Hello boys and girls. This is Tim Ferriss and welcome to another episode of The Tim Ferriss Show, where it is my job each and every episode to deconstruct world class performers of all different types, whether from chess, athletics, entertainment, military, otherwise, to tease out the habits, routines, favorite books, and so on, that you can test and apply in your own life. This episode is a little bit different. By popular request, we have Rhonda Patrick, PhD, at found my fitness on the socials, who is an American biochemist and scientist. Whether you want to extend life inexpensively by a stem cell insurance policy, you may have read about that in Tools of Titans, or guard against cancer, Rhonda has some very valuable insights and experiences, as well as recommendations.

In this episode, she tackles many of your most popular requested topics. This includes many things I’ve talked about before that you guys have wanted more detail and specifics on. Best practices for fasting, for instance. What blood tests are most important for analyzing overall health. The minimum effective dose for the benefits of sauna and different types of heat exposure. Heat versus cold exposure. We’ve talked about cold baths before. How can they be used and how should they be used effectively? The most effective smart drugs, nootropics. Thousands of you have asked me for this. The latest fat loss research and much, much more.

A little background on Rhonda. She is known for her studies of the mechanistic link between Vitamin D and Serotonin production, research that may have important implications for the understanding of Autism and other disorders. She also has a very popular podcast, Found My Fitness. Dr. Patrick also conducts clinical trials, has performed again research at the Salk Institute for Biological Studies and did graduate research at St. Jude’s Children’s Research Hospital, which I’ve had some involvement with, where she focused on cancer, mitochondrial metabolism, and Apoptosis. I hope you enjoy this conversation, which is really a master class with Rhonda Patrick, as much as I did. Thanks for listening.

Hi guys, Rhonda Patrick here. Happy to be here today. To get things started, let’s take an opening question from Tim Ferriss.

What new areas, experiments, discoveries, or hypotheses are you most excited about these days?

Thankfully, because I put a certain percentage of my brain out here on the internet, much of what I’m actively interested in these days, or have been interested in, is actually elucidated a little bit as necessary context for some of the questions I’m going to answer here shortly. But, Tim’s questions does sort of give a nice opportunity for an overview.

As a rule, the things that usually get me really revved up are ultimately optimizations that we can make to our lifestyles that might increase our functional health span, our wellbeing, and lastly, cognitive and physical performance, usually through deeper understandings of biology. Health span or healthy functional lifespan is especially of interest to me. I sort of lead with that. To me, health span is living for as long as we can while doing our best to prevent deterioration from the diseases of aging. Talking about increasing health span is one thing, though. Often, achieving it is a different thing.
altogether. The reason this is tricky is that the most reliable way to treat aging is to try to, instead, prevent it. A natural extension of that fact means that the earlier we start, the better shot we have of making a large cumulative effect over the course of our lives.

The specifics of how to best mitigate the damaging effects of aging, specifically, is subject to a little bit of individual variation as a consequence of each of our little genetic idiosyncrasies, the combination of which are unique to each of us. This is an area that I’m especially interested in and that I plan to invest a little bit more into intellectually in the coming months, especially the interface between nutrition and genetics, known as nutrigenomics. But, the good news is, there are certain rule of thumb strategies that are able to have a positive effect on health and possibly even longevity. In some cases, it might mean optimizing our diet around inclusion of specific nutrients.

One of the most interesting and exciting of which, to me right now, is the compound known as sulforaphane, spelled S-U-L-F-O-R-A-P-H-A-N-E, but also other related compounds that fall into the same class of compounds broadly known as isothiocyanates, all of which, including sulforaphane, being derived from cruciferous vegetables. What’s interesting about sulforaphane is that this compound, richly found in broccoli sprouts at about 50 to 100 times what’s found in mature broccoli, is that it activates a special genetic pathway in our cells known as NRF2, and it does so more potently than any other known naturally occurring dietary compound. This gene, a master regulator, controls over 200 other genes, effecting whether or not they’re activated and doing work.

These include genes that affect our own anti-inflammatory processes, antioxidant processes, and even the ability to inactivate potentially harmful compounds that we’re exposed to on a daily basis from breathing in carcinogens, like benzene from air pollution. In a sense, we’re talking about an on switch from some of our most native stress responses. Our ability to cope with physiological stress down to the cellular level ultimately affects how rapidly we accumulate the damage, which we often refer to as aging. But, here’s the interesting thing. The reason NRF2, a stress response pathway, is activated by sulforaphane is because the compound itself functions as what we know as a xenohormetic, a compound that, by virtue of being actually slightly stressful to cells, elicits a biological stress response. It has a cumulative effect that is otherwise a net gain in resilience that creates a benefit to the organism as a whole.

This is actually somewhat un-intuitive if you really think about that. We sort of have this very natural notion that, because excess stress is bad, we should venture to avoid stress at all costs. It turns out, though, that in fact, perhaps as a consequence of having received stressful compounds in our diets for millions of years, things that evolved in plants, such as insect antifeedants that help ward off insects, we sometimes function better for having them. They can even induce neuro stress responses that boosts neurotrophic factors that lead to the growth of new neurons and promote the survival of existing neurons, which may function to help make compounds like sulforaphane potentially a candidate as a mild nootropic.

We’ll probably come back to this in a little bit, but the bottom line is, if we take this same concept that stress can be beneficial, known as hormesis, and apply it to other things like exercise, fasting, heat stress, cold stress, some of the various benefits that may be had from these many strategies similarly come about as a consequence of sometimes overlapping stress response pathways. This idea of hormesis and trying to improve our capacity to be resilient to environmental stress and even the stress generated as a byproduct of normal metabolism and immune function in particular is a very useful framework for evaluating the potential strategies that might have promise in preventing even aging.
Okay. All of that said, this is a great opportunity to jump from these sort of big picture ideas back to things of a more practical application variety. Specifically, the next question evaluates a straightforward technique that has caught my interest and also happens to be broadly applicable to almost anyone. All right.

Brandon Beckett @ 14:23:
Dr. Rhonda Patrick, you interviewed Dr. Valter Longo, Dr. Satchin Panda, and Dr. Ruth Patterson on time restricted feeding and fasting. Can you summarize your best practices for time restricted eating and who it might not be a good fit for?

Rhonda @ 14:39:
Okay. This is a fun question, but before we dive right into best practices on time restricted eating, it probably helps to know what it is for the rest of you that may be listening. Time restricted eating, as it’s called in humans, or time restricted feeding, as it’s referred to in animal research, is this idea that by constraining our eating within a certain time window during the day, ranging from only eight hours up to 12 hours per day, usually earlier in the day, to align better with our circadian rhythm, we stand to benefit from a variety of different angles.

On the more extreme end of eight hours, you’re engaging in a slightly more extreme type of time restricted eating, which is more well known in the fitness world in particular as 16:8 intermittent fasting. Simply maintaining a slightly more conservative time window than you usually might has started to show advantages as well, potentially functioning as a lifestyle intervention that may be able to protect people from obesity, metabolic related disease, and more, at the population level. For example, even an 11 hour eating window has been associated in one study with a reduced risk of breast cancer and potentially recurrence by as much as 36% in women.

We’ll get back to what the research, both mouse and human, says about the duration of the time windows involved. But first, let’s talk a little bit about the circadian aspect. When healthy adults eat meals that are identical in terms of both their macronutrient and caloric content at breakfast, lunch, or dinner, the postprandial glucose increase is lowest after breakfast and highest after dinner, even though the meals were 100% identical. This is just one example that suggests metabolism changes throughout the day. We also know that in humans, metabolic genes are more active during the day and less active at night. The underlying reason for this is because humans are diurnal creatures, which means that we conduct most of our activities during the day, including feeding, exercising and working, and then resting at night.

What makes humans diurnal creatures is the presence of an internal clock in the brain, referred to as the suprachiasmatic nucleus, or SCN for short. The part of this internal clock that interacts with the external cue of light, the SCN is also referred to as the master oscillator. But, light isn’t the only external cue we have. We also have food influencing what are known as peripheral oscillators that occur in peripheral tissue, such as the liver, and influence metabolism. Whereas, light is the major cue for circadian rhythm, timing of food intake regulates circadian rhythm in peripheral tissues, as well. This fact helps to explain why time restricted eating, as it’s defined by Dr. Panda’s work and that of others, begins with the eating period with the very first bite or drink of anything non water, because even compounds that exist in black coffee, such as caffeine, can be reasonably expected to produce metabolic effects that influence these peripheral oscillators, including activity in the liver.

Everything from making neurotransmitters, to insulin, to glucose transport inside of cells, to oxidizing fatty acids, to repairing damage, is on a 24-hour cycle clock that is influenced by these external cues involving metabolism. To sort of illustrate the importance of circadian rhythm, these clocks regulate thousands, and thousand of genes, which is somewhere in the neighborhood of around 10 to 15 percent of the expressed human genome, which means that our basic metabolic physiology is meant
to be tuned to behave differently, depending on the time of day that it is, even the bacteria that we harbor on our guts have circadian rhythm, with the species of bacteria changing according to the time of day. Some bacteria dominate during the morning, and others during the evening, unfortunately with the invention of artificial lighting, and the varying work schedules, it has extended peoples eating times to occur much later in the evening, and this can have very negative consequences.

Eating late at night may also reset peripheral clocks, and result in misalignment of metabolism, which means when you wake up, your metabolism is already at the end of its cycle, so that’s the logic behind the circadian aspect, which gets left out of some of the intermittent fasting philosophies that are popular, and explains why time restrictive eating emphasizes an earlier eating window, and includes noncaloric xenobiotics as breaking the fast, something I’ve learned as a specific point of contention for people.

Okay, but shifting away from the xenobiotics, and circadian aspects, to talk more about the time window itself, animals that have been limited to nine to twelve hour feeding window, in which they can eat, but otherwise allowing them to eat the same amount of calories that they normally would, they have shown that they can attain some pretty amazing benefits, including decreased fat mass, increased lean muscle mass, improved glucose tolerance, improved lipid profile, reduced inflammation, higher mitochondrial volume, protection from mild age related fatty liver, protection from obesity, generally favorable improvements in gene expression, and increased production of ketone bodies, which is interesting for another reason we'll get back to in a minute.

Time restrictive eating also has a growing body of research in humans. Resent studies suggest that, mentioned briefly earlier, eating within an 11 hour window was associated with a decreased breast cancer risk, and reduction in recurrence by as much as 36%. Earlier meal timing associates with improved effectiveness of weight loss therapy in overweight, and obese people. For each three hour increase in nighttime fasting duration, was linked with a 20% lower odds of elevated glycated hemoglobin, HbA1c, which is a more longterm marker for blood glucose level. For each 10% increase in proportion of calories consumed after 5:00 pm, there was a three percent increase in the inflammatory biomarker C-reactive protein, otherwise known as CRP.

Eating one additional meal during the day, instead of the evening, was associated with an eight percent decrease in C-reactive protein. Eating within a 12 hour window improves sleep, and increased weight loss in normal weight people. As a rule of thumb, anything that has the potential to mitigate chronic systemic inflammation, is something I personally consider worth trying to dial in, since depression of inflammation is thought to be one of the most important predictors of successful longevity, that increases importance with advancing age, and also influences the risk of cancer, and even potentially mental health.

So putting aside the potential to have better blood glucose control, or protect myself from obesity, without actually changing the composition of my diet, reducing systemic inflammation has a lot of appeal to me. Now that we are all on the same page, in terms of what some of the research shows, on the benefits of time restrictive eating, I would like to go back and address Brandon’s question, about what my best practices are surrounding time-restrictive eating. How you choose to implement some of this information is ultimately going to be dictated by life circumstances, that include practical realities surrounding work schedule, and probably a million other things.

