

# Preventative Measures for Metabolic Syndrome

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*The occurrence of metabolic syndrome is of epidemic proportions in the United States and increasing globally. The outcome of this systemic wide inflammatory degenerative process may include accelerated aging, obesity, cardiovascular disease, glucose intolerance and hypertension. Although etiology remains elusive, this syndrome appears to be partially due to excess amounts of simple carbohydrates and poor quality fats. Our ancestors' daily intake of plant foods was chock-full of phytochemicals. Many of these compounds modulate gene activity, have antioxidant activity or other physiological activity. Considering that the human genome is now considered to operate as a network and that network pharmacology models often show better efficacy and safety for complex mixtures of pharmacologically active compounds, it is sensible that the dietary treatment of metabolic syndrome would include an increase of the consumption of various plant foods (excluding processed grains), due to increased phytochemical intake. Furthermore, supplementation for this condition would likely best consist of nutrients embedded in complex phytochemical mixtures.*

**M**etabolic syndrome is a condition first described by Dr. Gerald Reaven in 1988<sup>1</sup> as a cluster of risk factors that represent a major cause of coronary heart disease. An increasingly common condition, it has yet to have an agreed upon definition by the medical system. This syndrome is seen in people who are insulin-resistant and, similar to people with type 2 diabetes, insulin is less able to dispose of blood glucose by moving it into muscle and fat cells. Despite various descriptions of the disorder, all definitions have in common central obesity, dyslipidemia, hypertension and glucose intolerance.<sup>2-4</sup>

The prevalence of metabolic syndrome is alarming. Currently one in four people in the U.S. are estimated to be suffering from this systemic disorder. That is greater than 47 million adults and 2 million adolescents, with an increasing rate of occurrence in most ethnic groups, regardless of gender.<sup>5</sup> By all rights, metabolic syndrome is of epidemic proportions; all healthcare providers, regardless of medical creed, will frequently face this condition.

Other names for this cluster of signs and symptoms are syndrome X, deadly quartet, DROP syndrome

(dyslipidemia, insulin resistance, obesity and high blood pressure), Reaven syndrome, multiple metabolic syndrome, and insulin resistance syndrome.<sup>6</sup> Hallmark signs are elevated triglyceride (5.5-6.0) and reduced HDL levels and an elevated hip to waist ratio. In the early stages of the syndrome, modest elevations of hemoglobin A1C (>5.5%) are also seen and the postprandial insulin elevation is generally modest.<sup>7</sup> Due to visceral adiposity, the waist to hip ratio is elevated (male >1; female >.8-.9). This elevated hip to waist ratio is so predictable some clinicians suggest that an accurate diagnosis for metabolic syndrome requires only a tape measure.<sup>8,9</sup> Ford et al<sup>10</sup> suggest that elevated hip to waist ratio is an accurate and reproducible predictor of physiological dysfunctions associated with metabolic syndrome; insulin resistance, vascular endothelial function, lipid abnormalities and left ventricular hypertrophy. Others suggest that an even easier predictor of metabolic syndrome is a waist circumference greater than 40 and 36 in men and women, respectively.<sup>8,9</sup>

Considering that 50% of Americans are now overweight (BMI of  $\geq 25$  kg/m<sup>2</sup>) and an alarming 30% are obese (BMI  $\geq 30$ ) and that metabolic syndrome largely,

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but not exclusively, occurs in the overweight and obese ( 22% and 60%, respectively) with only a 5% prevalence in normal-weight adults,<sup>11</sup> it is surprising how little coverage this issue receives. Ulmer et al<sup>12</sup> found that the risk of the syndrome was lower among obese adults who had not been obese as children (10%) than among obese adults who had been obese in childhood (28%). It may be that a pathophysiological pattern is started early in the developmental process and becomes an alternate anchoring attractor as other conditions are known to do (e.g. the hypercortisolemia of depression). Regardless of the timeline for weight gain, insulin-resistance/metabolic syndrome is associated with a ~ 40% reduction in mitochondrial function.<sup>13</sup> Borrowing from James Fries' model of organ reserve<sup>14</sup> (see *UnifiedEnergetics*, Spelman, Spring 2007). This strongly suggests that those with this condition suffer from greater biological age than their healthy cohorts. The consequences may be a higher rate of decline and degenerative processes; cardiovascular disease, cancer, cognitive decline or other illnesses are likely outcomes.<sup>15</sup> As a result, we may have a socio-medical crisis on hand as this large section of our population will likely degenerate at a much higher rate than those without this condition. It is clear that responsible planning is necessary for the prevention of metabolic syndrome and the upcoming increased use of healthcare resources these patients will require.

