect DNA methylation directly at the genetic level, apparently with modulating effects that appear to be site selective and dose dependent. For instance, a number of phytochemicals as well as selenium have been shown, using high in vitro concentrations, to inhibit DNMT enzymes [39]. These include compounds found abundantly in plant foods such as apigenin, betanin, biochanin A, caffeic acid, catechin, chlorogenic acid, coumaric acid, curcumin, cyanidin, diadzein, ellagic acid, epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin 3-gallate (EGCG), galangin, genistein, hesperidin, luteolin, lycopene, myricetin, naringenin, quercetin, resveratrol, rosmarinic acid, and sulforaphane. The selective de-methylation of the promoter regions in tumor suppressor genes is suggested to be one of the mechanisms underpinning the anti-cancer effects of compounds such as genistein, anthocyanins and green tea polyphenols [34], [166].

Food bioactives have been shown to modulate genetic expression in other contexts such as Phase I and Phase II detoxification [167], and as such the inclusion of whole, colorful and varied plant foods in the diet is likely to be of benefit not only for nutrient status, anti-inflammatory and anti-oxidant benefit, but also directly for healthy DNA methylation and epigenetic expression.
Oxidative stress can be further reduced in the diet by limiting food preparation techniques that promote the formation of pro-oxidative advanced glycation end products [153]. Advanced glycation end products form primarily in animal-derived foods cooked in high, dry heat. Their formation can be minimized by cooking at lower heats and with moisture. Proper hydration is also an important factor in reducing oxidative stress [154]. Phytonutrients may be valuable in that they act as beneficial enzyme modulators [6], [155], [156] as well as antioxidants.

Controlled caloric restriction may be recommended since it is considered to slow or reverse the age-related decline in global DNA methylation and has been shown to favorably modulate the methylation of genes related to diseases such as cancer [157]. Coupled with a lower carbohydrate diet, an extended nighttime fast (such as by completing all food intake by 7pm) that stimulates the production of a low level of the ketone body, β-hydroxybutyrate, may also have protective effects on the epigenome [158], [159], as well as significant anti-inflammatory action [160]. While we do regularly use short-term, targeted ketogenic diets in clinical practice for their effective anti-inflammatory and weight loss outcomes, it should be noted that a full ketogenic diet, while used as an effective therapy for epilepsy and certain cancers [161], [162], is not suitable for long-term methylation support without careful monitoring due to the restriction on amino acid intake that can deplete methionine status [163].

Fortified grains should be reduced or eliminated, especially if methyl donor supplementation is not tolerated. Alcohol is inadvisable since it produces unfavorable DNA methylation patterns [5], may interfere with SAMe activity [89] and impedes folate metabolism [164] including via inhibition of MTR enzymes [165].

<table>
<thead>
<tr>
<th>Dietary guidelines</th>
<th>Foods dense in methylation-related nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optimal hydration (half your body weight in fluid ounces of non-caffeinated beverages per day)</td>
</tr>
<tr>
<td></td>
<td>Varied, colorful plant foods</td>
</tr>
<tr>
<td></td>
<td>High fiber intake</td>
</tr>
<tr>
<td></td>
<td>Organic as much as possible</td>
</tr>
<tr>
<td></td>
<td>“Low and slow” cooking and raw food</td>
</tr>
</tbody>
</table>
Low carbohydrate, especially if insulin resistance or inflammation is present
Consider caloric restriction

<table>
<thead>
<tr>
<th>What to avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified grains</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Added sugars</td>
</tr>
<tr>
<td>Foods from animals raised with antibiotics</td>
</tr>
<tr>
<td>Foods from animals raised with hormones</td>
</tr>
<tr>
<td>High-mercury fish, including tuna, King mackerel, shark and swordfish</td>
</tr>
<tr>
<td>High-heat animal food preparations such as grilling or deep frying</td>
</tr>
<tr>
<td>Plastic food and beverage containers</td>
</tr>
</tbody>
</table>

Further detail is outlined in Table 12, which specifies which foods to include, and which to exclude. Bolded foods are especially notable for their contribution to methylation-related nutrients. Bolded and capitalized foods are the most significant contributors to methylation-related nutrients.
Case 2.0: Lowering homocysteine with a combination of supplements, diet and lifestyle

Susan felt that she had been healthy up until having her first child. Now, at 57 and postmenopausal, she was recently diagnosed with latent autoimmune diabetes of adults (LADA), and Hashimoto’s thyroiditis. Her blood glucose was 335 ng/dL, with an HbA1C of 12.1. Of course, our work with Susan was multifaceted, tailored to address the various underlying factors that related to these concerns.

Her initial program included a lower carbohydrate, anti-inflammatory diet and micronutrient for gut repair, detoxification and blood sugar control. A modest methyl donor prescription included 400 mcg 5-mTHF and 1000 mcg methyl-B12. At two months, Susan’s blood sugar was 108. However, her homocysteine was 14.0. She was also identified as heterozygous for both the MTHFR 677 and 1298 mutations. These findings prompted the initiation of our MDL program and a modestly increased methyl donor prescription of 800 mcg 5-mTHF and 5000 mcg methylcobalamin.

Our nutritionist initiated a gluten-free, dairy-free, methylation Food Plan that also addressed her ongoing needs for blood sugar control, curbing inflammation, and balancing immune function. She helped Susan emphasize foods rich in methylation nutrients such as leafy greens, beets, daikon, shiitake, spinach, seeds and high quality protein. One of the principle challenges for Susan was her frequent business travel to Asia. Careful guidance for navigating restaurant food, as well as dry food supplies to take with her for meal replacements and snacks as needed, helped with compliance. Guidance for minimizing mercury exposure in food (her mercury levels initially showed high, and she did have some remaining amalgams which would also be contributing to that result), as well as working through strategies for “clean” living and stress management, rounded out her diet and lifestyle plan.

Four months later, labs are showing remarkable results. Her fasting blood glucose is down to 82 and her homocysteine is at 7.1. She reports feeling very well, and is motivated to continue the program.
Table 12: The Methylation Diet Food Plan – Foods to Include and Exclude

Bolding identifies foods of particular relevance to the Methylation Diet; Bolding and capital letters further identify some of the most important foods for the Methylation Diet

<table>
<thead>
<tr>
<th>Category</th>
<th>Eat this…</th>
<th>Not this…</th>
</tr>
</thead>
</table>
| Vegetables and fruits | *Include a variety of colorful vegetables and fruits, 8-12 servings per day.*  

**Red:** apples (with skin), **BEETS**, bell peppers, blood oranges, cranberries, cherries, grapefruit (pink), goji berries, grapes, onions, plums, pomegranate, radicchio, radishes, raspberries, strawberries, sweet red peppers, rhubarb, rooibos tea, tomato (including **sun-dried tomatoes**), watermelon.  

**Orange:** apricots, bell peppers, cantaloupe, carrots, mango, nectarine, orange, papaya, persimmons, pumpkin, squash (acorn, butternut, winter), sweet potato, tangerines, turmeric, yams.  

**Yellow:** apple, Asian pears, banana, bell peppers, corn, ginger root, lemon, millet, pineapple, starfruit, succotash, summer squash.  

**Green:** apples, **artichokes, asparagus**, avocados, bean sprouts, bell peppers, bitter melon, bok choy, broccoli, broccoli sprouts, Brussels sprouts, cabbage, celery, cucumbers, edamame, green beans, green peas, greens (arugula, beet, chard, **collard**, dandelion, escarole, kale, **lambsquarters**, lettuce (endive, green, mesclun, radicchio, red, romaine, spring), purslane, **mustard, SPINACH, turnip**), kiwi, kohlrabi, **leeks**, limes, **okra**, olives, parsley, pears, snow peas, sea vegetables (**agar, kelp, SPIRULINA, wakame**), watercress, zucchini.  