The flexibility of my schedule, however, has made implementing time-restrictive eating admittedly a bit easier. Unless I have a social reason that forces me to eat later in the day, I usually start my clocks as soon as I wake up, thus I don’t concern myself, a whole lot, about what counts as breaking the fast, and what doesn’t, and I go by the strictest of definitions. If it’s not water, it breaks the fast, unless it’s just brushing my teeth, I don’t count that. If I wake up at 8:00 am, and have my first sip of coffee at
8:15, then I make a note to myself, or I set an alarm on my phone to go off one and a half hours before the clock end, which is usually around 6:15 pm, since I aim for around a 10 hour eating window, and a 14 hour nighttime fasting window.

When I’m feeling especially motivated, I eat within a eight to nine hour time window, and fast for 15 or 16 hours during the night, which means, if I have my first sip of coffee at 8:15 am, that I stop eating by either 4:14 or 5:15 pm. I follow the same procedure on days I sleep in, even though animal research shows that this pattern has benefits even if you cheat on the weekend. Now the reason why I chose a 10 hour window, is because it’s a sufficiently tight window of time to likely confer some of the advantages of time restrictive eating, without being unduly burdensome. Personal compliance here being the issue. Stretching for the nine hour, or even eight hour window, however, can also be interesting, and may appeal to some. Some animal research has shown that a certain aerobic endurance benefit for time-restrictive feeding, in this nine hour range, but not for shorter fasts, and if you think about it, mice that only feed for nine hour periods, and are fasting for the other 15 hours, it makes sense.

It takes around 10 to 12 hours for liver glycogen’s stores to be depleted, which is then followed by fatty acids being liberated from adipose tissue, these fatty acids are then transported to the liver, where they are converted into ketone bodies, like beta-hydroxybutyrate, which are then transported to a wide variety of other tissues, such as the muscle, and used for energy. So it sort of makes sense that eating within a nine hour window, and fasting for 15 hours, overnight, may lead to endurance enhancements, if we’ve managed to kickoff a little more ketone production the evening before a run. Anecdotally I’ve observed that, personally, I feel an improvement in endurance ranging from slight to pretty significant in my morning runs, when I’ve tried a little bit harder to eat strictly within an eight or nine hour time window.

Just as a closing thought, I think there is still a lot of room for more emerging research in this area, to teach us things that may be important. Questions like, what influence later day endurance, or weight training, has on mitigating the deleterious effects of other suboptimal parameters, like a later in the day eating window. How large the effect of xenobiotics, like caffeine, and black coffee, is, compared to potentially a more important factor, like just keeping an otherwise tighter time window, with a slightly looser definition of what is considered eating.

If you’d like to see interesting questions answered about time-restrictive eating, you can actually participate in a mobile app powered distributed clinical trial, by heading over to Dr. Satchin Panda’s lab website, which can be found at mycircadianclock.org, available for iPhone, and Android. Basically you commit to a baseline, and then one of the patterns of time-restrictive eating, and then proceed to submit timestamped pictures of your food, over the course of 12 weeks. Of course, I'd also be remiss if I didn't mention that a mutual friend, and someone that has repeatedly been on The Tim Ferriss Show, Kevin Rose, has developed a cool mobile app, to help keep track of intermittent fasting, and time-restricted eating windows. You can also check that out if you're an iPhone user, it's in the app store under the name Zero, as in the number of calories you consume while fasting.

To sort of finish of this question, as for who time-restricted may not be a good fit for, I'm not sure. As an intervention, I believe it is actually broadly applicable, however, I’m 100% certain that there is someone, somewhere, for which a unique medical condition may make time-restricted eating inappropriate, especially if you expand the definition of time-restrictive eating, to mean long, multi-day fasts, which are the subject of Dr. Valter Longo's research in particular. Definitely check in with a physician, particularly if you're going to do a prolonged fast, or if you're thinking of trying time-restrictive eating, but may have a medical condition, that for some reason, might somehow make it unsafe.
Okay, next question.

**Jasky Sing @ 24:56:**
For all those that don’t understand the benefits of fasting, how does doing a fast differ from say eating a diet, low-carb, high fat, that puts you into ketosis, and what key metrics, for example blood tests, should someone look at to know it is benefiting you?

**Rhonda @ 25:11:**
Very interesting question, because as implied by the question, there are at least a few similarities between a low-carb, high-fat diet, and fasting, but there are also, obviously, some key differences. Probably the main similarity between the two, is that metabolism shifts from using glucose as the major source of energy, to primarily oxidation of fatty acids, and ketone bodies, as energy.

When it comes to fasting, there are a few things that really differentiate it from a low-carb, high fat diet. One of the major benefits of fasting, particularly prolonged fasting, which is around four to five days in humans, that is not found on a low-carb, high fat diet, is a dramatic increase in the autophagy and apoptosis, followed by a massive boost in stem cell production. Autophagy is a genetic program that is very important, it clears away damaged cells to use for energy, while apoptosis is a genetic program that causes damaged cells to self-destruct, both of these processes prevent damaged cells from becoming cancer cells. When we clear away damaged cells, this also means those damaged cells are less likely to become senescent, which is what can happen when too much damage accumulates. A senescent cell is technically a living cell, but it is not functioning in a way that is consistent with maintaining the overall health of an organ, in fact quite the opposite.

Senescent cells can accelerate the aging of nearby cells, and promote tumor growth, by secreting proinflammatory molecules, and other factors. Senescent cells are bad news, as we age, they are everywhere, from our livers, to our hearts, to our brains, and they accelerate the aging process. It has been shown in mice, when given a compound that increases the clearance of senescent cells, it actually extends their average lifespan by 20%. Another way that fasting really shines, particularly prolonged fasting, is that prolonged fasting has a very robust effect on increasing stem cell numbers.

The regenerative power of tissues, and organs, decline with age. It is stem cells that provide this regenerative power, and because stem cell numbers decline with age, so does organ function, which mean anything that can counter this, is a win. Fasting also causes cells to clear away damaged mitochondria, and recycle their defective components for energy, called mitophagy, followed by a concomitant generation of new mitochondria, called mitochondrial biogenesis.

This is a really great thing because mitochondria accumulate damage with age, just as cells do, and this can accelerate the aging process. Not only does fasting clear away old, damaged mitochondria, it also generates new, young, healthy mitochondria to replace the damaged ones. There has also been some evidence suggesting that a low carb, high fat diet may modestly increase mitochondrial biogenesis as well, but not mitophagy.

Another thing fasting does is it increases the levels of something called nicotinamide adenine dinucleotide or NAD Plus, which I will just refer to as NAD. NAD levels always increase during a fasted state and decrease during the fed state, no matter what food type. NAD is a very important co-factor for many metabolic enzymes which just means you need it for these enzymes to work properly. Your mitochondria need NAD to produce energy from glucose or fatty acids. Anytime there is chronic inflammation or DNA damage occurring, this sucks up the NAD and so the mitochondria suffer. Also, NAD levels decrease in multiple tissues with aging. There are several different compounds, which are various forms of vitamin B3, that dramatically increase NAD levels and have been shown to delay aging in multiple tissues in mice.
Yet another difference between fasting and a low carb high fat diet is that fasting activates many repair processes including repair of damaged DNA, damaged cells, damaged mitochondria and damaged proteins. You must be in a fasted state to repair damage which is why most repair processes occurring during sleep because that is when most people are in a fasted state. Fasting improves blood sugar, insulin sensitivity, and blood lipids and improves inflammatory markers including C-reactor protein and tumor necrosis factor, also known as TNF Alpha, and improves adiponectin, leptin, and brain-derived neurotrophic factor in humans. A low carb, high fat diet has also been shown to improve blood glucose and insulin levels and also reduce inflammation, but not always consistently and may be highly variable depending on the individual which is likely due to the fact that the way our bodies respond to food is also complicated by genetics.

We have variations in our genes that make them operate a little differently from similar versions in other members of the human population. These variations are known as genetic polymorphisms. One of the best examples I have seen yet demonstrating the immense variability in how people respond to the same foods was a publication that came out in 2015 in the Journal Cell. The study looked at the blood glucose responses of over 800 different people to various foods including fat. Without getting into all the details of this study, what is important to the topic of this discussion is that while most people had a low glucose response to dietary fat, some people had a high glucose response. There have even been a few important gene polymorphisms that have been identified to play a role in the context of high fat diet, such as FTO, PPR-alpha, PPR-gamma, and APOE4.

PPR-alpha is one of the most important genes that I’ll mention because it plays a very important role in the process of ketogenesis. Activation of PPR-alpha promotes uptake, utilization, and cannibalism of fatty acids by activating genes involved in fatty acid transport, fatty acid binding and activation, and fatty acid oxidation. There is a polymorphism in this gene that has been associated with lower PPR-alpha activity and a two-fold higher risk of type two diabetes, increased levels of triglycerides, increased total cholesterol, increased LDL cholesterol and, especially important, increased small dense LDL particles in the context of high saturated fat intake and low polyunsaturated fat intake. Obviously, measuring these blood biomarkers will help illuminate whether any type of diet works for you. There also a variety of resources on the web that can help you can your raw genetic data from services, like 23andMe, and find out whether you have some of these polymorphisms. I similarly offer some resources for this on my website, foundmyfitness.com, for this purpose.

In terms of biomarkers things that I would monitor, particularly if I were doing a ketogenic diet, might include biomarkers for lipid and glucose metabolism such as LDL, small dense LDL particles, total cholesterol, triglycerides, glycol and hemoglobins, HbA1c. You can also measure your fasting blood glucose levels and ketone levels at home using something like Precision Xtra, which I find to be mostly reliable and I also use.

I also like to be aware of any inflammatory biomarkers that I can get my hands on. There’s some common measurements like high sensitivities to reactor protein and also IL-6 and TNF-alpha. For those people experimenting with a strict ketogenic diet for greater than six months, it may be wise to measure thyroid function by doing a full thyroid panel. There was a recent publication where a ketogenic diet for nine months caused thyroid dysfunction in children with epilepsy. This may not be something to worry about in everyone, but it does not hurt to be cautious.

For autophagy related and stem cell related biomarkers, there are some used in research that you, unfortunately, can’t really get ahold of for self-monitoring purposes. For autophagy, LC32, and for stem cell self-renewal, lin-negative, CD184 positive, CD45 negative cells.

Okay, one quick closing point to sort of finish this section off. It’s important when we talk about fasting
that we make clear distinctions between the various duration of the fast we're talking about. If we discuss prolonged fasting, as I have done a lot in answering this question, that means we're talking about a water fast on the order of four to five days. However, in mouse research this level of fasting is actually achieved in two to three days. This has led to some confusion because people often attribute the so-called benefits of prolonged fasting to shorter intervals that are a bit more manageable because they might have ran across this rodent research.

The fact is that we may see some of the same benefits, such as autophagy, even with a shorter fast, but on an order of magnitude greater with prolonged fast. Also, with a prolonged fast, we see entire organ systems can shrink and then can experience renewal during the feeding period. It should be pretty clear that we're actually talking about a whole different level of cellular cleanup that can occur, which is above and beyond what we actually get in shorter fasts.

There's still a lot of research going on to better tease out the differences between shorter, let's say a two day fast, and fasts that meet the definition of being a prolonged fast. I'm optimistic that evidence will continue to merge and that even shorter duration fasts are still very beneficial. That said, as Tim likes to say, I'm not a medical doctor and don't play one on the internet. If you're thinking about giving prolonged fasting a shot, make sure to follow the prudent podcast listeners rule and run it by an actual physician. There's also an emerging body of literature surrounding a fasting mimicking diet that lasts five days instead of four and can be prescribed by a doctor by a packaged meal plan if having that structure is helpful.