### Metabolic Syndrome Biochemistry

New insight into the biochemical and molecular modes underlying metabolic syndrome have been provided by the observation that adipose tissue is both endocrinologically (e.g. leptin, resistin, adiponectin)<sup>16</sup> and immunologically active.<sup>5</sup> Adipocytes secrete several cytokines (TNF, IL-6, IL-1 $\beta$ , etc) that induce insulin resistance and correlate with metabolic syndrome<sup>5</sup> while retaining sensitivity to insulin.<sup>17</sup> Providing rather telling pathophysiological clues to follow, experimental models show that adipose tissue-specific and muscle insulin receptor knockout animals remain lean, whereas liver and CNS insulin receptor knockout animals become obese and insulin resistant.<sup>18-20</sup> Adipose tissue-derived messenger molecules, collectively known as adipokins, generate a state of low-grade inflammation resulting in troublesome shifts in metabolic and hemodynamic physiology.<sup>21</sup> Shoelson and colleagues<sup>22</sup> recently demonstrated that an inflamed liver plays a primary role in the factors that lead to the development of insulin resistance.<sup>22</sup> Insulin resistance in the overweight is associated with increased levels of NF $\kappa$ B, a key transcription factor.<sup>10</sup> Arkan et al<sup>23</sup> showed that a liver-specific impairment of NF $\kappa$ B, attenuates obesity-associated

insulin resistance. NF $\kappa$ B starts a cascade of immunological effects, including the release of the proinflammatory cytokines (e.g. TNF, IL-6, IL1). In Arkan's NF $\kappa$ B experimental model they found that although insulin signaling was preserved in the liver, there was insulin resistance throughout other tissues. Intriguingly, this hepatic effect suggests a paracrine rather than endocrine effect of NF $\kappa$ B, that commonly leads to fatty liver.<sup>24</sup> Of great concern, a worrisome 70-80% of the obese have been documented with fatty liver.<sup>25</sup> Considering that informational molecules released by the liver and adipose tissue lead to secondary changes in target tissue and in turn induce further insulin resistance, it appears likely that this is a feed-forward system capable of inducing insulin resistance throughout the body, including tissues that are seemingly healthy.<sup>24</sup>

Consequently, due to these changes in the cellular milieu we find at the heart of insulin resistance, as with cardiovascular disease, a state of inflammation. Bluher et al<sup>26</sup> demonstrate that subclinical chronic inflammation, measured by C-reactive protein (CRP), are related to insulin resistance. CRP, an acute phase protein that has become the sine qua non for systemic inflammation, is thought to be a surrogate marker for cytokine-mediated inflammatory disorders. CRP is a result of increased levels of NF $\kappa$ B<sup>10</sup> and has enabled the detection of low-grade



inflammation previously thought to be inconsequential, yet appears to be a key issue underlying seemingly disparate tissue defects, signs and symptoms in metabolic syndrome.<sup>21</sup> One of the central effects of metabolic syndrome is reflected in the new term cardiometabolic syndrome. Wong<sup>27</sup> suggests that a significant percentage of people who die from sudden coronary events that lack the traditional risk factors of heart disease, are actually suffering from cardiometabolic syndrome. Other markers that may be specific to the cardiovascular effects of metabolic syndrome include the apo B to apo A-I ratio, which is strongly associated with the presence of metabolic syndrome and can be used as an early-stage interventional risk factor marker for cardiometabolic syndrome.<sup>28</sup>

Although the cause of metabolic syndrome is not fully understood, diet and a lack of exercise are thought to be at the heart of it. This eventually leads to a concomitant increase in coronary heart disease (CHD), obesity and diabetes.<sup>6</sup> But the important issue here is that metabolic syndrome, a system-wide disorder involving multiple tissues and organ systems, is unlikely to be “fixed” by drugging a single target. Rather, a system-wide disorder will need a system-wide therapy. Chronic diseases are increasingly being recognized as multifactorial issues; hence, there is an increasing realization that modulating a multiplicity of targets can be an asset in the treatment of a range of disorders.<sup>29</sup> Researchers point out that the genetic component of all complex traits, such as hypertension, arthritis and cognitive function, is influenced by a broad range of effects spread across many genes.<sup>30,31</sup> Accordingly, trying to hit a single target to treat a complex disease such as metabolic syndrome is analogous to looking for one’s keys only where the light is good. A recent drug being removed from the market is a fitting example of single target failure. Avandia (rosiglitazone), a PPAR- $\gamma$  target (a receptor that is targeted to improve blood glucose utilization) has shown an increase MI occurrence of 30-40% in patients taking this drug for blood glucose issues.<sup>32</sup> Interestingly, this significant risk was known before market approval by the FDA<sup>32</sup> even though it is well established that the majority of people with insulin resistance die of cardiovascular disease.