**Blue/purple/black:** bell peppers, berries (blue, black, boysenberries, huckleberries, marionberries), cabbage, carrots, cauliflower, eggplant, figs, grapes, kale, kohlrabi, olives. | Deep-fried vegetables.  
Potato chips, fries, processed vegetable snacks. |
<table>
<thead>
<tr>
<th>Foods</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plums, potatoes, prunes, raisins, rice</td>
<td>(black or purple).</td>
</tr>
<tr>
<td>White/brown: cauliflower, celeriac, DAIKON</td>
<td>RADISH, garlic, horseradish, mushrooms (including SHIITAKE), onions.</td>
</tr>
<tr>
<td>Animal protein</td>
<td>Include, but in moderation (6-10 oz/day, based on 0.8 grams of protein per kg body weight).</td>
</tr>
<tr>
<td>Fish (anchovy, bass, mackerel, sardines,</td>
<td>SALMON, cod, FISH ROE, flatfish, halibut, haddock, herring, perch, snapper,</td>
</tr>
<tr>
<td></td>
<td>squid, tilefish, trout, WHITEFISH), shellfish (clams, crab, lobster, mussels, octopus, OYSTERS, scallops, shrimp), venison, beef, bison, buffalo, lamb, duck, elk, goose, skinless chicken, Cornish hen, turkey, pork, rabbit, quail. Organ meats such as LIVER, tongue, marrow, sweetbread. EGGS including chicken, duck and goose.</td>
</tr>
<tr>
<td></td>
<td>Fish in italics are good low-mercury, high omega-3 choices. Grass-fed/wild animal products are leaner and have higher omega-3 content. Choose eggs that are omega-3 enriched.</td>
</tr>
<tr>
<td>Nuts &amp; seeds</td>
<td>Almonds, Brazil nuts, black walnuts, butternuts, cashews, chestnuts, coconut, hazelnuts, peanuts, pecan nuts, pine nuts, pistachio nuts, walnuts. Chia seed, flaxseed, hemp seed, poppy seeds, PUMPKIN SEEDS, SESAME SEEDS, SUNFLOWER SEEDS, watermelon seeds.</td>
</tr>
<tr>
<td>Oils</td>
<td>Choose cold-pressed and unfiltered: Olive, flaxseed, coconut, sesame, almond, sunflower, safflower, avocado, red palm, walnut, and pumpkin seed oils. Grass-fed butter and ghee. Cook with butter, coconut oil, ghee, olive oil, or red palm oil.</td>
</tr>
<tr>
<td>Spices and herbs</td>
<td>All spices and herbs including salt, black pepper, anise seed, basil, bay leaf, cardamom, carob, cayenne pepper, celery seed, chervil, cilantro (coriander leaf), cinnamon, chili powder, cloves,</td>
</tr>
</tbody>
</table>

Methylation Diet and Lifestyle

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<table>
<thead>
<tr>
<th>Category</th>
<th>Items</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condiments</td>
<td>coriander seed, cumin, dill, fennel seed, fenugreek, garlic, ginger, marjoram, mustard, oregano, paprika, parsley, rosemary, saffron, sage, savory, spearmint, tarragon, thyme, turmeric.</td>
<td>Baker’s yeast, brewer’s yeast, cocoa (70%+ dark, not Dutch processed), coconut aminos, mustard, salsa (sugar-free), tamari/soy sauce (low sodium), vinegars. Store-bought condiments with sugar and additives.</td>
</tr>
<tr>
<td>Drinks</td>
<td>coriander seed, cumin, dill, fennel seed, fenugreek, garlic, ginger, marjoram, mustard, oregano, paprika, parsley, rosemary, saffron, sage, savory, spearmint, tarragon, thyme, turmeric.</td>
<td>Pure water (filtered, mineral or distilled), coconut water, herbal teas such as mint, chamomile, green, hibiscus, and Rooibos. Maximum 1-2 cups per day of caffeinated beverages (optional). Alcohol, fruit juices and soft drinks.</td>
</tr>
<tr>
<td>Dairy</td>
<td>Dairy and eggs (high quality sources): Milk, cheese, eggs, cottage cheese, cream, yogurt (no sugar added), butter, cow’s milk kefir, gruyere cheese, goat cheese, parmesan cheese, Romano cheese. Unsweetened, non-dairy milks including almond, cashew, coconut, and hemp milks. Coconut milk kefir.</td>
<td>Ice-cream, sweetened yogurts, frozen yogurt, non-dairy creamers.</td>
</tr>
<tr>
<td>Vegetable protein</td>
<td>Fermented soy such as tempeh, miso, tamari, natto, pickled tofu. Legumes including beans (adzuki, black, cannellini, fava, garbanzo, great northern, kidney, lima, mung, navy, pinto, red, turtle), black-eyed peas, hummus, lentils, split peas.</td>
<td>Other soy products: soy sauce, tofu, soybean oil in processed foods; soymilk, soy yogurt, textured vegetable protein.</td>
</tr>
<tr>
<td>Grains</td>
<td>Whole grains, preferably soaked and even sprouted before cooking, including amaranth, barley, buckwheat, bulgur, corn, kamut, millet, quinoa, oats, rice (basmati, bran, brown, wild), rye (including dark rye), sorghum, spelt, tapioca, teff, wheat.</td>
<td>Any flour-based products including breads, pastries and cookies.</td>
</tr>
<tr>
<td><strong>Sweeteners</strong></td>
<td>Very limited amounts of <strong>blackstrap molasses</strong>, honey, maple syrup, stevia or unrefined cane sugar allowed if needed.</td>
<td>Refined sugar, high fructose corn syrup, evaporated cane juice, artificial sweeteners.</td>
</tr>
</tbody>
</table>

Support for the implementation of the MDL Food Plan is important to continue to ensure desired levels of nutrient intake. Even ‘healthy’ diets can be lacking in nutrients, or fail achieve sufficient therapeutic nutrient levels if they are implemented incorrectly. To that end, we have created two sample menu plans that may be used, along with more than 45 recipes. We also recommend regular nutrient intake analysis, especially in the early stages of implementation, to elucidate any adjustments that may be needed.
## Menu Plans

### 9.1 Sample Menu 1: Gluten-Free, Dairy-Free

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Snack</th>
<th>Smoothie/ Juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon</td>
<td>Eggs with Swiss Chard</td>
<td>Chicken Caesar Salad</td>
<td>Beef and Vegetable Stir-Fry with Brown Rice</td>
<td>Roasted Spiced Chickpeas</td>
<td>Sea Green Smoothie</td>
</tr>
<tr>
<td>Tue</td>
<td>Chia-Berry Creamy Cereal</td>
<td>Pesto-Vegetable Frittata</td>
<td>Warm Artichoke, Tomato and Chicken Salad</td>
<td>Pâté with Cucumber “Chips”</td>
<td>Berry Bliss Smoothie</td>
</tr>
<tr>
<td>Wed</td>
<td>Cranberry-Apple-Cinnamon Oatmeal</td>
<td>Borscht with Seaweed Salad</td>
<td>Turkey Meatballs with Roasted Vegetables</td>
<td>Nutty Snack Balls</td>
<td>Sweet and Spicy Juice</td>
</tr>
<tr>
<td>Thu</td>
<td>Hardboiled Eggs, Sunflower Seed Hummus and Avocado</td>
<td>Warm Quinoa Salad with Wild Salmon and Asparagus</td>
<td>Red Lentil and Tempeh Curry with Brown Rice; Steamed Bok Choy</td>
<td>Hazelnut Butter and Apple Slices</td>
<td>Sea Green Smoothie</td>
</tr>
<tr>
<td>Fri</td>
<td>Grain and Nut Hot Cereal</td>
<td>Whole Beet Salad with Cashew Dressing</td>
<td>Lamb Curry; side of Simple Vegetable Stir Fry</td>
<td>Nori Chips</td>
<td>Ginger Greens Juice</td>
</tr>
<tr>
<td>Sat</td>
<td>Root Veggies and Poached Eggs</td>
<td>Colorful Quinoa-Lentil Salad</td>
<td>Mackerel with Ginger-Lime Marinade; side of Creamy Coconut Collards</td>
<td>Truffle Treats</td>
<td>Berry Bliss Smoothie</td>
</tr>
<tr>
<td>Sun</td>
<td>Turkey Breakfast Sausage with Chard and Fruit Medley</td>
<td>Kale and Crispy Chickpea Salad</td>
<td>Cauliflower Baked Eggs with Daikon and Dulse Salad</td>
<td>Hazelnut Butter and Apple Slices</td>
<td>Zesty Beet Juice</td>
</tr>
</tbody>
</table>
## 9.2 Sample Menu 2: Paleo