On to the next question.

Jeff Norton @ 33:58:
Rhonda, can you please share your thoughts on the minimum effective dose for sauna benefits, session time, temperature, and frequency? From this minimum effective dose, what types of changes/benefits can someone expect?

Rhonda @ 34:13:
With this question, I'm going to start with the benefits since as a point of logical progression, it's helpful to establish what the science says about the benefits before we talk about how to dose it. The good news is I've actually partly done a pretty good job of talking about some potential benefits for sauna use in a guest post that's features on Tim's blog entitled, Are Saunas the Next Big Performance-Enhancing Drug. It's possible Jeff's already seen that, but for the rest of you, make sure to check that out.

Since that initial blog post, however, some pretty research has come out related to sauna use and it touches on areas that I spent a lot of time thinking about; longevity and also Alzheimer's Disease. Humor me for a minute while I talk about some of this and then get back to Jeff's question surrounding what the minimum effective dose might be with respect to temperature, sauna session time, and frequency to illicit some effects that might be loosely characterized as ergogenic or enhancing physical performance in some respects.

A study published in Joma Internal Medicine in 2015 show that sauna use was associated with longevity. The study recruited over 2,000 middle-aged men in Finland and compared frequency of sauna use with sudden cardiac death, fatal coronary heart disease, fatal cardiovascular disease, and all cause mortality including cancer over the course of 20 years. Heart disease is the leading cause of death in the United States and many other countries as well. That should be a cue to listen up.

Here's what the study found that fatal cardiovascular disease was at 27% lower in men who uses sauna two to three times in week and 50% lower for men who use the sauna four to seven times per
week compared with men who just used the sauna once a week. In addition to lowering cardiovascular rate of mortality, the study also found that sauna use lowered all-cause mortality full-stop. Using the sauna two or three times per week was associated with a 24% lower all-cause mortality and four to seven times per week, lowered all-cause mortality by 40%.

Let’s talk about all-cause mortality. What does it mean? Does it mean that using the sauna four to seven times per week made 40% of people immortal? No. What it means is that for the individuals being studied, they had 40% less mortality than those of a similar age not being subjected to the same conditions. This reduction of mortality wasn’t strictly tied to heart disease, but instead something potentially more general. Keep in mind, the study also adjusted for other parameters that may affect the data including body mass, serum cholesterol, blood pressure, smoking, alcohol consumption, type two diabetes, and socioeconomic status.

We’ll come back to talk more about this generalized longevity effect in a minute since it’s interesting to discuss plausible mechanisms that underlie that effect. The effects on heart disease, however, are a little more straightforward to try to explain. Some of the more positive benefits of sauna use on heart health may have to do with similar benefits with regular, physical exercise. Heart rate can increase up to 100 beats per minute during moderate sauna bathing sessions and up to 150 beats per minute during more intense warm sauna use. 150 beats per minute corresponds to moderate intensity physical exercise, which is as we already know, has a very positive effect on cardiovascular health. Heat stress from sauna use also increases plasma volume and blood flow to the heart known as stroke volume. This result in reduced cardiovascular strain so that your heart has to do less work for each beat that it does to pump oxygen-rich blood to your tissues and to your brain. Additionally, long term sauna use has been shown to generally improve blood pressure, endothelial function, and left ventricular function. But crossing over from theory to more practical, what if improving heart health really just meant having a boost in endurance. In fact, that is exactly what has been demonstrated.

One study demonstrated that a 30 minute sauna session two times a week for three weeks post workout, increased the time that it took for the study participants to run to exhaustion by 32% compared to baseline. If you start to think of mild adaptation to heat stress as a proxy for some of the benefits of exercise. The generalized longevity effect starts to make sense, but there may be molecular mechanisms for this as well. There’s two pathways in particular I’d like to briefly highlight. Heat shock proteins produced by ourselves in response to heat stress and also another pathway known as FOXO3.

Sauna use robustly activates a class of stress response proteins known as heat shock proteins, and heat shock proteins have been implicated in aging. Where increased expression has been shown to mechanistically in lower organisms to confer increased longevity. And similarly, polymorphisms in human populations that increase heat shock protein production have also been shown to have an association with increased longevity. To understand why this is the case, it is helpful to know the purpose of heat shock proteins also known as HSP’s. Heat shock proteins help all other proteins maintain their proper three dimensional structure in the cell, which is important for each protein in order for it to be able to perform its function. If various interactions that occur disrupt the structure of that protein for example denaturing it, then this prevents the protein from doing its function and changing the half life of it.

As I briefly mentioned earlier, damaging products get created from normal immune system function and metabolism. These damaging molecules produced at a low level everyday even in the best of circumstances, but made worse by poor lifestyle choices damage proteins and disrupt their structure. Moreover, once a protein structure is damaged, it can then misfold preventing it from being degraded and can lead to the accumulation of toxic protein aggregates that can themselves damage cells as well.
Protein aggregates, something heat shock proteins specifically help prevent the accumulation of, are associated with neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease. In fact, when you take normal mice that have been engineered to accumulate amyloid beta plaques characteristic of Alzheimer’s disease, they do begin to manifest a pathology in the brain that is similar to what we might call Alzheimer in humans. But if you engineer these same mice to over produce one of the more well known heat shock proteins called HSP 70, it reduces the severity of this condition including reducing the associated loss of neurons and synapses.

So, if you think about it this might suggest something interesting. We know that heat shock proteins are produced in response to heat stress, and that they seem to help prevent symptoms of Alzheimer’s disease in mice by reducing protein aggregation and helping keep proteins from losing their structure in the first place. What if, by naturally increasing our heat shock protein expression we could reduce the risk of Alzheimer’s disease.

The same group that studied over 2000 male sauna goers found a very interesting association from the same cohort that they later published in another paper. They found that men that used the sauna 2-3 times per week had a 22% lower risk of dementia, and a 20% lower risk of Alzheimer’s disease compared to men that only used the sauna 1 time a week. Men that used the sauna 4-7 times a week had a 66% lower risk of dementia, and a 65% lower risk of Alzheimer’s disease compared to men that only used the sauna once a week. Once again just as before, this is after adjustment for age, alcohol consumption, body mass index, systolic blood pressure, smoking status, type 2 diabetes, previous myocardial infarction, resting heart rate, and serum LDL cholesterol. Now whether or not it was the heat shock proteins may be a great idea for future research, but as a plausible mechanism, heat shock proteins seems as a very good likely explanation for what is going on there.

Since we’ve also mentioned briefly the endurance and cardiovascular benefits of sauna use, particularly in a trial involving run until exhaustion aerobic activity, it’s also worth mentioning that VO2 max, which is the body’s maximum capacity to transport and use oxygen during exercise has a strong association with cognitive capability in old age, which may have something to do with the brain perfusion and even the ability for blood perfusion to wash away metabolic waste products including amyloid beta.

The other molecular pathway of interest that may help explain some of what’s going on with this association between the type of longevity in sauna use mentioned earlier, is a pathway known as the FOXO3 pathway. There is some evidence that part of this natural cellular stress response when confronted with heat, is an activation of this pathway. FOXO3 is one of the big aging genes for which regular old fashioned genetic variation has shown is involved in longevity. Humans with their polymorphism that make more FOXO3, have up to a 2.7 fold increased chance of living to be a centenarian. And in mice, having more of the homologies version of this same gene can extend their lifespan by up to 30%.

As a pattern of aging, our FOXO3 reactivation trends downward decreasing the expression with age. FOXO3 is a master regulator involved in autophagy, DNA repair, metabolism, endogenous antioxidant production, stem cell function, and immune function. Since we’ve already spent so much time navigating the especially relevant waters of HSP’s, I’ll leave the discussion of FOXO3 alone for now.

We got a little bit distracted talking about mechanism and other various odds and ends surrounding sauna use, but to return to part of the core of the question asked by Jeff, we need to address minimum effective dose. For the minimal benefits of lower cardiovascular disease mortality, lower all cause mortality, and lower Alzheimer’s disease risk, we have to address the literature that actually observed these effects. In this case, that would be 20 minutes at 174 degrees fahrenheit or 79
degrees Celsius, 2-3 times per week. Remember though, that those that use the sauna 4-7 times a week had an even more robust effect. This is actually a pretty great guide because we’ve got a range of effects based on dosing and a pretty large trial of around 2000 participants.

If we turn our attention to smaller studies such as the run until exhaustion endurance trial we mentioned earlier, the minimum effective dose for endurance appeared to be 30 minutes in a 194 Fahrenheit or 90 degrees Celsius sauna twice a week. A dose, which by the way produced a maximum heart rate of 140 beats per minute. This last point is especially interesting if you consider the fact that maximal heart rate might be an appealing candidate for quantified selfers to track their physiological response to heat stress, when other variables may differ. Take for example, the fact that not all saunas get as hot. Especially the infrared ones that run cooler. It does seem reasonable to think however, that turning the knobs on other aspects of the sauna session by making changes for example to the duration, you can probably still elicit comparable effects.

What I have not discussed yet but mentioned in guest post on Tim’s blog, certain studies have demonstrated some effects on muscle mass and recovery in animal and human trials. For endocrine effects in the area of growth hormone for example, multiple studies report ranges of 20-30 minutes at around 176 degrees fahrenheit or 80 degrees Celsius, in the neighborhood of 2-3 times a week. Again, pretty similar to the larger 2000 person mortality and Alzheimer studies mentioned earlier.

Finally, molecular evidence for heat shock protein induction seems to indicate that healthy young men and women, sitting at around 163 degree fahrenheit or around a 73 degree celsius sauna for 30 minutes, are able to increase their heat shock protein levels including Hsp72 by 49%. And that the elevation in heat shock protein levels persist for 48 hours after the initial heat stress, suggesting 2-3 times per week is again a good moderate frequency to hit a threshold for some of these sustained effects.

So it’s pretty clear we have a few options available to us. Some more mild than others. More popular here, where I live in the United States are infrared saunas which don’t get quite as hot, often limited to about 140 degrees fahrenheit or 60 degrees Celsius. For reasons of practicality and because I believe that benefits from the sauna are primarily conferred directly by heat, I tend to prefer a hotter sauna. But it seems wholly reasonable that making other adjustments like preceding the sauna session with a light cardio for example, might help make up for other little differences. It’s hard to know for absolute certain, but I’m optimistic.

All of that said I think it’s a good moment to make a point to give the same warning Tim gives on his blog surrounding sauna use and heat stress in general. Try to exercise good judgment, if you have some sort of medical condition all bets are off. Even if you don’t think you have a medical condition, it’s reasonably worth checking in with a doctor before becoming some kind of mega sauna enthusiast. Heat can be no joke, and it’s important that you don’t hurt yourself.

Finally, there’s other so called benefits that I have suggested may exist on Tim’s blog, but that I didn’t get to talk about today. Areas where the science may be promising but not quite as robust or otherwise confer itself well to talking about a minimum effect of dose. Including the possibility that sauna use could play a role in mood and attention by increasing norepinephrine, and affecting our sensitivity to and production of beta-Endorphin, giving us as sort of runners high. The potential of which was something that initially appealed to me when experimenting with my own personal sauna use. Or the possibility that sauna use may reduce muscle atrophy and then affect muscle regrowth, an effect which while very interesting is mostly shown in animal studies that might be hard to then try to apply back to humans. So definitely go check out that post.

Moving forward, we can now talk about the flip side of the coin with our next question
Thanatos Moores @ 46:58:
I would like to know about the interaction between heat and cold exposure, and if they will cancel one another out. For example, if I do a workout and then sauna for 10-20 minutes to engage the heat shock proteins to maximize the hormonal response and then proceed to take a cold shower, will that cancel out the benefit of the sauna and heat exposure. Also, will that make the cold exposure less effective?