### **The Human Genome – Network Properties**

The hunt for pharmacological agents to treat metabolic syndrome offers enormous economic reward for the pharmaceutical companies considering that an effective drug could reach about 25% of the current population and this number is increasing rapidly. The majority of the efforts by the drug companies are

based on the hunt for single agents. This search for isolated chemicals fits quite nicely into the current view of pharmacology. From this perspective, the human genome is tidily composed of independent genes linked only to a single function. Find the right gene related to a physiological function that needs to be altered, target that gene with a compound with the proper selectivity and potency and a new drug is born; or so the thinking goes. However, evidence from cell and animal models have for many years called into question this simplistic assumption. A recent four-year effort by the United States National Human Genome Research Institute that included 35 groups from 80 international organizations has essentially put this oversimplification to rest.<sup>33</sup> This group has confirmed that genes, in this case the human genome, operate in complex networks. Moreover, they have essentially generated the fodder for expanding the number of pharmacological targets by a great magnitude. Consequently, we may see new drug targets and more importantly, new pharmacotherapy strategies relying on multiple targets and pathways to treat chronic disease.

In the last two decades, there is a notable increase in the use of pharmacological therapy designed to interface with multiple targets and pathways. This reveals a necessary re-evaluation of the ‘one-disease-one-drug’ paradigm that has dominated thinking in the pharmaceutical industry for the past many decades. For example, it is now well known that in the treatment of psychosis, pharmacological activity at a single receptor is therapeutically insufficient and new drug design attempts are focusing on both dopamine (D-2) and serotonin receptors (5HT2a).<sup>34</sup> Development of antidepressants is following the same trend in that dual inhibition at both serotonin and norepinephrine transporters demonstrates increased efficacy.<sup>35</sup> Thus, pharmacological design has now progressed to the point where multiple modes of activity have become prerequisites for identifying highly efficacious pharmacological therapies.<sup>36</sup> On a practical level, clinicians have managed unresponsive patients with combination drug therapy for many decades only to have the mode of activity elucidated retrospectively.<sup>37</sup>

Borisy<sup>38</sup> points out that when using therapeutic chemical combinations, unexpected synergistic interactions occur that are likely due to the interconnected signaling networks existing within and between cells. In a comparison of various pharmacological strategies, Ágoston et al<sup>39</sup> found that multiple but partial perturbations of selected targets in a network are almost always more efficient than the knockout of a single, well-selected target. This is likely due to the redundant pathways of cellular networks that are not

inhibited by just one pharmacological agent.<sup>40</sup> These “back-up” systems may possess enough qualitative differences that they don’t respond to the same pharmacological interventions. Further, the robust nature of biological networks generates resistance to major changes in function even with dramatic changes in their constituents.<sup>40-42</sup> Such robust living molecular networks are commonly resistant to high-affinity, high-selectivity single hits such as generated by the current pharmacological methodology.<sup>39</sup> While a high-affinity compound can knock out a single interaction, a compound with less specificity can interact with more targets of a particular protein or operon.<sup>39</sup> Such network activity is very similar to the interface between plant compounds and a human system when a person ingests a plant food.<sup>39</sup> This may very well be the appropriate strategy for preventing and treating a system-wide disorder such as metabolic syndrome.

#### **Understanding Prevention; a disorder of dietary deficiency or dietary excess?**

The fast-food industry has done well in a profit at any cost environment. There are over 240,000 fast food restaurants in the United States. Fast food is readily available; just look in schools, offices, airports and sadly, even hospitals. “Foods” from the fast-food world consists of energy-dense bites high in fat (poor quality fats e.g., lipid peroxides and TFAs) and fiber-free simple carbohydrates (as opposed to complex carbohydrates) washed down in either chemical-laden diet drinks or sugary fluids, while they are almost void of micronutrients and other important phytochemicals. As a result of our health crisis, the scientific and mainstream press are just beginning to dissect fast food’s impact on public health.