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Snack</th>
<th>Smoothie/ Juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon</td>
<td>Eggs with Swiss Chard</td>
<td>Chicken Caesar Salad</td>
<td>Beef and Vegetable Stir-Fry with Cauliflower Rice</td>
<td>Nori Chips</td>
<td>Sweet and Spicy Juice</td>
</tr>
<tr>
<td>Tue</td>
<td>Chia-Berry Creamy Cereal</td>
<td>Pesto-Vegetable Frittata</td>
<td>Warm Artichoke, Tomato and Chicken Salad</td>
<td>Hazelnut Butter and Apple Slices</td>
<td>Sea Green Smoothie</td>
</tr>
<tr>
<td>Wed</td>
<td>Salmon Cakes with Cantaloupe Melon</td>
<td>Borscht with Seaweed Salad</td>
<td>Turkey Meatballs with Roasted Vegetables</td>
<td>Nutty Snack Balls</td>
<td>Sweet and Spicy Juice</td>
</tr>
<tr>
<td>Thu</td>
<td>Hardboiled Eggs, Sunflower Seed Hummus (Paleo version) and Avocado</td>
<td>Cauliflower-Celeriac Soup</td>
<td>Grilled Beef and Vegetable Skewers with Basil Dressing; Steamed Bok Choy</td>
<td>Pâté with Cucumber “Chips”</td>
<td>Sea Green Smoothie</td>
</tr>
<tr>
<td>Fri</td>
<td>Fruit Medley with Nuts</td>
<td>Whole Beet Salad with Cashew Dressing</td>
<td>Lamb Curry; side of Simple Vegetable Stir Fry</td>
<td>Nori Chips</td>
<td>Power Protein Smoothie</td>
</tr>
<tr>
<td>Sat</td>
<td>Root Veggies and Poached Eggs</td>
<td>Warm Cauliflower Couscous with Wild Salmon and Asparagus</td>
<td>Mackerel with Ginger-Lime Marinade; side of Creamy Coconut Collards</td>
<td>Truffle Treats</td>
<td>Ginger Greens Juice</td>
</tr>
<tr>
<td>Sun</td>
<td>Turkey Breakfast Sausage with Chard and Fruit Medley</td>
<td>Kale and Cranberry Salad</td>
<td>Cauliflower Baked Eggs with Daikon and Dulse Salad</td>
<td>Hazelnut Butter and Apple Slices</td>
<td>Zesty Beet Juice</td>
</tr>
</tbody>
</table>
9.4 **Menu Nutrient Analyses**

Both menu plans above provide ample methylation nutrients (Table 14). In our practice, we also find it prudent to conduct periodic nutrient intake analyses on patients following a long-term Methylation Diet and Lifestyle, to ensure that individuals are able to maintain that intake beyond just one week.

*Table 14: Average daily methylation-related nutrient intake of Sample Menus*

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Sample Menu 1 (Daily Average)</th>
<th>Sample Menu 2 (Daily Average)</th>
<th>RDA (adult male/female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate</td>
<td>625 mcg</td>
<td>626 mcg</td>
<td>400/400 mcg DFE(^1)</td>
</tr>
<tr>
<td>Folic acid</td>
<td>0 mcg</td>
<td>0 mcg</td>
<td>400/400 mcg DFE(^1)</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>4.8 mcg</td>
<td>5.6 mcg</td>
<td>2.4/2.4 mcg</td>
</tr>
<tr>
<td>Betaine</td>
<td>321 mg</td>
<td>233 mg</td>
<td>-</td>
</tr>
<tr>
<td>Choline</td>
<td>455 mg(^2)</td>
<td>414 mg(^2)</td>
<td>550/425 mg</td>
</tr>
<tr>
<td>Riboflavin (Vitamin B2)</td>
<td>1.8 mg</td>
<td>1.9 mg</td>
<td>1.3/1.1 mg</td>
</tr>
<tr>
<td>Niacin (Vitamin B3)</td>
<td>19 mg</td>
<td>22 mg</td>
<td>16/14 mg</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>2.7 mg</td>
<td>2.8 mg</td>
<td>1.3/1.3 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>13.4 mg</td>
<td>13.9 mg</td>
<td>11/8 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>605 mg</td>
<td>569 mg</td>
<td>420/320 mg</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>5.3 g</td>
<td>4.9 g</td>
<td>-</td>
</tr>
<tr>
<td>Total calories</td>
<td>1792 kcal</td>
<td>1743 kcal</td>
<td>-</td>
</tr>
<tr>
<td>% calories from carbohydrates</td>
<td>35%</td>
<td>30%</td>
<td>-</td>
</tr>
<tr>
<td>% calories from fats</td>
<td>47%</td>
<td>52%</td>
<td>-</td>
</tr>
<tr>
<td>% calories from protein</td>
<td>18%</td>
<td>18%</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^1\) Dietary folate equivalents

\(^2\) Actual choline intake is underreported since many foods in the USDA database have not been evaluated for choline content
10 RECIPES
BREAKFAST
Eggs with Swiss Chard

Servings: 1

Cook time: 10-15 minutes

- 3 organic, omega 3 eggs prepared any style

For the Swiss chard:

- 1 tablespoon olive oil
- 1 clove garlic, crushed
- 6 cups Swiss chard leaves, stalks removed, roughly chopped into large pieces
- 1/4 teaspoon salt
- Black pepper, to taste
- 1/4 fresh lemon

Heat oil in a sauté pan over medium heat. Add garlic and cook for 2-3 minutes, taking care that it does not burn. Add chard, salt and pepper and continue to cook on medium heat until wilted, about 3-5 minutes. The excess liquid from the chard can be drained. Serve the Swiss chard alongside the eggs, with a squeeze of lemon on the top. Adjust seasonings if necessary.
Chia-Berry Creamy Cereal

Servings: 1

Cook time: 5 minutes plus overnight soaking

- 3/4 cup water
- 1 tablespoon sunflower seeds
- 1 tablespoon flaxseeds
- 2 tablespoons chia seed
- 1/2 cup mixed raspberries and blueberries
- Sweetener of choice (such as stevia, coconut sugar, or lucuma), optional
- 1/4 teaspoon cinnamon

Blend almond milk, sunflower seeds and flaxseeds in a high-speed blender until creamy. Soak chia seeds overnight in the milk/seed mixture. In the morning, add berries and sweetener and top with cinnamon.
Cranberry-Apple-Cinnamon Oatmeal

Servings: 2

Cook time: 20 minutes, plus overnight soaking for the oats

- 1 teaspoon olive oil or coconut oil
- 1 cup steel-cut oats or thick-cut rolled oats*
- 2 cups water
- 1 apple, diced
- 1/2 cup fresh (not dried) cranberries (if using dried cranberries use only 1/4 cup)
- Dash of cinnamon, to taste
- Pinch of salt
- 1/4 cup walnuts for topping
- 1/2-1 teaspoon maple syrup/raw honey, optional

*Soak oats overnight before using.

Heat the oil/butter for a couple of minutes. Add the oats to the oil and stir to coat (toasting gives the oats more flavor and helps it from getting clumpy.)

Add the 2 cups of water and cover pot, allow to boil up and simmer on low for 5-7 minutes. Add apples, cranberries, cinnamon and salt, and stir oatmeal well. Continue to simmer on low-medium heat for another 5-10 min, stirring occasionally. Remove from heat when the liquid is absorbed and it reached the consistency you like. Top with walnuts and maple syrup or honey.
Hardboiled Eggs, Sunflower Seed Hummus and Avocado

Servings: 4, with some leftover hummus
Cook time: 10 min, plus extra for roasting the sunflower seeds

For the hummus:

- 15 oz. can chickpeas (drained)*
- 1 cup sunflower seeds (roasted)
- 3 tablespoons tahini (sesame paste)
- 3 cloves garlic
- 1/3 cup olive oil
- Juice of lemon (2 or whole)
- 2-4 tablespoons water
- Sea salt and fresh pepper to taste

For serving:

- 8 organic, omega 3 eggs, hard boiled
- 1 ripe avocado, sliced
- 2 handfuls of baby spinach

*For a Paleo/low-lectin version substitute 1 cup canned pumpkin puree

Combine all hummus ingredients in a food processor or blender and process to a smooth paste. This may take five minutes or so. Add more liquid slowly if necessary and check seasonings. Best if chilled before serving.

Serve each person 2 eggs with 2 tablespoons of hummus and 1/4 avocado, on a bed of spinach.
Grain and Nut Hot Cereal

Servings: 2

Cook time: 20 minutes, plus overnight soaking

- 1 teaspoon coconut oil
- 1/2 cup steel-cut oats or thick-cut rolled oats (not instant)*
- 1/2 cup quinoa*
- 1/2 cup coconut milk
- 1 1/2 cups water
- 1/4 cup chia seeds
- 1/4 teaspoon cinnamon
- Pinch of salt
- 2 tablespoons sunflower seeds (hulled), roughly chopped
- 2 tablespoons almonds, roughly chopped

*Soak oats and quinoa overnight before using

Heat the oil/butter for a couple of minutes. Add oats and quinoa to oil and stir to coat oats (toasting gives the oats more flavor and helps keep it from getting clumpy).

Add the 2 cups of liquid and cover pot, allow to come to a boil. Reduce heat, remove cover and add chia seeds, cinnamon and salt. Stir in. Continue to simmer on low-medium heat for another 5-10 min stirring occasionally. Remove from heat when the liquid is absorbed and it reached the consistency you like. Before serving top or mix in sunflower seeds and nuts.
Root Veggies and Poached Eggs

Servings: 4

Cook time: 20-25 minutes

- 3 tablespoons olive oil
- 1 large onion, chopped
- 3 cloves garlic, minced
- 1 teaspoon fresh ginger, minced (or 1/2 teaspoon ground)
- 1 teaspoon ground cumin
- 1 teaspoon turmeric
- 1 teaspoon chili powder (reduce or eliminate if you prefer less spicy)
- 1/2 teaspoon Cayenne pepper
- 1 teaspoon sea salt plus 2 tablespoon for cooking the eggs
- 2 lbs mixed root vegetables (celeriac, rutabaga, parsnip, beets), peeled and cut into 1/2 inch cubes
- 1/2 cup tomato puree
- 1 1/2 cups chicken stock
- 1 tablespoon mild tasting vinegar, such as rice vinegar
- 8 eggs (organic, omega 3)
- 2 tablespoons dulse sea vegetable flakes

Heat oil over med-low heat. Add onion and cook for 6-8 minutes, until it begins to soften. Add garlic and ginger and cook for an additional minute. Stir in additional spices and 1 teaspoon sea salt, then add the cubed root veggies, tomato puree and stock. Stir then cover and allow to simmer for an additional 10-15 minutes (until the root vegetables are tender). Stir frequently.