Rhonda @ 47:22:
For this question, I'm going to chose to focus on discussing the question of combining heat stress and cold stress in rapid succession, rather than a discussion of the combination of either with exercise, which is sort of a different overlapping discussion, which comes up in a different question, which I'll get to in a moment.

So to answer this question, with our slightly narrowed parameters, I've been trying to find empirical evidence in the scientific literature discussing various aspects of combining heat stress and cold stress, and have come up pretty dry. When it comes to answering a lot of the big questions surrounding the combination of both these modalities in rapid succession, frankly, it's hard to find good information, whether we're talking about winter swimming, as done by sauna goers in Finland, or simply a cold shower. Or far more extreme, alternating between sauna and ice bath as described by Rick Rubin and Tim Ferriss during their sauna podcasting experience.

One thing we can do a little bit of, however, is turn to the molecular evidence. What may surprise many of you is that both heat stress from the sauna, and even cold stress, are both able to activate heat shock proteins. This is because heat shock proteins respond to cellular stress in general, and not exclusively heat stress. Heat as a cellular stress, does cause a more robust activation than cold though. Still, it's sort of good to know that both types of thermal stress seem to positively affect heat shock protein expression, which we sort of established may have something to do with some of the benefits we might ascribe to sauna use.

But it's sort of important to ask yourself what you're trying to accomplish with cold exposure aspect. One of the main reasons I like to expose myself to cold are the effects it seems to have on the brain, mood, and possibly attention. One of the most likely candidates for listening and effect is norepinephrine, which is also the catecholamine that is actually responsible for triggering the browning of fat, making our fat more metabolically active. In fact, in terms of pathways, or physiological responses to cold, the release of norepinephrine into the bloodstream, as well as in the locus coeruleus region of the brain, is one of the more profound.

Guess what else increases norepinephrine release? Heat from sauna use. So this is the second way in which both hot and cold, instead of having opposing effects, where one cancels out the other at the molecular level, are nudging some of the same pathways in the same direction. But to elicit these same overlapping stress responses, you have to actually get cold enough for that to happen. Otherwise, you're just taking some of that heat burden you've created on your own body, and removing it.

How cold is cold, is the real question we have to ask here. In the case of an ice bath, I suspect the stress is almost certainly additive in nature. The extremes of going from a 200 degree Fahrenheit sauna to near-freezing water isn't a walk in the park. In the case of a 30 second cold shower that isn't sufficient to even trigger momentary discomfort, is probably not adding stress, but in fact simply removing it. This isn't strictly a bad thing, if that's what you're wanting to do.

That said, to give you an idea for some of the threshold temperatures involved to elicit the
norepinephrine response of cold stress, studies have shown that people that immerse themselves in cold water at 40 degrees Fahrenheit, or 4.4 degrees Celsius, for 20 seconds, increase their norepinephrine two to three-fold. Or 200 to 300%. And this release in norepinephrine didn’t seem to be reduced with habituation to cold. Long durations of cold water exposure under more moderate temperature have a more potent effect for norepinephrine release. For example, in another study, people that spent one hour in 57 degree Fahrenheit, or 14 degrees Celsius water, increased norepinephrine in their bloodstream by 530% over baseline.

As anyone who has swam the Pacific ocean knows, this is still quite cold and certainly sufficiently uncomfortable. But it’s probably very possible, depending on where you live, and the season, to get a shower that is similarly cold, or even more cold. Something I personally observed, that's sort of interesting, is that after a sufficiently intense sauna session, it can be very hard to stop sweating, and even potentially hours after you’ve cooled down, unless you’ve had a very borderline painfully cold shower. For social reasons, at least for me personally, it can almost be a requirement.

One last quick note before we move on to the next question, which shares some overlap with this one. I mentioned a moment ago that the information surrounding going from hot to cold, such as combining ice baths with the sauna, or even just doing the sauna and winter swimming combination as done in Finland, or elsewhere, is lacking. One of the areas I’d like to see more information on is actually safety. There's clearly a cultural history in some places of going from a hot sauna, right into an icy lake. But there is at least one case study reported in the literature of a heavy smoker having a heart attack, possibly as a result of a plaque rupture caused by a coronary artery spasm after doing many, many rounds of contrast immersion over several hours.

I’ve personally done ice baths interspersed with sauna use, Rick Rubin style, and found it to be very, very enjoyable. It seems to help me sleep better, and I definitely felt like my mood was significantly affected for even the next 24 hours. More so than either alone. So I’m hopeful we'll see some research come out that proves the case report to a relevant association, and somehow demonstrating ultimate safety. But in the meantime, I’m hesitant and a little cautious. For the broader audience listening now, I will make the same advice I made earlier. Please, please, be careful what you subject yourself to, especially if you have a condition that might warrant such caution. If in doubt, check with a physician before you take up a new polar plunge habit.

Okay, on to our next question.

Rob Schlicker @ 52:38:
Can you explain your thoughts on how regular hyperthermic conditioning and hypothermic stress relate to muscle hypertrophy and strength training?

Rhonda @ 52:46:
First, for our listeners, since Rob is clearly in the know, let me define what hyperthermic conditioning is. Hyperthermic conditioning refers to deliberately acclimating yourself to heat, either independent of, or in conjunction with exercise. I typically refer to hyperthermic conditioning in the context of using the sauna, because this is where most empirical evidence is. But there are other modalities of heat exposure, including hot baths, steam showers, and hot yoga. And they probably create a qualitatively similar type of heat stress, that approximates sauna use, on some level, depending on the intensity.

There are a couple of main mechanisms that hyperthermic conditioning through using the sauna may plausibly effect muscle hypertrophy. First, is through the robust activation of heat shock proteins. I mentioned earlier how heat shock proteins play a role in preventing neurodegenerative diseases, such as Alzheimer’s disease, by helping proteins maintain their proper three dimensional structure. Not only does this have a role in preventing the aggregation of proteins, but it also plays a role in
muscle hypertrophy. Here’s why: Muscle hypertrophy is ultimately the delta between protein degradation and new protein synthesis. When we train for muscle hypertrophy, we often put a lot of thought into how to increase muscle protein synthesis. But if we reduce protein degradation, which is an effect heat shock proteins have, we still are increasing our net protein synthesis by increasing the difference between the amount of new synthesis of muscle protein versus the amount of degradation that is happening.

This type of effect has been shown in rats, where it was shown that a 30 minute heat treatment at a temperature of around 106 degrees Fahrenheit, or 40 degrees Celsius, given every 48 hours over a seven day period, caused a sustained increase in heat shock proteins during that timeframe. Big surprise. But more importantly, this actually correlated with a whopping 30% more muscle regrowth than the control group during the seven days after immobilization. Which is not bad, right?

Putting aside heat shock proteins for a moment, the other way that hyperthermic conditioning through using the sauna could plausibly affect hypertrophy, is by robustly increasing growth hormone. For example, two 20 minute sauna sessions at around 176 degrees Fahrenheit, or 80 degrees Celsius, separated by a 30 minute cooling period, elevated growth hormone levels two-fold over baseline. An even more robust effect was found with men using higher sauna temperatures. For example, two 15 minute sauna sessions at around 212 degrees Fahrenheit, which is around 100 degrees Celsius, separated by a 30 minute cooling period, resulted in a five-fold increase in growth hormone. The boost in growth hormone levels is transient, only last a couple of hours.

To understand why this might be useful, it’s helpful to understand a little bit more about this pathway. Many of the effects of growth hormone are mediated through another hormone, known as IGF-1, or Insulin-like Growth Factor 1. IGF-1 activates another pathway in skeletal muscle known as mTOR, which is responsible for new protein synthesis. Muscle cells require amino acids for both growth and repair, so if we can also plausibly activate mTOR, we’re now sort of completing the circle. With heat shock protein induction, we reduced protein degradation. And through these endocrine effects, actually we are increasing protein synthesis by increasing net protein synthesis. We effectively increase hypertrophy. In fact, if you sort of reverse engineer the habits of body-builders, IGF-1 is actually one of the major pathways most robustly activated by dietary protein intake. So the next time you’re shoveling down protein powder, or essential amino acids like leucine, you can be aware that part of what you’re doing in the first place is robustly activating the production and release of IGF-1, and thus mTOR.

Protein, and specifically essential amino acids, are the major dietary regulators of IGF-1. IGF-1 plays a very important role on muscle growth and repair. For example, mice who have been engineered to express high levels of IGF-1 in their muscle, develop a greater degree and diversity of skeletal muscle hypertrophy. Similar experiments have also shown some promise in combating age-related muscle atrophy, especially the kind found in a mouse model of Duchenne Muscular Dystrophy. I’ve previously talked a little bit about a so-called trade-off when it comes to IGF-1. I’m not going to dive into that yet. We’ll talk a little bit about that more in some of the diet-related questions, but suffice to say, I think that in the context of sufficient physical activity, this so-called trade-off may become a bit less important.

That said, let’s take a minute to talk about the timing of sauna use, in particular, and then we can talk about cold showers or ice baths. I like to sauna after a work-out. First, there’s entirely practical reasons. Doing an intense sauna session prior to working out, can increase exhaustion a little bit too quickly, making it very hard to finish a work-out. Studies have shown that to be the case empirically too. But it’s also intuitively obvious. Adding on top of that, the social aspect of potentially drenching gym equipment in your profuse sweating, makes it a little more sensible to sauna afterwards. But if were not for those reasons in particular, there’s also just the issue of when we most want to boost IGF-1.
To answer that question, it’s helpful to be aware of the mechanism involved in hypertrophy, one of which, in fact, becomes especially relevant when we talk about the effect cold stress has after training in a moment. That mechanism is inflammation. When we train, as a result of mechanical work being done, we produce metabolic byproducts like reactive oxygen species. We also activate inflammatory cytokines. This is actually necessary to activate genetic pathways that contribute to creating more mitochondria, mitochondrial biogenesis, as we talked about earlier, and also plays a role in muscle hypertrophy. In fact, it is inflammation that recruits immune cells, such as macrophages, to skeletal muscle in order to produce IFG-1 that helps induce acute muscle repair.

There has also been some experimental evidence that indicates that these specific immune cells are also likely involved in satellite cell migration, which is a type of muscle stem cell that serve as precursors to actual muscle cells and for which the raw numbers are actually very closely associated with the amount of actual hypertrophy that occurs as a result of strength training. As we can see, inflammation seems to play a pretty important role in the benefits of actual training, and this inflammation, as measured by an inflammatory cytokine known as “IL-6,” actually peaks during training and also right after, but then falls by 50% of its initial peak after the first hour.

In a way, if you’re gonna try to pick a time to increase growth hormone or IFG-1 activity, it makes sense to probably do so in close proximity to when it’s actually peaking. In my mind, I interpret this to be pretty much immediately on the tail end of my workout. This peak of inflammation potentiating IFG-1 synthesis that goes on to play a role in hypertrophy may become especially relevant if we talk about the mixed research surrounding cold stress, such as ice baths or cryotherapy, especially when used in conjunction with working out. Whereas the sauna seems to be just fine, and maybe even beneficial, to do immediately after exercise, cold water immersion and possibly other modalities of cold exposure are a bit more nuanced in the context of strength training.

Specifically, studies have shown mixed results when paired with strength training. For example, one 2015 study in The Journal of Physiology showed that a 10-minute cold water immersion immediately following heavy leg training dramatically decreased hypertrophy by almost 2/3 at a 10-week followup. The active cold treatment group also had a reduction in muscle strength and showed smaller increases in Type II muscle fibers, which are required for very short duration, high-intensity bursts of power. All of this coincided with a reduction in biomarkers that are usually associated with hypertrophy, including the activation of satellite cells.