In the 1950s, fast food accounted for only 4% of total sales of food outside the home; this had increased almost nine times by 1997. In regard to total energy intake, fast food increased five times, from 2% in the 1970s to 10% in 1995.<sup>43</sup> One in three US adults are eating at fast-food outlets on any given day.<sup>44</sup> We have complicitly slumbered into an “obesogenic” diet (highly processed convenience foods and soft drinks providing a glut of calories) while lifestyles have become increasingly sedentary.<sup>5</sup> This has not been without costs. Adults who report eating fast food have higher average BMIs than those who do not, even taking demographic variables into account.<sup>45</sup> For example, individuals with greater than two visits to fast food restaurants per week gained ten pounds over 15 years and were more likely to become insulin resistant.<sup>46</sup> In a prospective trial, an increase in frequency of fast-food restaurant use by a mere one meal per week was associated with an

increase in body weight of 1.6 lb, even if the average weight gain over a three-year period was accounted for.<sup>47</sup> In a revealing study on our youth, every daily portion of sugared drinks consumed by 6th and 7th graders led to a 60% increase in relative risk of obesity.<sup>48</sup> Further evidence shows that these “make-believe foods” are one of the major causes of insulin resistance and obesity.<sup>5, 47, 49</sup> Fast-food, based on all its inherent properties, must not be viewed as a marker, but rather as a primary etiologic agent in the genesis of the current obesity epidemic.<sup>5</sup>

Although numerous studies have examined the relation between intake of individual nutrients or foods and risk of disease, less research has been done on the effects of dietary patterns.<sup>50</sup> Dietary patterns are crucial to identify because of the complexity of diets and the resulting mixture of chemical compounds that result with any given meal. Only recently has this methodology been applied to metabolic syndrome resulting in a key question: Is metabolic syndrome due to a dietary deficiency or a dietary excess? The astute observer might follow this question with another: Is it just a deficiency or excess of a few compounds or is the overall qualitative composition of the diet crucial?

Two major dietary patterns have been identified: prudent and Western.<sup>51, 52</sup> The former is characterized by higher intakes of fruits, vegetables legumes, fish, poultry and whole grains; the latter with higher intakes of red and processed meats, sweets and desserts, french fries and refined grains.<sup>53</sup> Through



the use of reduced rank regression, Schulze et al<sup>54</sup> identified a dietary pattern that was strongly related to inflammatory markers. Consumption high in sugary soft drinks/diet soft drinks, refined grains and processed meats, but low in wine, coffee, cruciferous vegetables and yellow vegetables, are associated with an increased risk of diabetes.

Before the advent of the agricultural revolution, humans consumed a vast variety of wild plants - green leafy vegetables, fruits, nuts and berries - chock-full of phytochemistry. Plant foods, abundant in nutritive and non-nutritive compounds, with the addition of lean meat, fish and small amounts of honey, were the foods that shaped modern humans' genetic nutritional requirements. Cereal grains as a staple food are a relatively recent addition to the human diet and represent a dramatic departure from those foods which we are genetically selected for and to which we are adapted.<sup>55</sup> For 99.9% of human history, with few exceptions, we did not consume cereal grains until 10,000 years ago.<sup>55</sup> Today, about 17% of plant species provide 90% of the world's food supply and unfortunately, most of this 17% represents cereal grains.<sup>56</sup> Three cereals: wheat, maize and rice together account for 75% of the world's grain production.<sup>55</sup> In a telling fact that reflects on our chronic health crisis in the United States, it seems that of the 12 micronutrients which are plentiful in wheat (including vitamins B1, B2, B3, B5, B6, folic acid, E and the minerals iron, zinc, copper, manganese and selenium) more than 70% - and in some cases more than 90% - of these key nutrients have been removed.<sup>57</sup>

As previously stated, the etiologies of chronic disease involved complex processes that take many

years to manifest. O'Keefe and Cordain,<sup>58</sup> on examining the diet of Paleolithic man, a recent 500 generations ago, show that our ancestors diets were abundant in phytochemicals. After reviewing the data, Eaton<sup>59</sup> suggests that our ancestors had up to eight times more vitamins, minerals, associated food factors and fiber than in the typical American diet. Considering that plant foods contain hundreds, if not thousands of biologically active compounds, it may be that metabolic syndrome is not just due to excess but is a deficiency condition: a condition in which our genes are not interfacing with sufficient phytochemistry, as was so routine 500 generations ago. Many of these phytochemicals, still poorly identified and understood, are likely to be imperative for the modulation of gene expression and therefore, likely play an important role in the modulation of physiological processes.<sup>60</sup> Muller and Kersten<sup>60</sup> point out that many of the previously unstudied plant chemicals and antioxidants (phenols, flavonoids, glucosinolates, etc.), have a positive impact on tissue and organ function. Others suggest that many plant chemicals and antioxidants have a positive impact on highly conserved longevity and survival pathways.<sup>61</sup>