While that cooks, poach the eggs. Bring a large saucepan 2/3 full of water to a simmer. Add the vinegar and 2 tablespoon salt to the water. Gently crack the eggs into a measuring cup, then ease them into the water one at a time. Depending on the size of your pan, you will need to work in batches to give each egg enough room. After four minutes (if you like the yolk still a little soft), remove carefully with a slotted spoon. Serve 2 eggs on a large spoonful of root vegetables. Sprinkle with dulse flakes.
Turkey Breakfast Sausage with Chard and Fruit Medley

Servings: 4 (makes 12 patties)

Cook time: 30-40 minutes

For the sausage:

- 1 1/2 lb. ground turkey breast
- 1/2 cup finely diced dried cherries
- 1 small onion, minced
- 1 tablespoon fresh sage, minced
- 1 tablespoon thyme, minced
- 3 tablespoons extra-virgin olive oil
- 3/4 teaspoon sea salt
- 1/2 teaspoon freshly ground black pepper

For the Swiss chard:

- 1 tbsp olive oil
- 8 cups Swiss chard, stems removed and torn into pieces
- Salt and pepper, to taste

For the fruit medley

- 1 cup berries (blueberries, raspberries, blackberries)
- 1/2 cup apple, diced
- 1/2 cup cantaloupe melon, cubed

In a large bowl, mix together the turkey, cherries, onion, sage, thyme, 1 tablespoon of the extra-virgin olive oil, salt, and pepper until thoroughly combined. Divide and form the mixture into 12 patties.

Heat the remaining 2 tablespoons of extra-virgin olive oil in a nonstick skillet over medium heat. Cook the patties for about 5 minutes each side, until fully cooked through.

For the Swiss chard, heat the oil in a large skillet or saucepan. Rinse the leaves, then add them, still slightly wet, directly to the pan and steam/sauté for about 5-10 minutes until wilted. Season to taste.

For the fruit medley, simply combine the fruits together and serve a 1/2 cup serving alongside the sausage patties and Swiss chard.
**Salmon Cakes**

Servings: 4 (approximately 12 cakes)

Cook time: 45 minutes

- 1 medium sweet potato, baked whole then flesh scooped out and reserved
- 1/3 cup coconut flour
- 1 clove garlic, minced
- 1/2 onion, finely chopped
- 1/4 cup red bell pepper, finely chopped
- 1/4 cup cilantro or parsley, finely chopped
- Juice of 1/2 lemon
- 1 teaspoon Cayenne pepper
- 1 teaspoon salt
- Black pepper, to taste
- 2 eggs
- 2 x 6 oz-ounce cans Wild Alaskan Pink Salmon, skinless and boneless, flaked

Preheat the oven to 400° and line a baking sheet with parchment paper.

Combine all ingredients in a large bowl and mix thoroughly.

Form the mixture into 12 patties of roughly the same size. Using a 1/3 cup measure can be helpful for this!

Place on the baking sheet and cook in the oven for 20-25 minutes, until turning golden brown. Remove from the oven, turn over with a spatula, and return to the oven to cook for 10 minutes more.
Fruit Medley with Nuts

Servings: 1

Cook time: 5 minutes

- 1 cup berries (blueberries, raspberries, blackberries)
- 1/2 cup apple, diced
- 1/2 cup cantaloupe melon, cubed
- Add 1/4 cup cashews, almonds, or mix of both

Toss all ingredients together and serve immediately.
LUNCH
Chicken Caesar Salad

Servings: 4
Cook time: 30 minutes, plus extra for preparing the chicken

For the chicken:

- 4 x 3 oz chicken breasts (or two large, divided)
- 3 tablespoons olive oil
- 4 cloves garlic, crushed
- 1 tablespoon lemon juice

For the dressing:

- 2 organic egg yolks
- 2 tablespoons lemon juice
- 1 tablespoon Dijon mustard
- 1 tablespoon minced anchovy fillets
- 1/3 cup olive oil (extra virgin)
- 3 garlic cloves, minced or pressed
- Sea salt and ground black pepper to taste

For the salad:

- 10 cups romaine lettuce, washed and torn into bite sized pieces

Set the oven to 375°F. Marinade 2 chicken breasts in olive oil, crushed garlic and lemon juice for a couple of hours. Bake for 20 minutes until cooked all the way through. Set aside and allow to cool. Slice into pieces or cubes.

Make the dressing: Mash 1 small garlic clove and a pinch of kosher salt until reduced to a paste (mortar and pestle is best, but you can improvise with knife or spoon). Add anchovies, continue to mash and chop until well combined and nearly smooth. Move to a medium bowl, and whisk in Dijon mustard, then the egg yolks, followed by lemon juice. Blend well. Slowly, drop by drop, add olive oil whisking constantly until dressing is thick and glossy. If desired add more sea salt, freshly ground black pepper, and more lemon juice.

In a large bowl, toss the lettuce, chicken and dressing until everything is evenly coated. Serve immediately.
Pesto-Vegetable Frittata

Servings: 4
Cook time: 40 minutes

For the pesto:
- 2 cups fresh basil leaves (packed)
- 1/2 cup fresh parsley leaves (packed)
- 2 garlic cloves
- 1/3 cup olive oil
- 1/2 cup walnuts
- Sea salt
- Black pepper

For the frittata:
- 1 tablespoon coconut oil
- 1 medium onion, finely sliced
- 1 cup shitake mushrooms, sliced into small pieces
- 3 cups broccoli, chopped into small pieces
- 6 eggs (organic)
- 2 tablespoon ground golden flaxseed mixed with 6 tablespoons water
- 1/4 teaspoon oregano
- 1/4 teaspoon thyme
- Sea salt and fresh black pepper to taste

First make the pesto: In a food processor, blend basil, parsley, garlic and walnuts together using pulse setting till they’re well mixed. Slowly add in olive oil and continue blending until smooth. Season with sea salt and black pepper to taste.

Preheat the oven to 375˚F. Heat the oil in an oven safe skillet over medium heat, add the onion and allow to soften for 5 min. Add the mushrooms and continue to sauté for another 5-10 minutes. Meanwhile, steam the broccoli for 3-4 min, then add to the skillet.

Beat 3 of the eggs with 1/4 teaspoon salt and pour into the same skillet containing the onions, broccoli and mushroom. Stir briefly. Spoon about half of the pesto into the skillet but don’t stir any more. Beat the remaining eggs with another 1/4 teaspoon salt, mix in the flax and water mixture, then pour into the skillet.

Bake for 20 minutes, then broil for an additional 2 minutes. Allow to cool, then top with remaining pesto and serve.

Follow with 1 cup cubed cantaloupe melon.
Borscht (Beetroot Soup)

Servings: 4
Cook time: 60 minutes

- 1 tablespoon olive or coconut oil
- 1 yellow onion, chopped
- 4 garlic cloves, peeled and smashed
- 1 bay leaf
- 6 cups beets, peeled and cubed
- 1.5 cups carrots, peeled and chopped
- 1/3 cup cashews
- 3 cups vegetable or chicken stock
- 1 tablespoon lemon juice
- 1/2 teaspoon sea salt and black pepper to taste
- Fresh chives for garnish, chopped

In a large saucepan, heat the garlic and onions in the oil for about 10 minutes. Add the bay leaf, beets, carrots, cashews and stock. Bring to a simmer and stir. Add more liquid if needed to just keep the vegetables covered. Allow to cook on low, covered, for 30 minutes, until the beets and carrots are soft. Add the lemon, salt and pepper.

Remove the bay leaf, then puree the soup with an immersion blender, or in batches in a high-speed blender. Garnish, and serve.
Warm Quinoa Salad with Wild Salmon, Asparagus and Kale

Servings: 4

Cook time: 30-35 minutes

- 1.5 lb wild salmon filet
- 1 red bell pepper
- 2 tablespoons pine nuts
- 3/4 cup quinoa, soaked for at least 20 minutes, then rinsed well (will yield 1 1/2 cups cooked)
- 2 cups asparagus, cut into thirds
- 6 cups kale, wash and trim heavy stems, torn into pieces
- 1 tablespoon fresh chives, chopped
- 2 tablespoon fresh parsley, chopped
- 2 teaspoons lemon juice, freshly squeezed
- 1 teaspoon tahini (sesame seed butter)
- 3 tablespoons water
- Salt and freshly ground black pepper

Heat the oven to 400F. Line a baking sheet with parchment paper. Season the salmon lightly with salt and bake with the red bell pepper (whole) for 20-25 minutes. Add the pine nuts for the last 5-7 minutes of baking.