That’s pretty alarming if you think about it, but maybe it shouldn’t be too surprising. Let’s impact this anti-hypertrophy effect of cold a little bit. One of the reasons ice baths became popular in professional sports, for example, is because cold exposure blunts inflammation, and specifically, it’s been shown to dramatically decrease the production of what are known as the E-2 series prostaglandins, which are one of the factors that have specifically been shown to induce the synthesis of IFG-1 by macrophages, that growth factor mentioned earlier, because it’s important for hypertrophy.

In addition to this cold exposure also causes vasoconstriction, which may acutely prevent immune cells from migrating to places like muscle tissue. Knowing how to reduce inflammation when needed is good, but only if we account for the various downstream effects that this may have. This is not the only study, although it’s the best one, that has shown that cold water immersion done immediately after strength training may blunt some hypertrophy. There are others, but again, all of those studies use cold exposure sometime immediately after strength training. That leaves us with a few open questions, but the most important one is this: Would we still have seen the blunted or reduced hypertrophy effects if cold water immersion was done at literally any point other than immediately after strength training?
I don’t think that based on the current literature we can state this with 100% certainty at this stage, but if we take into the account this potentially inflammatory mediated anabolic window that seems to peak, especially in the first hour post-exercise, then it might help to explain some of the mixed results we see surrounding the use of cold stress with various forms of strength training. Specifically, one 2013 study from The Scandinavian Journal of Medicine & Science in Sport showed the exact opposite effect. This study showed that whole-body cryotherapy for a couple of minutes done one hour after squat jumps and leg curls was actually associated with performance enhancements, which included improvements in power at the start of the squat jump and squat jump workout, and improved pain measures up to 72 hours after the cold treatment.

This isn’t the only study showing an enhancement in performance from cold, either. We see in a study published in PLoS ONE in 2011 that elite runners that engaged in whole-body cryotherapy one hour, 24 hours, or 48 hours after doing some hill sprinting ultimately had a 20% increase in speed and power up to two days later. What’s interesting about the cold is that it may also be conducive to enhancing endurance-related activities in particular. Like fat, whereby cold can increase the number of mitochondria and white adipose tissue in order to transdifferentiate into a brown fat, a form of that that is metabolically active, protective against obesity, and naturally declines with age, muscle also experiences an increase in mitochondria as a consequence of cold exposure.

These mitochondria are the energy-producing machinery of our muscle cells. The density, or number of them, on a per cell basis affects our aerobic capacity. Mitochondria are what give us the ability to use oxygen in order to produce cellular energy. If we have more of them it can be said we may be more adapted to aerobic activity. Okay, all of that said to get to the point and to summarize my thoughts on sauna and cold water immersion or cryotherapy in the context of exercise, I think that sauna use after exercise seems to be a good time to do it, generally speaking.

We need more research, but cryotherapy or cold water immersion may be better to hold out on until at least an hour after training. Finally, the effects of and the appropriateness of cold-related activities on performance may, for a few different reasons, be very dependent on the actual activity we’re actively training for.

Alright, on to the next question.

**Kevin Noonan-Thick @ 1:03:02:**
What are your thoughts on Nootropic cognitive-enhancing supplements? Do you take any yourself? For example, choline, lion’s mane mushroom, etc..

**Rhonda @ 1:03:09:**
I do take some things that might qualify as nootropics. I am, however, very cautious in what I choose to experiment with, at least over the long term. My biggest concern comes down to one simple fact. When we introduce outside compounds that too directly perturb complex biological systems, we open up the possibility of triggering feedback systems that can then result in unintended consequences, such as receptor down regulation. What do I mean by that? For example, let’s say we take a pharmacological drug that inhibits transporters that reuptake and metabolize neurotransmitters. This causes these neurotransmitters to then stay around in the synapse for a longer period of time, exerting more biological effects. This might be perceived as a good thing, but the trade-off is that this causes the receptors that bind this various neurotransmitters, which is how they actually exert their biological effect, to decrease in number.

This is what we call “down regulation.” What happens when you do not take that same drug for a few days? Your baseline level has changed so that in the absence of those drugs that inhibit reuptake, your neurotransmitters will not by themselves exert the same effect that they might have had before
your pharmacological intervention due to the changes in receptor density, or the number of receptors we have for the neurotransmitter to interact with. This is one reason why I prefer to instead focus primarily in the realm of nutrition, since it usually works a little bit more indirectly by providing compounds that are found in and needed by the body and, in the context of this conversation, the brain.

Additionally, when compounds are identified in food, such as xenohormetic compounds, we have a better chance of achieving benefit without deleterious effects because the fact that we’ve likely evolved alongside the presence of that compound. If the compound or compound don’t have that same history, it takes a little bit more scrutiny before we can be sure that there isn’t some sort of significant side effect we just haven’t taken the time to observe yet. Maybe we won’t even know about it for years.

For this reason, I tend to stay away from compounds that are inhibitors of enzymes in the brain, which I know are ubiquitously found in many nootropic stacks. Even though they likely work in the short term, we don’t have any good evidence of what, if any, long term effects that may occur. With that said, there are some nootropics that I have tried. Choline is one of them. Choline can be either used to make acetylcholine, Acetylcholine is a neurotransmitter that connects neurons together, or phosphatidylcholine, or methyl groups. In humans, choline supplements increase choline plasma levels within one hour after ingestion with brain concentrations peaking around two hours until at least up to three hours after ingestion.

Choline effects on the cholinergic peripheral system peaks between one and two hours after ingestion. Choline itself, without forming acetylcholine acts on a subtype of nicotinic receptors called “Alpha-7 nicotinic receptor” that is involved in long-term memory. Acetylcholine also acts on all the nicotinic receptors. Choline does not cause desensitization of this receptor like other agonists do, like nicotine, for example. In fact, supplementing with choline increases this receptor subtype. Certain neurodegenerative disorders like Alzheimer’s disease are linked to decreased acetylcholine, so there has been a lot of interest and investigating whether certain choline supplements and other compounds that affect the cholinergic system can improve cognition and memory in people with cognitive decline and dementia and Alzheimer’s disease, for example.

There are different forms of choline supplements, but I think the choline that is complex to phosphatidylcholine is the best, because it is 12 times more bioavailable and gets into the brain faster. There’s a decent body of evidence that has looked at the effects of various types of choline on brain function. L-Alpha glycerylphosphorylcholine, more commonly known as “Alpha-GPC,” is a naturally occurring form of choline and it’s thought to be a form of choline that crosses the blood-brain barrier quickly. I came across this compound when doing a literature review of various phospholipids and their role in Alzheimer’s disease.

The study that put this on the map was an old study published in 2003 that demonstrated 1,200 milligrams a day, split up over three daily doses, was able to enhance cognitive performance and slow cognitive decline in Alzheimer’s patients. The problem is this study was done in Mexico City 13 years ago. Since then, another study in 2011 attempted to repeat this, but in addition to Alpha-GPC about 10 other compounds were given. It improved cognitive function, but it’s impossible to pinpoint this effect specifically to Alpha-GPC.

Finally, there is yet another interesting study that showed that Alpha-GPC, along with other natural compounds, reduced reaction times and prevented mental exhaustion after intense exercise, an effect that is likely due to the replenishment of choline that is actually temporarily reduced in the brain as a consequence of
endurance exercise such as long runs. I have personally tried Alpha-GPC before at a dose of around 600 mg a day, an amount that is half the dose that was given to the demented patients in Mexico City and I noticed that it did seem to improve my focus and attention. You should always leave a little room for the possibility that there may be a placebo effect. Since it's my antidote a smaller dose of 300 mg didn’t really seem to have much of an effect on me. In general, I do not take Alpha-GPC every day. I take it on rare occasions when I’m doing a lot of writing or some sort of event that I’m speaking at.

There is another popular form of choline called CDP choline, which is an intermediate produced during the generation of phosphatidylcholine from Choline. There are a couple of human studies looking at the effects of CDP choline in cognitive function of healthy young or middle aged adults. Usually in the range of around 1,000 mg a day. The only benefits we’re seeing in young adults that had poor processing speed and verbal memory test at baseline. Strangely, those individuals had performed well at baseline actually had impaired performance after supplementation, which may have to do with genetic variance in the receptor density or something, which just sort of goes to show you how complicated neurobiology is and how even seemingly straightforward relationships can turn out to be not so straightforward.

I have personally tried CDP choline and never really noticed any enhancing effect like I seem to with Alpha-GPC. The other nootropic I’ve tried and used semi-frequently is Yamabushitake extract, which is also more commonly known as Lion's Mane. The main active compound in Lion's Mane is Hericenones, which is found in the fruit body of the mushroom. This compound is capable of activating nerve growth factor. Nerve growth factor is essential for the growth of new neurons and survival of existing neurons. Nerve growth factor acts on the cholinergic neurons in the central nervous system. What got me interested in Lion’s Mane as a nootropic is a Japanese study, which was a double blinded, placebo controlled trial where elderly men with conative decline were given one gram doses of 96% Yamabushitake dry powder three times a day for 16 weeks for a total of three grams a day. Those individuals given the Lion’s Mane extract but not placebo had a significant improvement in cognitive function at weeks 8, 12, and 16 of the trial. The cognitive effect wore off four weeks after discontinuing the treatment suggesting that a continuous intake was necessary to maintain the effect, at least, in cognitively impaired older adults.

Lately, I do use Lion’s Mane extract pretty regularly from Four Sigmatic. They come in packets and each packet contains around 1.5 grams of Lion’s Mane extract from the fruit body only, which would contain Hericenones. I have no affiliation with them. They sent me some free packets a couple of years ago and I liked them so I continue to buy them. When I use them, which only again happens to be during intense writing or creative work, I actually use two packets. A dose that is around three grams of Lion’s Mane extract and the same dose used in the clinical study I mentioned a moment ago out of Japan.

No discussion of nootropics would be complete if I didn’t at least briefly mention two hobby horses of mine: Vitamin D and Omega 3. The effects of both of these are pretty far reaching and extend far, far beyond the realms of just cognition. But, even if one were only concerned with just cognition they would still both have special relevance. First, let’s talk Vitamin D. This one is near and dear to my heart since it was some of my work that actually identified that Vitamin D effects Serotonin production, which I believe has very far, far reaching implications. Not just for adults trying to stay healthy and live optimally but also for neurodevelopmental disorders as well. Where impaired Serotonin production may be particularly important for early brain development where the fetus relies on the mother as it’s source for Vitamin D. A whopping nearly 70% of people in the United States can be classified as Vitamin D insufficient. That includes pregnant women.

Okay, returning to the main topic after that brief digression. Vitamin D is something that should be periodically monitored by a blood test in order to titrate to a dose that’s appropriate. I personally shoot
for 14 to 16 anagrams per milliliter since there have a few all cause mortality studies that seem to indicate that this may be a so-called “sweet spot”. Because Vitamin D can be toxic in the high upper ranges, doing too much can also be problematic. It’s an absolute fact that what may work for one person, especially in terms of dose, may not for another because of the individual variation involved and can affect how deficient you are, including genetic polymorphisms, weight, age, the latitude at which you live, ethnicity, how much time you spend outdoors, whether or not you wear sunscreen, and so many other things. I personally found that the tolerable upper intake level recommended by the Institute of Medicine of just 4,000 IUs usually taken with a Vitamin K2 supplement is actually the amount that lands me right in the middle of that target range. That said, I’m probably not even in the highest risk category for Vitamin D deficiency.