For instance, consider that dietary intakes of foods rich in flavanones and anthocyanidins were associated with reduced risk of death due not only to CHD and cardiovascular disease (CVD), but to all causes.<sup>62</sup> Vegetarians have a lower mortality rate of all causes.<sup>63</sup> Populations consuming diets rich in fruits and vegetables are protected from atherosclerosis, stroke, coronary artery disease and cancer.<sup>64</sup> Jang et al<sup>65</sup> found that replacement of refined rice with whole grain and legume powder led to significant reductions in fasting glucose and insulin, homocysteine



and lipid peroxidation in patients with CVD, consistent with those from other clinical intervention studies.<sup>53</sup> Literally hundreds of plants have shown inhibitory activity on the inflammatory processes.<sup>66</sup> Recalling that NFκB is a cornerstone of the inflammatory process and insulin resistance, it has been found that salicylates, a group of constituents quite common in plant-based foods, can inhibit NFκB activity.<sup>10, 67</sup> Additionally, triterpenoid saponins, common in leguminous plants, also are known to inhibit NFκB<sup>68</sup> as do many flavonoids common to fruits and vegetables.<sup>69</sup> Fats, long known to play a crucial role in the inflammatory process also have a crucial role in preventing the development of metabolic syndrome: Evidence suggest that the type of fat in plant-based diets is more important than the amount of fat in determining risk of CHD. Hu et al<sup>53</sup> found a significant positive association between intake of trans fatty acids and risk of CHD and an inverse association between PUFA and CHD. It seems obvious that obesity, the resulting metabolic syndrome, cardiovascular disease and many other conditions are easily remedied, but it isn't a fix available at a drive-thru.

### **To supplement or Not to Supplement**

Metabolic syndrome, as suggested above, may well be not only an excess condition of poor quality foods, but a deficiency in phytochemistry. If this is the case, then one must ask: Should a person with metabolic syndrome be given supplements? The issue of supplements is somewhat controversial as more and more 'spin,' sometimes good and sometimes bad science support or refute supplement use.

In this author's opinion, the insistence that supplements and dietary quality have little bearing on health status suggests that those touting this party line have either very limited understanding of the biochemical processes of life or are proselytizing a pharmacoprosit-driven agenda. Mainstream medical institutions like the American Medical Association continue to perpetuate myths about the lack of usefulness of antioxidants. The recent publication by Bjelakovic et al<sup>70</sup> which surprisingly passed editorial criteria by the Journal of the American Medical Association, claimed that antioxidant supplementation increased mortality as opposed to those not using antioxidant vitamins and supplements. It appears that these authors had a remarkable lapse in memory and forgot to point out that synthetic vitamins/antioxidants often act differently than the naturally occurring molecules. Furthermore, and rather disturbing for a meta-analysis studying the death-rate of those using antioxidants, the primary reason given for dropping 747 out of 815 antioxidant clinical trials was that

these articles had a mortality of "0 in both study groups."<sup>70</sup> Something is seriously remiss in this "science" to the point that the statistics and data selection were so inappropriate that the conclusions have been deemed invalid by various scientists and statisticians.<sup>71</sup> Yet, it was apparently peer-reviewed and published in what is considered to be a bastion of medical sciences.

However, there is a problem with much of the antioxidant research due to its focus on one isolated vitamins/antioxidants. Just as the drug companies still labor under the single lesion theory - one target for one disease - using isolated antioxidants makes the same error. Supplementation modeled after the pharmacological model, isolated constituents with no inclusion of cofactors and associated food factors as well as other co-occurring phytochemicals, is not based on a rational evaluation of past human diet. Evolutionary biology points at a very different approach: The human genome has been selected to respond to low-dose, complex mixtures of plant compounds. Seven to ten million years of human evolutionary history should make it obvious that exposure to one chemical at a time has no precedent in human history (or any other organism's history). Therefore, while this strategy may represent the latest methodology and technology, it does not represent a therapeutic strategy founded on the principles of evolutionary biology.<sup>72</sup>