Meanwhile, bring the quinoa to a boil in plenty of salted water (3 cups), and simmer for 10-12 minutes until tender (the quinoa seeds will uncurl and will be just soft to taste). Drain and return to the pan, covered. Let sit for 5-10 minutes.

In a separate saucepan, cover and cook the asparagus in an inch of water until tender, about 10 minutes. Right before removing, add the kale and cook for another minute or two until it wilts. Drain and set aside.

In a small bowl, make the dressing: whisk the chives, parsley, lemon juice, tahini and water together until smooth. Add salt and pepper to taste.

Assemble your warm salad: Flake the salmon into a bowl. Chop the red pepper (removing the stalk and seeds) and add that too. Add the pine nuts, quinoa, asparagus and dressing. Toss to combine everything.
Warm Cauliflower Couscous Salad with Wild Salmon, Asparagus and Kale (Paleo version)

Servings: 4

Cook time: 30-35 minutes

- 1.5 lb wild salmon filet
- 1 red bell pepper
- 3 tablespoons pine nuts
- 1 head cauliflower
- 2 tbsp dried parsley
- 2 cups asparagus, cut into thirds
- 6 cups kale, wash and trim heavy stems, torn into pieces
- 1 tablespoon fresh chives, chopped
- 2 teaspoons lemon juice, freshly squeezed
- 1 teaspoon tahini (sesame seed butter)
- 3 tablespoons water
- Salt and freshly ground black pepper

Heat the oven to 400F. Line a baking sheet with parchment paper. Season the salmon lightly with salt and bake with the red bell pepper (whole) for 20-25 minutes. Add the pine nuts for the last 5-7 minutes of baking.

Meanwhile, prepare the other ingredients:

Chop the cauliflower into large chunks and pulse in the food processor until the texture resembles couscous. Be careful not to over process. Heat a sauté pan over medium heat and gently fry the cauliflower together with the parsley, and some salt and pepper, stirring frequently, until tender, about 5-7 minutes. Take off the heat and set aside.

In a separate saucepan, cover and cook the asparagus in an inch of water until tender, about 10 minutes. Right before removing, add the kale and cook for another minute or two until it wilts. Drain and set aside.

In a small bowl, make the dressing: whisk the chives, lemon juice, tahini and water together until smooth. Add salt and pepper to taste.

Assemble your warm salad: Flake the salmon into a bowl. Chop the red pepper (removing the stalk and seeds) and add that too. Add the pine nuts, cauliflower couscous, asparagus and dressing. Toss to combine everything.
Whole Beet Salad with Cashew Dressing

Servings: 2

Cook time: 15 minutes for assembly, more for cooking beets and soaking cashews (can be done the day before and kept refrigerated)

- 6 medium beets (buy with leaves)
- Beet leaves from those 4 beets, trim heavy stems
- 6-8 oz kale, wash and trim heavy stems, torn into bite-sized pieces
- 1 gala apple, cubed into small pieces
- 1/2 cup seedless grapes, halved
- 1/2 red onion, chopped
- 2-3 celery stalks, diced
- 3 tbsp fresh parsley, chopped

- 1/4 cup olive oil
- 1/4 cup walnuts, halved

Dressing:

- 1/3 cup cashews (soak for at least 1 hour prior)
- 2 cloves garlic
- 1/4 cup apple cider vinegar
- 1/4 cup water
- Sea salt and ground black pepper

Roasting beets (this can be done up to 36 hours beforehand and kept refrigerated): Preheat oven to 350 degrees F. Place rack in middle of oven. Prepare the beets by trimming the stems (reserve) and ends. Scrub well and cut in half. Toss with olive oil (enough to coat lightly). Place the beets in an oven-proof dish (with a tight-fitting lid, or covered with aluminum foil, sides pinched to seal), and add 1/2 an inch of water to the bottom of the dish.

Cover the beets and roast in the oven for 1-2 hours (depending on the size of the beets) until tender. Remove from the oven and set aside to cool. Once cooled enough to handle, peel the skin by hand or using a knife.

Prepare the dressing: Blend the dressing ingredients in a high power blender or food processor until completely smooth and not grainy. Set aside.

Assemble the salad: In a large mixing bowl, combine greens, roasted beets, walnuts and other fruits and veggies. Add dressing and toss well. Serve immediately.
Colorful Quinoa-Lentil Salad

Servings: 3
Cook time: 30-40 minutes

- 1 cup lentils*
- 1/2 cup quinoa*
- 1 cup water
- 1 cup vegetable broth
- 1 tablespoons extra virgin olive oil, plus extra for drizzling
- 1 lemon, juiced
- 1-2 cloves garlic, pressed
- 1/4 teaspoon cumin
- 1/4 teaspoon dried ginger
- Salt and pepper to taste
- 1 red pepper, diced
- 1/4 red onion, diced
- 2 medium carrots, grated
- 3 omega 3 eggs, hard boiled, roughly chopped
- 3/4 cup parsley, roughly chopped
- 3 cups arugula

*Soak, together, overnight before cooking.

In a pot, bring the water and broth to boil. Add quinoa and lentils and reduce heat to simmer. Allow to cook for about 12-15 minutes until both are soft. Stir occasionally. When done, cover and set aside to cool.

In a large mixing bowl, stir together the olive oil, lemon juice, garlic, cumin, ginger, salt and pepper. Add the red pepper, onion, carrot, eggs and parsley and toss with the dressing.

When the quinoa and lentils have cooled, add to the veggies and mix thoroughly. Divide the arugula between two plates and top with the quinoa-lentil salad. Drizzle with extra olive oil.
Kale and Crispy Chickpea Salad

Servings: 2
Cook time: 35 minutes

Crispy chickpeas

- 1 can (15 oz) chickpeas (garbanzo beans), rinsed, drained and thoroughly dried
- 1 tablespoon avocado oil
- 1 tablespoon cumin
- 1/2 teaspoon garlic powder
- 1/2 teaspoon ground ginger
- 1/2 teaspoon Cayenne pepper
- 1/2 teaspoon paprika
- 1/2 teaspoon sea salt

Dressing

- 1 small head of garlic, whole, roasted with the chickpeas (see below)
- 1/4 cup tahini (sesame seed paste)
- 1 tablespoons extra virgin olive oil
- 1/2 cup lemon juice (from approximately 2-3 lemons)
- 2 tablespoons raw honey
- Sea salt and pepper to taste
- Hot water

Other Ingredients

- 6 cups kale, chopped or torn into large pieces
- 2 omega 3 eggs, poached

Preheat oven to 375°F.

Place the thoroughly-dry chickpeas in a mixing bowl. Add the avocado oil and chickpea seasonings and toss to coat well. Transition to a baking sheet and spread out evenly. At this point, also add the whole head of garlic (for the dressing) to the baking sheet, to roast alongside the chickpeas. Bake for 18-25 minutes, until chickpeas are slightly crispy and golden. Remove from oven and allow to cool.

Make the dressing: Slice the roasted head of garlic across-ways and squeeze out the garlic cloves (they should come out easily when cooked). Add the garlic to a mixing bowl, along with the remaining dressing ingredients. Using a fork, crush the garlic and whisk dressing ingredients together. Adjust seasonings and add extra water as needed. Set aside.

In a large mixing bowl, add a small amount of dressing to the kale and massage with your hands; this will help soften the kale. Add the remaining dressing (you may have extra left over), and toss well. Divide the kale onto two plates, top with the chickpeas and poached eggs, and serve.
Cauliflower-Celeriac Soup

Servings: 4
Cook time: 40 minutes

- 1 medium celeriac (celery root), skin trimmed and roughly chopped
- 1 medium cauliflower, cut into chunks
- 2 cloves garlic, peeled
- 1/4 cup cashews
- 1 small onion, peeled and quartered
- 1 cup unsweetened almond milk
- 4 cups chicken stock (homemade if possible)
- 1 teaspoon sea salt
- Black pepper, to taste
- 1/4 cup fresh parsley, chopped

Place all ingredients except black pepper and parsley in a large, deep saucepan. Bring to a boil and simmer for 20-25 minutes, until all the vegetables are tender. Let cool slightly and then puree in a high-speed blender (best), or with an immersion blender. Thin with hot water if necessary. Check seasonings and adjust as needed. Serve garnished with black pepper and parsley.
Kale and Cranberry Salad

Servings: 2

Cook time: 15 minutes

- 1 tablespoons pine nuts
- 1 tablespoons pumpkin seeds
- 5 cups kale, washed, large stems removed and torn into medium pieces
- 2 tablespoons olive oil
- 1 tablespoon flaxseed oil
- Juice of 1 lemon
- 1 teaspoon maple syrup
- 1/2 teaspoon salt
- Freshly ground black pepper
- 1/3 cup dried cranberries, soaked for at least 20 minutes

Set the oven to 350˚F. Toast the pine nuts and pumpkin seeds for 5-10 minutes, until fragrant.