Next, a quick mention for Omega 3. Approximately 8% of the brains weight is actually Omega 3. The number of studies that demonstrate optimizing intake of Omega 3 has some effect cognition or behavior are extremely diverse. Today we’ve talked a little bit about nerve growth factors, so just by way of example, I literally ran across an animal study that showed that supplemental Omega 3 increases nerve growth factor, which increases the enzyme responsible for producing acetylcholine. It also increases vascular epithelial growth factor and brain drive neurotropic factor and has generally been shown to improve cognition. I’ll talk a little bit more about this in another question.

Getting past all the usual suspects on our list of nootropics here, the other nootropic that I actually take frequently is Sulforaphane. It’s not even usually considered a nootropic by most people but I think it has potential to be considered at least a mild nootropic for a variety of reasons. One of the best reasons to make this argument is the fact that Sulforaphane crosses the blood-brain barrier, at least in mice. This is the first criteria that a substance must meet in order for there to be a compelling argument that it someone exerts effects on the brain. But, in addition to that, it also effects the activities of the immune system, which is now known to effect the brain through a series of the lymphatic vessels.

This new understanding of the immune system’s ability to interact with the brain also helps to explain why manipulating levels of the systemic implementation has, in clinical trials, been shown to effect feelings of depression. Either inducing depression in the presence of an artificial increase in activity in the immune system by injecting things like interferons into human trial participants or reducing depression caused by this artificial increase in inflammation through the co-administration of natural anti-inflammatory such as Eicosapentaenoic acid, better known as the Omega 3 Fatty Acid EPA. In addition to Sulforaphane crossing the blood-brain barrier in mice, the compound has been shown in a couple of randomized double blinded placebo controlled studies in humans, to have one sort of effect or another on brain and behavior.

For example, treatment with Sulforaphane extracted from broccoli sprouts from doses ranging from around 9 mg to 25 mg, which is an amount that might be found in around 65 grams of fresh broccoli sprouts on the high end, was able to improve autistic behavior check list scores by 34% and significantly improved social interaction, abnormal behavior and verbal communication in young men with autism spectrum disorder. Similarly, some measurable effects have been shown in a small trial of people with schizophrenia. The fact that Sulforaphane is exhibiting clear effects on the brain and behavior of people such as those with autism spectrum disorder, hints that it might continue to show promise in other areas of cognition too. This is because animal studies have really shown a diversity of very interesting effects on the brain that are really just waiting to be replicated in humans.

For example, Sulforaphane has been shown to improve spacial working memory and short term memory in mice in the context of conditions that can affect memory in a deleterious way such as Alzheimer’s disease. It has been shown to increase neurite outgrowth, which is how damaged neurons and synapsis repair themselves after damage from traumatic brain injury. The effect of
Sulforaphane at a rodent model of Alzheimer’s disease in some respects, is particularly interesting because if we go back to our conversation a little bit earlier about the potential choline may have for mitigating some of the negative affects of this disorder, Sulforaphane has also been shown to significantly reduce memory impairment that has been experimentally induced by a drug that works specifically by interfering with the affects of acetylcholine in the nervous system, a drug known as Scopolamine. Sulforaphane was, in this animal trial, to which I’m referring to, able to improve the cholinergic system by increasing acetylcholine levels, decreasing Acetylcholinesterase activity and increasing choline acetyltransferase which is the enzyme responsible for synthesizing acetylcholine in the hippocampus and frontal cortex. This ties in nicely with some of our discussion earlier about the potential importance of choline system in cognition.

Finally, Sulforaphane has been shown to have a positive effect on mood and alleviated depressive symptoms and anxiety as effectively as the anti-depressant Prozac in a mouse model of depression. I understand that there is at least one trial currently in the beginning stages looking to confirm this effect in humans as well. If you consider that the variety of brain and other behavioral effects demonstrated already in humans, I am optimistically hoping that some of the groups out there working on these questions will have something good to show for it in the near future.

If you’re looking to supplement Sulforaphane there is a few options available. First of all, the most confusing thing that is necessary to understand when gaging the various supplements for usefulness is that Sulforaphane is made from a precursor known as glucoraphanin. Many supplements on the market are actually just glucoraphanin. You know this because it either says glucoraphanin on the bottle or it says “Sulforaphane Glucosinolates” which is actually somewhat confusingly just another name for glucoraphanin. Then, there are a few supplements on the market that has glucoraphanin and the enzyme needed to convert it into Sulforaphane, an enzyme called myrosinase. One example of this combination is a product known as Avmocol.

Finally, there is an actual stabilized Sulforaphane. This includes a French product that hasn’t been introduced to the US yet, known as Prostophane. These three categories of products that I’ve mentioned have very, very large differences in terms of the bioavailability. Around 10% on average for glucoraphanin by itself, 40% for the glucoraphanin and myrosinase combination, and then around 70% for the stabilized Sulforaphane. By the way, I have no affiliation with any of those supplement brands I just mentioned. The dosage range that strikes me as particularly interesting because they have shown up often in clinical trials range between 30 and 60 mg of Sulforaphane a day. These doses however, actually make most of the supplements out there, somewhat costly in my opinion.

The good news is that many studies seem to be showing promise even at a lower dose, and if you’re doing an N of 1 experiment, it may be useful to be able to get a reliable product like the ones I just mentioned. That said, this cost factor has been a big reason for why I’ve simply taken up growing broccoli sprouts at home, which is extremely inexpensive. The main challenge being keeping a clean environment with little possibility of contamination from pathogenic bacteria, which can definitely happen.

Some estimates land fresh broccoli sprouts at a concentration of about one gram fresh weight to about 0.45 milligrams of Sulforaphane, but it depends on seed quality and genetic background, the age of the sprouts, how you consume the sprouts, whether you froze them and threw them immediately in to a blender, which is what I tend to do and tends to increase the amount of Sulforaphane derived or if you instead just chew them up the good old fashioned way.

The drawback to using sprouts is that dosing them becomes tricky. The fact of the matter is that I found my own personal digestion is probably a more reliable source of feedback than trying to work out the dosage math. That’s kind of embarrassingly imprecise, I have to admit. But it just comes down
to the fact that there’s a tremendous number of variables that can influence how much Sulforaphane in a given dose of broccoli sprouts, and on top of that, what an appropriate amount of Sulforaphane to even supplement is.

I’ve been known to consume up to four ounces of broccoli sprouts a few times a week and I will likely continue for the foreseeable future. That said, there are concerns that isothiocyanates like Sulforaphane may reduce iodine uptake by the thyroid gland. While right now I don’t think the evidence is especially strong that this is cause for great concern unless a person is iodine deficient, which is an uncommon deficiency. It may be prudent to exercise some degree of caution. Some of the effects of these compounds present in cruciferous vegetables and broccoli sprouts in particular are persistent for several days, so you don’t necessarily need to take an extreme approach in order to reap some benefit. Again, run it by your doctor, et cetera, et cetera.

Okay, on to the next question which is somewhat related.

**Jez Theory @ 1:19:13:**
Is one able to cold press juice broccoli sprouts and still receive high amounts of Sulforaphane from ingesting it this way?

**Rhonda @ 1:19:19:**
To answer your question, yes, you should be able to cold press broccoli sprouts and make a juice. The myrosinase enzyme, which again is needed to activate Sulforaphane begins to get activated once you cold press the sprouts because by cold pressing you are breaking open plant cell walls and causing the mixing of glucoraphanin in the plant with the my myrosinase enzyme which is stored away in specialized vacuoles. This mixing then allows Sulforaphane to form. Ultimately, you would not be getting the same dietary fiber which is why I prefer to blend things rather than juice them, but the Sulforaphane would be concentrated and since it may be less aversive, it seems like an interesting option.

**William McGrath @ 1:19:57:**
Besides a low-carb diet which reduces inflammation, what is the most effective non-pharmaceutical pain reliever for arthritis sport injury sufferers?

**Rhonda @ 1:20:07:**
Okay, William’s question here is an interesting one. The reason for that is because of the fact that many NSAIDs, as in Non-Steroidal Anti-Inflammatory Drugs, which are often used for mild pain relief are actually not especially safe to take on a daily basis. This is even more true of people that tend to take them in larger than recommended doses and is why the FDA recently strengthened their warning that Non-Steroidal Anti-Inflammatory Drugs again, known as NSAIDs, with the exception to aspirin, significantly increase the risk of heart attack or stroke even with short term use.

What these NSAIDs, including ibuprofen, that cause this increased risk have in common is that they all inhibit COX-2, an enzyme involved in inflammation and pain. There are a few fundamental mechanisms that increase the risk of heart attack and stroke. First, NSAIDs that inhibit COX-2 inhibit the production of a molecule called prostacyclin, which is produced by COX-2 and relaxes blood vessels and sort of unglues platelets. Second, they inhibit the production of nitric oxide which is also regulated by COX-2 to some degree and needed for proper vascular function.

Finally, one more mechanism by which chronic NSAIDs may increase heart attack risk is through the disruption of mitochondrial function in heart cells. Knowing these risks sort of motivated me to put avoiding the use of NSAIDs such as ibuprofen, Aleve and Naproxen, just to name a few, at a generally
higher priority than it may have been previously for me on a personal level.

As an alternative to the use of NSAIDs, however, I found that curcumin is actually very helpful. Curcumin is sort of an interesting compound, it exhibits a pretty diverse array of potentially beneficial properties, but as a xenobiotic that the body actively makes an effort to get rid of, its activity can be limited unless care is taken to try to make it more bio-available. There’s a few different formulations that attempt to do that, but the one that I found most interesting is a formulation known as meriva which has been shown to exhibit certain pain-relieving properties.

Meriva, a form which is available from a few well-known brands, consists of a phospho-lipid complex with 20% curcumin dispersed throughout the phospho-lipid. This helps to get the curcumin past the stomach lining and from being cleared by enzymes in the liver too rapidly. A few clinical trials have looked in to the effects of meriva on pain and inflammation. For example, runners that were given one gram of meriva twice a day found that it reduced delayed onset muscle soreness by about two fold and caused a sixty percent decrease in markers of muscle damage and inflammation, specifically IL-8 and C-reactive protein after running until exhaustion downhill.

There have also been a couple of other clinical studies published looking at the efficacy of one gram of meriva a day in reducing symptoms of osteoarthritis and increasing mobility. After three months of treatment, people with osteoarthritis and joint pain had a four-fold increase in mobility. C-reactive protein decreased by 67% and they had around a 58% reduction arthritis symptoms including pain. There was a similar study that included a longer followup which was eight months and found similar increases in mobility and reductions in inflammation and pain.

What’s interesting is that meriva has also been compared directly to common pain relievers in terms of ability to give pain relief in a small clinical study which found that people taking two grams of meriva a day experienced pain relief equivalent to one gram of acetaminophen or Tylenol, an amount by the way which has been associated with liver damage in conjunction with long-term use. Another study also found that two grams a day of meriva of six weeks was equivalent to around 800 milligrams a day of ibuprofen for pain relief.

The study found that the analgesic effect of curcumin lasted for approximately four hours, and a second dose, administered around six to twelve hours after the first dose, was necessary for controlling pain. On the whole, curcumin is also a surprisingly safe compound. One study out of Japan, published in 2011 in the Journal of Cancer, Chemotherapy and Pharmacology showed that curcumin in amounts as high as even 8 grams per day for up to 14 days at a time was safe and tolerable. These were cancer patients and this wasn’t a curcumin formulation. However, seeing how well tolerated very high clinical doses are generally, for occasional pain relief I tend to be pretty liberal with popping a few grams of curcumin in the form of meriva throughout the day.