Nevertheless, the hunt for single nutrients or antioxidants have been borne due to epidemiological studies clearly indicating that populations partaking of diets rich in plants foods have a reduced risk of degenerative diseases.<sup>63, 73-78</sup> Given that the risk of premature death is inversely related to the dietary intake of particular antioxidants (vitamin C, E, A, carotenoids),<sup>74</sup> the natural products industry, as well as investigators involved in healthcare, had assumed that these effects were due to such single compounds as vitamins A, C, E, folic acid, flavonoids and other phytochemicals. However, the research supporting this reductionist assumption (for nutrients or pharmaceuticals) has not been favorable.

For example, a recent analysis of nearly half a million subjects reports that supplements of vitamins A, C, E and folic acid do not reduce the risk of lung cancer.<sup>79</sup> Similarly, isolated β-carotene has failed to show an effect on coronary artery disease (CAD), yet consumption of foods high in β-carotene show a respectable 26% reduction in CAD.<sup>80</sup> Vitamin E supplementation has not demonstrated activity against the development of type 2 diabetes, while foods rich in vitamin E demonstrate a protective effect against type 2 diabetes.<sup>81</sup> What is currently happening in molecular biology is the recognition of patterns of

phytochemicals and nutrients on the molecular level, rather than focusing on one molecule's properties. A key understanding of antioxidants is that they work in redox networks that are dependent on not one, but many different compounds (Bland, 1995). For example, in an analysis of over 400,000 people, Cho et al<sup>79</sup> determined that the disease protective effect of vitamin C was, at least partly, due to the co-occurring phytochemicals (e.g.  $\beta$ -cryptoxanthin) that are naturally present with vitamin C. Rather intriguingly,  $\beta$ -carotene levels have been observed to go up in people who are taking supplements without  $\beta$ -carotene, while 500 mg of vitamin C have been shown to increase glutathione levels in red blood cells.<sup>74</sup> Messina suggests that the influence of diet on health and disease is likely due to the vast multitude of individual interactions that occur among phytochemicals.<sup>31</sup>

But the real issue may be qualitative differences, rather than the specific amounts of any one particular compound. McCarty<sup>82</sup> argues in favor of this point when he suggests the use of a "phytochemical index," a measure of the exposure to dietary phytochemistry, to predict health status of individuals. He postulates that the more phytochemistry in the diet, the higher the health status of the individual.<sup>82</sup> If this is so, then taking a handful of isolated compounds to make up for a sugar-laden, fiberless, trans fatty acid rich diet, is likely to do very little for human health and, at times, may even be detrimental. Thus, one nutrient or antioxidant given in inappropriate doses could detrimentally throw off a redox network (Bland, 1995). Therefore, if supplementation is to be utilized, it would best attempt to mimic the diet our ancestor's genes knew: low-dose nutrients embedded into a phytochemical mixture. Such a strategy may not only become state of the art pharmacology, but is evolutionarily familiar.

Plants in the diet, whether food plants or medicinal plants, offer low-affinity, multi-target pharmacotherapy. Intriguingly, low-affinity, multi-target pharmacological strategies have demonstrated improved safety profiles (lower occurrence and reduced range of side-effects) than high-affinity, single-target drugs.<sup>40, 83, 84</sup> High specificity for a single protein does not always deliver the required benefit/adverse events profile.<sup>37</sup> Hence, isolated nutrients, antioxidants or synthetic chemicals have less favorable benefit/risk profiles. Treat your genes to what they know.

## Conclusion

The daily intake of plant foods contain hundreds of biologically active compounds that wash over our genes. This symphonic process is unlikely to be duplicated by single chemical interventions. This daily intake would almost certainly engage numerous

genes and thus many physiological processes. For instance, vegetarians not using dietary supplements exhibit a greater activity of their endogenous antioxidant enzymes.<sup>74</sup> Considering disease processes are complex processes that involve multiple genes<sup>85</sup> and may take many years to onset<sup>31</sup> and that genes function in networks, attempting to understand diet and its connection to disease by studying isolated constituents is of limited value. Messina<sup>31</sup> astutely points out that the subtle effects of an array of compounds and their interactions is the key to the understanding of diet as related to health and disease. Further, studying isolated components in lieu of dietary patterns is likely to lead to misunderstandings about nutritional supplements and the impact of diet on health.

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