Combine the kale with the oils, lemon juice, maple syrup, and salt and massage for a few minutes to soften the kale and distribute the dressing. Add black pepper to taste.

Toss the kale with the cranberries and toasted pine nuts and pumpkin seeds.
DINNER
Beef and Vegetable Stir-Fry

Servings: 4

Cook time: 20-30 minutes

- 2 tablespoons coconut oil
- 1 tablespoon finely chopped fresh ginger
- 1 lb boneless sirloin steak, cut into 2-inch long thin strips (grass fed, organic if possible)
- 2 cups Brussel sprouts, washed and quartered
- 1 medium onion, sliced into strips
- 2 cloves garlic, minced
- 1 red bell pepper, cut into strips
- 1 zucchini, diced
- 1 tablespoon apple cider vinegar
- 2 tablespoons fresh lemon juice
- Salt and black pepper, to taste
- 2 tablespoons sesame oil
- 2 tablespoons sesame seeds
- 3 tablespoon chopped cilantro

Heat a large skillet or wok over medium heat. Add 1 tablespoon coconut oil to the pan. Add half the ginger and half the beef. Stir intermittently for about 2 minutes then transfer to a plate in a warming oven. Repeat with another tablespoon coconut oil and the remaining ginger and beef.

Return the pan to the heat and add the remaining 1 tablespoon coconut oil. Add the Brussels sprouts, onion, garlic, pepper and zucchini. Stir intermittently for 5-10 minutes. Add the vinegar, lemon juice and return the meat to the skillet and stir together well. Season with salt and pepper.

To serve, drizzle with sesame oil and sprinkle with sesame seeds and cilantro.
Warm Artichoke, Tomato and Chicken Salad

Servings: 1

Cook time: 15 minutes

- 1 tablespoon extra virgin olive or coconut oil (plus olive oil for drizzling)
- 1 clove garlic, finely chopped
- 1 cup artichoke hearts (frozen or water packed, drained)
- 1/3 cup cooked, shredded chicken (organic, free range if possible)
- 2 tomatoes, cut into 1-inch pieces
- 2 cups arugula
- Salt and pepper, to taste
- 2 tablespoons pumpkin seeds
- 2 tablespoons sesame seeds

Heat the oil in a medium skillet over low heat. Add the garlic and cook 1-2 minutes, watching to check it doesn’t burn. Add the artichoke hearts and chicken and cook 5-10 minutes more, until fully heated through. Take off the heat, add the tomatoes and toss to combine. Season with salt and pepper to taste.

Serve on a bed of arugula. Drizzle with olive oil and season with salt and pepper. Sprinkle the seeds on top.
Turkey Meatballs

Servings: makes 12-16 meatballs (serves 2)

Cook time: 40 minutes

- 1 packet (1/2 lb) of ground turkey
- 1/2 cup nut flour (e.g. hazelnut, walnut) or ground seeds
- 3 tablespoons ground flaxseed
- 1 cup green leaves (choose the more tender varieties such as spinach, Swiss chard, arugula)
- 2 tablespoons dried parsley
- 1 teaspoon onion powder
- 1/2 teaspoon garlic powder
- 3/4 teaspoon salt
- 1/4 teaspoon black pepper

Set the oven to 375°F. Using a food processor, combine all ingredients until you have a near-smooth mixture. If you don’t have a food processor, you can finely chop the greens, then mix all the ingredients in a large mixing bowl until well-combined.

Form the mixture into about 12-16 meatballs, and place on (a) baking sheet(s) lined with parchment paper. Bake for 15-25 minutes (for sizes 1-2” diameter) until cooked through.

These refrigerate and freeze well, and are great for snacking or adding to meals.
Red Lentil and Tempeh Curry

Servings: 4

Cook time: 1 hour

- 2 tablespoons coconut oil
- 1 tablespoon ground cumin
- 1 teaspoon ground turmeric
- 1/2 teaspoon ground cinnamon
- 1/2 teaspoon ground coriander
- 1/4 teaspoon ground nutmeg
- 1/8 teaspoon ground clove
- 1 inch fresh ginger, peeled and grated
- 1 onion, minced
- 2 cloves garlic, minced
- 8 oz packet of tempeh, crumbled
- 1 cup red lentils, debris removed and rinsed
- 2 cups vegetable stock
- 6 oz (1/2 a can) coconut milk
- 1 tbsp tahini (sesame butter)
- 2 teaspoons apple cider vinegar
- 1 teaspoon salt
- Black pepper, to taste

For serving:

- 2 cups cooked brown rice
- 4 cups steamed bok choy

In a large saucepan, heat the oil and sauté the spices for 2-3 minutes until fragrant. Add the onions and cook, stirring, for 5 minutes, until translucent. Add the garlic and tempeh and cook for another 5-10 minutes. Add the remaining ingredients and simmer for 30-45 minutes. Add water if more liquid is needed. You may also transfer to a slow cooker and cook on low for 6 hours. Check seasonings and adjust if necessary.

Serve with 1/2 cup cooked brown rice and 1 cup steamed bok choy per person.
Lamb Curry

Servings: 6

Cook time: 50 minutes

- 2 tablespoons coconut oil
- 2 tablespoons curry powder
- 1/2 teaspoon turmeric
- 1/8 teaspoon cayenne pepper, or to taste
- 1 medium onion, chopped
- 1 1/2 lbs boned lamb shoulder, cubed
- 2 carrots, chopped into rounds
- 2 cloves of garlic, minced
- 2 teaspoons finely minced ginger
- 1/4 cup golden raisins
- 1 cup water
- 1 can (13.5 oz) full fat coconut milk
- Salt and pepper to taste
- 1/2 cup finely chopped fresh cilantro

Gently heat the oil in a large saucepan. First toast the spices until fragrant. Then add the onion and sauté 2-3 minutes until starting to turn translucent. Add the lamb, carrots, garlic, and ginger and sauté for a further 10-12 minutes. Add the raisins, water, coconut milk and seasonings and bring back to a gentle simmer. Cook on low for 30 minutes until the lamb and carrots are tender.

Check the seasonings, then stir in half the cilantro to wilt. Use the remaining cilantro for dressing.
Mackerel with Ginger-Lime Marinade

Servings: 4

Cook time: 30 minutes, plus time to marinade.

- 1 lb Atlantic Mackerel fillets (not King Mackerel)
- 2 limes, zested and juiced
- 2 teaspoons fresh grated ginger
- 3 cloves garlic, crushed
- 2 tablespoons extra virgin olive oil
- Salt and pepper, to taste

Rinse the mackerel and place, skin side up in a glass baking dish. Mix remaining ingredients in a small bowl and stir/massage into the fillets. Cover, and marinade for 30 m to 2 hrs.

Preheat the oven to 400°F. Flip the fillets over. Cook for 15-25 minutes, until done. Extras can be flaked, then refrigerated or frozen for easy additions to other meals.
Cauliflower Baked Eggs

Servings: 4
Cook time: 30-40 min

- 1 tablespoon coconut oil
- 6 eggs (organic, omega-3)
- 1/2 cup coconut milk
- 2 tablespoons ground flax seed mixed with 6 tablespoons water
- 1/8 teaspoon cumin
- 1 teaspoon sea salt
- 2 cups cauliflower, grated
- 1/3 cup onion, finely diced
- 2 cloves garlic, minced
- 1 leek, finely diced

For serving:
- 4 cups cantaloupe melon, cubed

Preheat the oven to 350˚F. Grease a 9 inch glass baking dish with the coconut oil (a pie dish works well).

In a mixing bowl, beat the eggs and blend with the coconut milk, flax-water mixture, cumin and sea salt. Add the cauliflower, onion, garlic and leek and stir well. Pour the mixture into the baking dish and bake for 20-30 minutes until firm. Slice like a pie and serve with the melon
Grilled Beef and Vegetable Skewers with Basil Dressing

Servings: 2

Cook time: 25 minutes, plus more extra for marinating

For the marinade:

- 1/4 cup olive oil
- Juice of 1 lemon
- 2 cloves of garlic, minced
- 3/4 teaspoon sea salt
- Freshly ground black pepper

For the skewers:

- 3/4 lb grass-fed sirloin steak, cubed
- 8-10 crimini mushrooms, larger ones halved
- 1 zucchini, sliced and cut into bite sized rounds
- 1 yellow summer squash, sliced and cut into bite-sized rounds
- 1 red bell pepper, stem and seeds removed, cut into bite-sized squares

For the dressing:

- 1 cup packed basil leaves
- 1/4 cup olive oil
- 1 tablespoon lemon juice
- 1/4 cup water or vegetable stock
- Sea salt to taste

For serving:

- 2 cups steamed bok choy

Combine the marinade ingredients in a large dish or bowl. Add the chopped beef and vegetables and allow to marinate for at least 2 hours, up to 6.