There’s a few popular brands offering meriva or sometimes simply marketed as phytosomal curcumin. Right now, the one I’m taking is the product from Thorne. Again, like every other supplement brand I’ve ever mentioned on this podcast, no affiliation whatsoever. Since I’ve sort of put curcumin and meriva out there specifically as a nice NSAID alternative, I need to address the gorilla in the room. Quite recently, a very sensational scientific review was making the rounds claiming that curcumin basically had no health benefits and that because of a quirk of an investigative method used to look at protein-protein interactions that may be subject to some degree of imprecision because of how it can behave in a manner that produces background noise, all curcumin research up until this point should be considered more or less null and void.

That was sort of the crux of the argument and a handful of unsuccessful trials were also cited to support, in my opinion, poorly, this argument. The problem is that the specific quirk of the research
The assay being discussed is rendered absolutely and completely irrelevant in the context of the massive body of clinical curcumin research done in humans that has shown the compound is exceedingly versatile. Moreover, even if we put aside the enormous amount of clinical research, it’s been demonstrated that curcumin works in a manner that, at the cellular level, exhibits broad changes in gene expression. Something that cannot be dismissed simply because one specific assay does not even measure gene expression exhibits some degree of artifact.

If you couldn’t tell, I’m not a big fan of this particular review article published and may even feel a little bit of desire to sort of heap mountains of admonishment on the authors. That said, I will conceded that there is a need for more double-blinded placebo-controlled studies on curcumin and specifically the meriva phytosomal complex of curcumin, which does significantly bypass the bio-availability issues associated with the compound which has also been the source of some criticism. I am, however, very very optimistic about future research surrounding curcumin in general and meriva in particular.

Finally, one more thing I should bring up in the context of joint health is hydrolyzed collagen powder. What first sparked my interest in this was a study shared with me by a colleague that established the fact that, at least in an animal model, hydrolyzed collagen supplemented in the diet did find its way into the cartilage. Sometimes the nutrition relationships don’t tend to be so straight-forward as it may seem intuitive on the surface. Cholesterol is a great example of this. We actually create cholesterol and the consumption of dietary cholesterol is not necessarily strictly a cause of high cholesterol as we think of it.

In the case of hydrolyzed collagen powder, however, the relationship does seem to be straightforward. The study to which I’m referring to used radio-labeled collagen which allowed the scientists that were doing the investigation to see what happened after the hydrolyzed collagen was consumed. They saw two things happened: That the collagen ended up being broken down into amino acids, but more importantly that some of it was also absorbed intact and shown to accumulate in cartilage long-term, which is pretty cool.

So, little bit about collagen. Collagen is an important component of tendons, ligaments, cartilage and skin but also an important component of gums, muscle and the gut. About 33% of collagen is made from proline and glycine, which most dietary sources are not especially high in. Proline may also have a special place in wound-healing as well. The first 10 days after a wound occurs, proline levels at the site of the wound are 50% higher than plasma, which might suggest that proline is actively being transported to the site of the wound and probably a necessary part of the wound healing process. As an interesting aside, proline can also be used by the mitochondria to produce energy. It is converted to glutamate and alpha-ketoglutarate and used by mitochondria to produce energy. The reason this pathway exists is because during conditions when glucose levels drop, proline is actually released from connective tissue to be used to make energy.

I’ve heard Tim mention Great Lakes brand hydrolyzed collagen powder which happens to be the same brand that I’ve used for the last few years. It does not have any particularly strong taste so it can pretty much be added to anything, including a beverage like tea or coffee or pretty much anything else.

Next question…

Guy Fashiona @ 1:27:58:
What brands can we trust for dietary supplement brands? How can we find trustworthy brands?

Rhonda @ 1:28:03:
This is a great question and an important question because the FDA does not require dietary supplements to be tested before they are marketed. As a result, products may contain unlisted ingredients and contaminants. Some products have even tested positive for prescription drugs not listed on the label. Many supplements do not contain what they are actually supposed to contain and instead may be a combination of fillers like cloverleaf.

There’s a few things you can do. One thing you can do is make sure the product is certified by NSF International which stands for the National Sanitary Foundation, which independently tests and certifies dietary supplements and nutritional products and ensures that they do not contain undeclared ingredients or contaminates. To earn NSF dietary supplement certification, products must undergo rigorous testing and inspection. The standard requires label claim testing verification and contaminate review and a facility audit. You can look for products containing the NSF label by searching your dietary supplements online product database found at info.NSF.org/certified/dietary.

I usually will just type in the manufacturer name, for example Nordic Naturals or I will type in a specific product that I’m looking for like meriva. The drawback to relying on this particular certification is that their database can be pretty restrictive. While being in the NSF database is a good sign, not being in it strictly is not a deal-breaker.

Here’s another option. Look for products that are USP certified. The USP, which stands for the United States Pharmacopeial Convention is a scientific nonprofit organization that sets standards for the quality and purity of dietary supplements that are manufactured, distributed and consumed worldwide. In the United States, the FTI relies on standards the USP has developed so you can just go to their website, which is usp.org and click verified supplements to see a list of brands and products within brands that the USP verifies.

In addition to the USP and NSF, there are independent companies that also test supplements and then rank those products and provide reports to customers, sometimes for a cost. However, I found these to be either misleading or sometimes coming to conclusions that give me pause. Doing the type of validation necessary, may require technical skills that might be executed poorly or sometimes just plain weird ranking criteria may be at play. For that reason, I don’t trust these independent ranking companies as much but absent other information it may still be better than just blindly grabbing something off the supermarket shelf.

On to the next question.

James Enright @ 1:30:24:
Rhonda, what are your core supplements and core foods for health or brain and daily, weekly health routine.

Rhonda @ 1:30:30:
Okay, first my perspective on food. I think it’s helpful to understand what I’m about to say because it to a great degree informs other opinions I may have about different approaches on diet. Food is in a big way, a vehicle to deliver micronutrients or compounds that are beneficial to health but not just micronutrients. Other compounds such as polyphenols and other xenohormetic compounds as well.

Approximately 22% of all the genes that encode for enzymes require micronutrients as cofactors, which means that the machinery doing work inside your cells actually needs micronutrients to function properly. These are enzymes that are involved in metabolism, neurotransmitter production, repairing damage. Basically, everything that you want to be working optimally needs more than just energy. It needs micronutrients. It needs minerals like magnesium which we find particularly abundant in green, leafy vegetables because it’s at the center of our chlorophyll molecule.
Micronutrients are about 30 to 40 essential vitamins, minerals, fatty acids and amino acids that we must get from our diet because they are essential for life. That means without them, you die. Recommended daily intakes of these vitamins and minerals have been set to ensure we get adequate amounts of them but we really do not know how much of these micronutrients we need to stave off aging as best we can. If the proteins in your body start operating more poorly; let’s say they stop repairing DNA damage quite as well or they aren’t cleaning up amyloid beta as well or any of the almost infinite number of other potentially affected processes, you might not notice this as a disease. Instead, we might just call it aging.

It’s important therefore to keep in mind that preventing aging is not the goal of the RDA. It is to prevent easily observable, obvious diseases of deficiency and figuring out what those optimal levels are for this more subtle and widespread thing we call aging is a bit more challenging. Adding some complication to this is the fact that this optimal level is probably not the same for everyone. Perhaps is the function of the agricultural practices or constraints placed by food dictated partly by the geographic area our ancestors resided in. There’s a great degree of genetic influence in how much we absorb, metabolize and use micronutrients.

Understanding just some of these interactions between genetic polymorphisms and food is an area of study known as nutrigenomics. It is fascinatingly complex and there’s a great deal of opportunity for understandings in this area to improve the human condition. As an extension of this fact, I think the specifics of diet will eventually be better understood to not be a one size fits all. That said, I found some things that have worked for me personally and some of them are probably still relatively generalizable enough as to be useful for others. Here they are.

I know most people are focused on macronutrients. That makes sense in certain contexts so long as it isn’t the complete and utter exclusion of all else. Instead, I just mainly follow rule of thumb that I should eliminate refined carbohydrates in particular and refined sugar especially and then I try to eat with a special attention to nutrient density. I often enjoy wedging a smoothie in, sometimes as a partial meal substitute that is particular focused on cramming in some extra servings of some fruits and vegetables. I consider this to be a pretty important lifestyle hack that can sort of just be thrown on top of whatever else you’re doing and it will help recalibrate a lot of important health parameters in a very useful way.

As for actual meals, I always eat breakfast and as mentioned earlier I practice time-restricted eating so that all of my meals are consumed earlier in the day and within a sensible time window. While some degree of diversity is ideal, for breakfast I often do rotate between a few reliable meals. First, one of the main meals that I eat for breakfast are scrambled eggs, usually topped with tomatillo salsa which helps make the eggs less boring. Sauteed kale and garlic topped with olive oil, salt and mustard powder and a grapefruit on the side.

I scramble my eggs and saute my kale in avocado oil because it is high in monounsaturated fat and low in polyunsaturated fat. I tend to stay away from cooking oils that are high in polyunsaturated fat because it’s so easily oxidized and can be very harmful consuming oxidized fat. The avocado oil also has a very high smoke point so it can withstand some heat. The reason why I saute the kale is very practical. It’s easier to eat. I add mustard powder to the kale as well as other cruciferous vegetables I may cook with other meals to facilitate the conversion of precursors into isothiocyanates like the Sulforaphane obtained from broccoli.

One of the main reason I eat eggs, is that eggs provide me with choline. We already talked about how choline affects the acetylcholine levels but it also serves as a methylation source and thus affects global epigenetics, which is a way of changing the activation or deactivation of various genes. One
extremely common genetic polymorphism is eno gene that encodes for an enzyme that catalyzes the synthesis of phosphatidylcholine and thus choline. Postmenopausal women in particular with this polymorphism need to increase their dietary intake of choline. Eggs happen to be a great source of choline. I spread some tomatillo sauce on top of my eggs because I like it foremost, but it helps that it's also high in tomatidine, which has been shown to boost muscle mass in mice by reducing the activity of a gene called ATF4 known for inhibiting muscle protein synthesis. In addition to the Sulforaphane and micronutrients another reason why I like kale a lot is because it is one of the vegetables that is highest in lutein and zeaxanthin, two carotenoids that most people associate with eye health because they accumulate in the rods and cones of the eye and protect them from singlet oxygen which is generated from blue light and can be very damaging to the eye.

Recently there have been a fair amount of studies published showing that these carotenoids accumulate in large quantities in the brain. I mean, what are they doing in the brain? There is no singlet oxygen from light exposure in the brain. Plasma and brain levels of lutein turn out to be associated with a higher volume of gray matter in the brain and improved crystallized intelligence in the elderly, which is the ability to use the skills and knowledge that one has acquired over a lifetime.

A double-blinded randomized control trial showed that lutein and zeaxanthin supplementation, including 8 milligrams of lutein and 26 milligrams of zeaxanthin improved neuroprocessing speed time in young individuals. Decreased processing speed is a major hallmark of cognitive decline. Lutein and zeaxanthin have been shown to improve memory recall while using less brain power in older individuals. Something that's known as neural efficiency. An aging brain has to use more and more energy to maintain normal brain functions and so neural efficiency is said to decline.

The icing on the cake is that eating eggs with a salad increased the absorption of carotenoids like lutein and zeaxanthin which are found in dark green leafy vegetables, particularly in kale by up to four fold which is one reason why I like to have a side of eggs with my kale. The grapefruit provides me with ferulic acid, a potent molecule that inhibits a pro-inflammatory cytokine TNF alpha and E2 series prostaglandins, also inflammatory. Ferulic acid has also been shown to be anti-carcinogenic. The grapefruit is also a source of naringin, which has a variety of very interesting properties.