Make up the skewers with the marinated beef and vegetables. Cook on a grill or grill pan over medium-high heat for 4 minutes each side.

While the skewers cook, make the dressing: place the dressing ingredients in a food processor (without the water/stock) or blender and process until smooth. With the motor running, slowly add the water/stock until fully incorporated. Check seasonings.

Serve the skewers drizzled with the basil dressing, accompanied by steamed bok choy.
SIDE DISHES
Basic Fluffy Quinoa

Start with white quinoa if you are new to the flavor. Red and black quinoa are also tasty variations.

Serves: 6

Cook time: 25-30 minutes, plus soaking time

- 2 cups quinoa (yields about 6 cups cooked)
- 6-8 cups water
- 1 teaspoon salt

First you need to remove the bitter-tasting saponins from the quinoa. Soak the quinoa for at least 20 minutes, and up to 12 hours. If you are planning to cook quinoa in the evening, setting it to soak before leaving for work in the morning works well. After soaking, drain and rinse well.

In a medium saucepan, bring the water to a boil. Add the quinoa and salt, and cook for about 10-15 minutes until the ‘grains’ have ‘opened’ and are just tender (start tasting them from 10 minutes). Drain all the water through a sieve, return the quinoa to the pan, and let sit (covered) for 10-15 minutes.

Fluff with a fork and serve. Save any leftovers in the refrigerator or freezer. Quinoa is a perfect base for adding flavors and more nutrients (such as herbs, garlic, spices, onion, sesame seeds) as well as vegetables, legumes, and meats.

Variation in a rice cooker: Combine 1 cup soaked/rinsed quinoa with 2 cups water and 1/4 teaspoon salt in the rice cooker; cook for 15 minutes.
Seaweed Salad

Servings: 4
Cook time: 15 min

- 2 oz dried assorted seaweeds or wakame (such as Eden Foods Brand)
- ¼ cup scallions
- 2 tablespoons coconut aminos
- 1 tablespoon apple cider vinegar
- ½ tablespoon sesame oil
- Pinch of cayenne pepper
- 1 tablespoon sesame seeds

In a large bowl, rinse and soak the seaweed in water enough to cover 10 times its volume. After about 5 minutes, it should be tender, drain to remove excess water.

While the seaweed is soaking, make the dressing. Combine the scallions and remaining ingredients in a small bowl and stir well.

Sort through the seaweed to make sure there aren’t any hard parts and cut it if it’s excessively long (kitchen shears are useful for this task). Pour in the dressing and toss well to combine.
Roasted Vegetables

Servings: 2

Cook time: 45 min

- 1 cup carrots, peeled and sliced into 1-inch pieces
- 2 cup Brussels sprouts, tough outer leaves and stems removed, larger ones halved
- 1 head of garlic, cloves separated, and peeled
- 2 tablespoons coconut oil, melted
- 2 tablespoons Italian herb seasoning (rosemary, oregano, thyme, marjoram)
- ½ teaspoon salt

Preheat oven to 400°F. Place the veggies and garlic in a large mixing bowl, add oil and seasoning. Mix so that everything is coated evenly. Spread flat on a roasting pan or baking sheet. Roast for 15 minutes, then mix and turn as much as possible, then roast for another 10-15 min. When the garlic and Brussel sprouts brown a little, and the carrots are tender, then they’re done.
Simple Vegetable Stir Fry

Servings: 2 as a main course, 4 as a side dish

Cook time: 20 minutes

- 1 tablespoon sesame oil
- 1/2 teaspoon sesame seeds
- 3-4 cloves of garlic, minced
- 1/2 teaspoon cayenne pepper (optional)
- 2 cups Shiitake mushrooms, stems removed and sliced
- 1/2 head of cabbage, sliced into thin strips
- 8 cups bok choy, chopped
- 1 tablespoon fresh chives, chopped
- Sea salt and freshly-ground black pepper

Heat the oil in a large sauté pan. Add the sesame seeds, garlic, and cayenne pepper. Toast the seeds and spices in the oil for 1-2 minutes. Add the veggies one at a time, starting with the mushrooms (cook 3-4 minutes until browning), then the cabbage, then bok choy. Cook, stirring until just softened - the ends of the leaves will wilt. You’ll want them al dente, but not overcooked. Add the chives and toss to combine. Season to taste with salt and pepper.
Creamy Coconut Collards

Serves: 4

Cook time: 25 minutes

- 1 tablespoon coconut oil
- 1/2 onion, diced
- 2 lb collard greens, large stems removed, washed and torn into large pieces
- 2 cloves garlic, minced
- 1/2 cup full fat coconut milk
- 2 tablespoons coconut aminos
- 1/2 teaspoon red pepper flakes (optional)
- 1/2 lemon
- Sea salt, to taste

Heat the coconut oil in a large sauté pan on medium heat. Gently cook the onions for 2-3 minutes, stirring intermittently, until starting to turn translucent.

Place remaining ingredients into the pan and continue to cook, stirring, until the collards wilt and the liquid reduces (about 10 min). Check seasoning, squeeze the juice of 1/2 lemon over the greens, and serve.
Cauliflower ‘Rice’

Servings: 4

Cook time: 15-20 minutes

- 1 head of cauliflower, roughly chopped into medium sized pieces
- 4 tablespoon extra virgin olive oil
- 1 teaspoon salt

Place the cauliflower into a food processor and pulse until the texture resembles rice.

Heat the oil in a large skillet. Add the cauliflower and salt, and sauté, stirring, until just tender (about 8-12 minutes). Serve immediately.

If you don’t need all the cauliflower straight away, save the ‘riced’ cauliflower raw, ready for the next meal.

Optional extra flavors and add-ins include garlic, onion, saffron, fresh parsley or other herbs, curry spices, or peas.
Daikon and Dulse Salad

Servings: 4

Cook time: 20 minutes

- 1 lb daikon (mild Japanese radish), peeled
- 1 cup dried dulse sea vegetable, chopped (such as Eden Foods brand)
- 1/4 cup sun dried tomatoes, oil-packed, drained and diced
- Juice of 1 lime
- 2 tablespoons sesame oil
- Sea salt and freshly ground pepper, to taste

Using a course grater, grate the daikon into a med-large bowl. Add in the dulse, sun-dried tomato and mix for a minute. Add the lime juice and sesame oil, mix well and season to taste.
SNACKS
Roasted Spiced Chickpeas

Servings: 3

Cook time: 35 minutes

- 1 can chickpeas (garbanzo beans)
- 2 tablespoons olive oil
- Sea salt, to taste
- 2 teaspoons of total spices- like chili powder, curry powder, garam masala, cumin, smoked paprika, rosemary, thyme, nutmeg, cinnamon or any combination you enjoy

Heat the oven to 400°F. Rinse, drain then pat dry the chickpeas. You more moisture you can get off the better. In a mixing bowl, combine the chickpeas with olive oil and salt, then place them in an even layer on a backing sheet. Roast for 20 to 30 minutes, stirring the chickpeas every 10 minutes. They’re done when they turn golden brown- dry and crispy on the outside, soft in the middle. Back in your mixing bowl, toss the chickpeas with the spices, stirring to coat evenly. They’re most crispy when they’re warm, so serve immediately for most crunch!
Pâté with Cucumber “Chips”

Servings: Makes about 2 cups

Cook time: 30 minutes

- 6 tablespoons olive oil
- 1 packet of organic chicken livers (about 1lb), trimmed (remove the sinew parts with kitchen shears) and rinsed
- 1/4 cup cashews or macadamia nuts
- 1 small onion, chopped
- 2 cloves garlic, chopped
- 1 teaspoon fresh thyme (or ½ teaspoon dried)
- Salt and pepper
- Cucumbers, sliced into rounds, for serving

Heat the oil in a medium saucepan over a gentle heat. Add the chicken livers, cashews, onion, garlic and sauté gently until cooked through, about 15-20 minutes. Add the thyme and transfer everything to a food processor. Process until smooth and creamy, about 5 minutes (takes a little longer to get the cashews really smooth). Add salt and pepper to taste, and process to combine well. Transfer the mixture to a container (with lid) and store in the refrigerator. It will thicken as it cools.

As a snack, serve 1/4 - 1/3 cup of pâté with 6-8 sliced cucumber “crackers.”
**Nutty Snack Balls**

Serves: Makes 3 dozen, Serving Size 2 balls

Cook Time: 20 minutes

- 3 cup mixed nuts and/or seeds (such as macadamia nuts, pumpkin seeds and sunflower seeds)
- 1 cup unsweetened coconut, shredded
- 6 Medjool dates
- 2 tablespoons coconut oil
- 1 lemon, zested
- 1 lemon, juiced
- 1/4 teaspoon salt

In a food processor, combine all ingredients and blend until a sticky dough is formed. It doesn’t have to be completely smooth, but it does have to stick together. Keep going with the food processor until it does. Remove the processing blade and form into 1-inch balls.

Store in an air-tight container in the refrigerator for 1-2 weeks. Can also be frozen.
Hazelnut Butter and Apple Slices

Servings: 1

Cook time: 5 minutes

- 1 apple, cored and sliced
- 2 tablespoons unsweetened hazelnut butter (may substitute almond butter)

Spread the nut butter on the apple slices and enjoy. Make a sandwich for easier portability—spread the nut butter on one slice and top with a second slice.
Nori Chips

Servings: 4 snack-sized servings
Cook time: 25 minutes

- 5 sheets nori (a type of seaweed used for making sushi)
- 2 tablespoons olive oil
- Sea salt to taste
- Optional spices: garlic powder, onion powder, cayenne, miso*

Preheat oven to 350°F. Using kitchen shears, cut the nori into squares and arrange on a baking sheet without overlapping. Using a pastry brush, or your fingers, lightly coat the nori with oil then sprinkle with seasoning. Flip and repeat on the other side. Bake for 15 min, then transfer to a wire rack to cool and crisp. Will last about 4-5 days in an airtight container.
Truffle Treats

Servings: makes 16-20 balls, serving size 2 balls

Cook time 15 minutes, plus extra for soaking cashews

- 1 tablespoon coconut oil, melted
- 3/4 cup organic cocoa powder
- 2 cups cashews, soaked overnight and drained
- Pinch of sea salt
- Stevia, to taste
- 1 cup shredded dried coconut flakes

In a food processor, add the first four ingredients and blend until completely creamy. This may take about 5 minutes, so that the cashews are completely smooth and no longer grainy. Slowly add stevia until you reach the desired sweetness.

Remove the blade and, taking a small amount of the mixture each time, roll into small balls. Roll each ball in the coconut flakes to coat. Keep refrigerated to harden the truffles.
SMOOTHIES & JUICES
Sea Green Smoothie

Servings: 1

Cook time: 5-10 minutes

- 1/2 cup cantaloupe, cubed
- 1/2 banana
- 1 handful of kale or spinach
- 1 handful of Swiss chard
- 1/4 avocado
- 2 teaspoons spirulina powder
- 1 cup water
- 3 or more ice cubes

Blend all ingredients in a high speed blender until completely smooth and enjoy!
Berry Bliss Smoothie

Servings: 1

Cook time: 5-10 minutes

- 1/2 cup blueberries (fresh or frozen, preferably wild)
- 1 medium carrot, roughly chopped
- 1 tablespoon ground flaxseed or chia seed
- 1 tablespoons almonds
- Water (to desired consistency)
- Ice cubes (optional, may omit if using frozen blueberries)

Blend all ingredients in a high-speed blender until smooth and creamy. Best served immediately.
Sweet and Spicy Juice

Servings: 1

Cook time: 5-10 minutes

- 1 cup honeydew melons
- 3 cups spinach, rinsed
- 3 cups Swiss chard, rinsed
- 1 bunch cilantro (leaves and stems), rinsed
- 1-inch knob of ginger, rinsed, peeled and chopped
- 2-3 knobs whole turmeric root (optional), rinsed, peeled and chopped

Juice all ingredients in a high quality juicer. Best served immediately.
Ginger Greens Juice

Servings: 1

Cook time: 5-10 minutes

- 1 cup pineapple cubes
- 1 apples, sliced
- 1-inch knob of ginger, rinsed, peeled and chopped
- 3 cups kale, rinsed and roughly chopped or ripped
- 5 cups Swiss chard, rinsed and roughly chopped or ripped

Juice all ingredients in a high quality juicer. Best served immediately.
Zesty Beet Juice

Servings: 1

Cook time: 5-10 minutes

- 1 grapefruit, peeled and sliced
- 1 apple, washed and sliced
- 1 whole beet, and leaves if you have them, washed and sliced
- 1-inch knob of ginger, rinsed, peeled and chopped

Juice all ingredients in a high quality juicer. Best served immediately.
Protein Power Smoothie

Serving: 1

Cook time: 5 minutes

- 1 scoop protein powder
- 1 tablespoon ground flaxseed
- 1/2 banana
- 1 kiwi, peeled
- 1/2 teaspoon cinnamon
- Pinch of cardamom
- Non-dairy milk or water, enough to achieve desired consistency

Blend all ingredients in a high-powered blender until completely smooth. Best served immediately!
11 Appendix A: Checklist for Methylation Assessment

- Genetic Profiling
  - AHCY
  - BHMT
  - CBS
  - COMT
  - MAO
  - MAT1A
  - MTHFR
  - MTR
  - MTRR
- Nutrient Status (dietary intake and laboratory)
  - Methionine
  - Cysteine
  - Taurine
  - DHA
  - Zinc
  - Magnesium
  - Potassium
  - Riboflavin
  - Niacin
  - Pyridoxine
  - Folate
  - Vitamin B12
  - Betaine
  - Choline
  - Sulfur
- Methylation Metabolites
  - Homocysteine
  - SAMe
  - SAH
  - SAMe:SAH ratio
  - Cystathionine
- Other Methylation-Related
  - Glycine
  - Serine
  - Threonine
  - Sarcosine
  - Phosphoserine
- Nutrient Assimilation Capability
  - Gastric function
  - Pancreatic function
  - Dysbiosis
  - Intestinal permeability
  - Food sensitivities
  - Malabsorption
- Inflammation
  - Weight
  - BMI
  - Waist circumference
  - CRP
  - Ferritin
  - ESR
  - Dysbiosis
  - Small intestine bacterial overgrowth (SIBO)
  - Periodontitis
  - Comorbidity such as autoimmunity or infection
- Oxidative Stress
  - 8-OHdG
  - Alpha-hydroxybutyrate
  - Pyroglutamate (5-oxoproline)
  - Lipid peroxides
  - F2-isoprostanes
12 Appendix B: Checklist for Methylation Interventions

- Food-Based Nutrients
  - Dietary planning and intake assessment
  - Consider adjustments for methylation SNPs

- Five-R Gut Protocol
  - Remove
  - Replace
  - Re-inoculate
  - Repair
  - Rebalance

- Microbiome
  - Butyrate production
  - L. plantarum
  - B. bifidum
  - B. infantis
  - B. breve
  - B. longum
  - B. adolescentis (high mTHF production)
  - B. pseudocatenulatum
  - Prebiotics

- Inflammation
  - Blood glucose management
  - Healthy weight
  - Resolve gut-driven inflammation
  - Food allergens
  - Anti-inflammatory diet
  - Stress management
  - Regular moderate exercise

- Oxidative Stress
  - Diet
  - Exercise
  - Sleep
  - Environmental toxins
  - Infections
  - Dysbiosis

- Consider NAC, alpha lipoic acid, coQ10

- Detoxification
  - Reduce exposure
  - www.ewg.org
  - Hydration
  - Fiber
  - Organic, antibiotic-free, hormone-free foods
  - Colorful plant foods especially deep greens and berries
  - Cruciferous
  - Protein
  - Micronutrient intake

- Stress Management
  - Reduce exposure
  - Stress management techniques

- Exercise
  - Regular, moderate exercise
  - Personalized to fitness/strength level
  - Avoid over-training

- Check Nutraceutical Interactions
  - Niacin
  - Selenium
  - Phosphatidylethanolamine
  - Supraphysiologic doses of plant bioactives

- Check Medication Interactions
  - Antacids, PPIs
  - Cholestyramine
  - Colestipol
  - Metformin

- NO
  - Niacin
  - Theophylline
  - Phenytoin
  - Carbamezepine
  - Antimalarials, pyrimethamine, proguanil
  - Sulfasalazine
  - Triamterene
  - Oral contraceptives
  - Cyclosporin A

- The Methylation Diet Food Plan
  - Foods dense in methylation nutrients
  - Hydration
  - Varied, colorful, whole plant foods
  - High fiber intake
  - Organic
  - “Low and slow” cooking
  - Low carbohydrate (for glucose control)
  - Caloric restriction
  - Avoid alcohol
  - Avoid added sugars
  - Avoid antibiotics in foods
  - Avoid hormones in foods
  - Avoid high mercury fish
  - Avoid high/dry heat food preparations
  - Avoid plastic food and beverage containers
  - See Food Plan handout
13 REFERENCES


Methylation Diet and Lifestyle