Another breakfast that I have is a nut and berry cereal with hydrolyzed collagen powder and coconut milk. My cereal also contains an array of chopped nuts, including walnuts, pecans and macadamia nuts. The nuts provide me with a host of micronutrients including magnesium, calcium, zinc and a modest amount of protein and the omega 3 fatty acid ALA, which is not meant to be a substitute for the marine omega-3's. Along with the nuts, I often toss in some blueberries for pterostilbene, which is a plant compound present in blueberries that is chemically related to resveratrol except it's about four times more bioavailable than resveratrol. Test tube and rodent studies also suggest that pterostilbene is more potent than resveratrol when it comes to improving brain function, warding off various types of cancer and preventing heart disease. The blueberries are also very high in anthocyanins, which evidence suggests can lower DNA damage. DNA damage has been shown to cause cancer and lead to depletion of stem cells pools, so it also plays an important role in the aging process as well.

I also like to add some pomegranate into the cereal. One of the compounds in pomegranate is transformed by gut microbes into a molecule called urolithin A which causes mitophagy, a process important for the renewal of mitochondria mentioned in an earlier question. Urolithin A has shown some pretty spectacular things in research on other organisms, including improving muscle function and endurance by up to 42% in mice and increasing life span by more than 45% in worms.

Finally, as a finishing touch to the breakfast cereal, I often throw in some flax seeds for more of the
Omega-3 ALA and fiber. Some unsweetened coconut milk, which contains some medium chain triglycerides. Some raw cacao nibs which has a plethora of polyphenols, including EGCG, which activate many antioxidant genes and have been shown to kill cancer cells. Occasionally some almond butter for some protein and sort of to make it delicious. Hydrolyzed collagen powder which provides me with proline, as I mentioned earlier is important for wound healing and also has glycine which is an important inhibitory neuro transmitter.

One reason I use coconut milk as opposed to regular milk, or dairy milk, is because dairy milk contains salivary proteins, which bind to anthocyanins and polyphenols and limits their bioavailability. Sometimes I’ll also throw in the cereal concoction some yogurt and possibly a packet of the probiotic VSL#3 which contains 450 billion probiotic cells per serving.

Okay, let’s talk lunch. This is the where the smoothie often comes in. As a base, it can often contain kale or frozen berries, an avocado, hydrolyzed collagen powder and water. Then a number of variations on top of these. I have a couple of popular smoothie recipes that are floating around on the internet and a person can find them by searching ‘Rhonda Patrick smoothie’. As a breakfast or lunch I occasionally have an avocado topped with fresh lemon juice and wild Alaskan salmon roe possibly accompanied by a side of sauerkraut. This is another variation I sometimes do.

Avocados are really high in potassium and provide all the various forms of Vitamin E. In other words both tocopherols and tocotrienols, something it’s good to get a balance of by a diet instead of only one form as from some supplements. The avocado is also a great source of mono and saturated fats. Salmon or caviar is a very good source of omega-3 fatty acids. Approximately 438 milligrams of EPA and 514 milligrams of DHA per ounce. I particularly like this source of omega-3 because the fats are in phospholipid form, which has greater bio-availability to be transported into the brain via the mfsd2a transporter. This is a form that is best taken up by the brain, including the developing brain.

It also has a good amount of astaxanthin which protects the omega-3’s from oxidation and does the same for neurons. Studies looking at DHA and EPA levels in red blood cells have shown a correlation between higher omega-3 status and having a two centimeter larger brain volume. Getting omega-3 into and keeping it in the brain is definitely a brain aging priority for me.

The sauerkraut is a good source of fermentable fiber also known as prebiotics that is fuel for the commensal gut bacteria so that they are able to produce compounds such as short chain fatty acids that feed more commensal gut bacteria and also feed gut epithelial cells which are required to make the gut barrier. These compounds produced by the gut bacteria serve as signaling molecules to make specific types of immune cells, an important indirect role that fiber also has in the diet that helps influence it's immune activities. The sauerkraut itself contains various probiotics as well. Mostly the lactobacillus strains which are beneficial lactic acid producing bacteria which have recently been suggested to possibly play a role in cancer prevention.

For dinner, I usually have some cooked vegetables, like sauteed spinach, which is very high in folate, as are all greens. Folate provides an important precursor that makes a DNA nucleotide called thymine. Every time you repair a damaged cell or make a new cell in your liver, muscle, brain, etcetera, you need to make new DNA which means you need folate. Folate was also very recently shown to increase the growth of stem cells, which is important because stem cells pools deplete with age and are a major cause of organ aging and dysfunction. Folate has also recently been shown to play a role in protecting telomeres, the tiny caps on the ends of chromosomes that are a biomarker for age because they get shorter every year. A recent study showed that mothers with the highest folate levels had newborns with telomeres 10% longer and every 10 nanogram per milliliter increase in serum folate levels, newborns had a 5.8% increase in telomere length which actually suggests that maternal nutrition may actually play a role in determining the length of telomeres that we have to start
Sometimes instead I’ll have some collard greens, bok choy, broccoli, brussel sprouts, parsnips. Of course, since all of these are cruciferous vegetables, I usually have them with mustard powder sprinkled on top since that provides an additional source of myrosinase. Cruciferous vegetables in general are among my favorite types of vegetables to eat because they contain isothiocyanates. Associative studies have shown that the top 20% of consumers of cruciferous vegetables have a 22% reduction in all caused mortality. Or instead, I’ll have a big salad full of lots of different greens which provide me with a cornucopia of micronutrients, including folate, magnesium, calcium, Vitamin K1, lutein, zeaxanthin and sulfoquinovose, which is a prebiotic that feeds beneficial bacteria in gut and is found in green vegetables.

By the way, salmon has a very low mercury content with only two micrograms per four ounces cooked. EPA, as I mentioned earlier in another question, is a powerful antiinflammatory fatty acid that has been shown to lower brain inflammation. As I mentioned earlier also, DHA is a critical component of all cell membranes that makes up 30% of the fatty acids in the brain, or about 8% of the total weight. Omega-3 fatty acids have recently been shown to positively change gene expression in several brain regions and also generally shown to stave off brain aging. But also important is just not dying. People with the highest Omega-3 fatty acid intake have been associated with having a 9% reduced risk of all caused mortality and for each 1% increment in Omega-3 fatty acids in their blood, there was an associated 20% decrease in risk for all caused mortality.

Another protein that I rotate for dinner is chicken legs from pasture raised chicken, which I like because in addition to the protein, I also get some cartilage which is high in collagen, proline, glycine, which is interesting for reasons I already discussed earlier. Sometimes I throw the chicken bones in some water with some spices and vegetables to make chicken bone soup which gives me all the same goodies I talked about with hydrolyzed collagen powder. Chicken is also very high in selenium, which is a co-factor for all glutathione related enzymes and it’s needed for them to work. It also has a modest amount of zinc, copper and iron.

Finally I also sometimes have a grass-fed filet steak a few times per month which is a good source of Vitamin B-12, iron and zinc. Approximately 16% of all menstruating women are actually iron deficient. For the vegetarians out there, it has been recommended to take in about twice the RDA for iron, since iron, which is found to phytate in plant sources is about two times less bioavailable. As I mentioned earlier, I also make a broccoli sprout smoothie usually consisting of anywhere between 100 grams fresh weight, or sometimes a bit less of frozen, since freezing them actually increases the sulforaphane content. I do this about three times a week usually.

I talked about some of the interesting effects that sulforaphane has on the brain, but I actually think that this might be, in some respects, a compound versatile enough to actually possibly even slow the aging process in general. We’ll need more studies to establish that fact, but I’m optimistic because of the already numerous associative studies that have shown in humans that high intake of cruciferous vegetables have about a 40% or 50% reduction in multiple types of cancer, ranging from bladder to breast, prostate to lung cancer. But that’s the associative studies. What gets me really excited are the clinical studies on sulforaphane that show some pretty amazing things.

For example, men with prostate cancer that were given 60 milligrams of stabilized sulforaphane per day, resulted in slowing the doubling rate of a cancer biomarker known as prostate specific antigen, or PSA, by 86% compared to placebo, which is pretty amazing. Another really cool thing about sulforaphane is that it activates detoxification enzymes and causes our bodies to excrete carcinogenic compounds. For example, people that were given a daily broccoli sprout beverage containing around 262 milligrams of glucoraphanin, the precursor to sulforaphane, plus an additional 7 milligrams of
sulforaphane, increased the rate of excretion of benzene by about 61% and acrolein by 23% beginning on the first day of consuming the drink and continuing throughout the entire 12 week period of the trial.

Benzene is a nasty carcinogen that is known to cause cancer in humans and animals, particularly leukemia. Some of the major sources of benzene that people are exposed to are from automobile exhaust fumes and air pollution and cigarette smoke. Acrolein in found in most of the major sources already mentioned for benzene, including air pollution, but it is also formed when carbohydrates, proteins and fats are heated, so we get exposed to a fair amount of acrolein from cooking our foods.

Sulforaphane has also been shown to improve markers are cardiovascular healthy. For example, people with Type 2 diabetes, given 10 grams of broccoli sprout powder per day for four weeks, lower their serum triglycerides by around 19% and lowered their oxidized LDL to total LDL cholesterol ratio by around 14% and reduced their atherogenic index by 50%, which is a measure of cardiovascular disease that incorporates a wide variety of factors. Again, pretty amazing results for not changing anything else in the diet or lifestyle except adding sulforaphane to the diet. Finally, sulforaphane also lowered inflammatory biomarkers in people with Type 2 diabetes who were given broccoli sprout powder containing 40 milligrams of sulforaphane for four weeks reducing TNF alpha by 11%, lowering C-reactive protein by 16%. I can tell you from my own experience being involved in clinical trials with unhealthy people with metabolic syndrome, it is very hard to get drops in biomarkers of inflammation after just one month with no other dietary or lifestyle changes.

The fact that sulforaphane has such a profound impact on lowering inflammation is of great interest to me because it is now believed that suppression of inflammation is the single most important driver of successful longevity and that this actually increases importance with advancing age. I don’t just mean living long either, but also a strong association with capability, meaning the ability to adequately perform activities of daily living as well as cognition in all major age groups including elderly, centenarians which are 100 years old, semi- super centenarians which are 105 to 109 years old, and super centenarians, which are 110 years old and greater.

In fact, inflammation has been shown to be the single most important predictor of cognitive abilities surpassing it’s predictability only by a person’s chronological age itself.

This Japanese study that I’m referring to was a bit of a surprise to me because several different biomarkers were looked at including blood glucose levels, insulin sensitivity, and even telomere length, but none of those predicted successful aging in each age group up to the super centenarians. Low inflammation was the only predictor of successful aging in all age groups. Now you know in a more comprehensive way for those of you that have heard me mention sulforaphane a few times already what’s behind some of that.

To sort of dive into some of the supplements that I happen to be taking at this moment, I’m taking a multivitamin called One by a company called Pure Encapsulations. People ask about the brand so I’m sharing that. I like this multivitamin because it covers some of the basis for various micronutrients that I just talked about, and also interestingly has some trace elements including boron, which has been shown to reduce double stranded breaks, accelerate wound healing, significantly increased mean plasma free testosterone in a small trial in men, and increased the half life of vitamin D. Boron is definitely sort of interesting and has caught my attention recently.

The multivitamin I just mentioned also has 2,000 IU of vitamin D. If I’m getting a lot of sunshine I might leave it at that. More often, I’ll add an additional 2,000 IU of vitamin D. I also usually take around 135 milligrams of magnesium citrate malate from Thorne. I usually try to get most of my magnesium from foods since it’s a measure of how many greens I’m getting. Even with my modest
supplementation I get a good bit, but around 45% of the US population does not have an adequate intake of magnesium, which for adults is roughly around 400 milligrams a day.

For a little perspective, one cup of cooked spinach contains around 156 milligrams. I'll save a little bit magnesium for a later discussion in a few moments, but it's really important.

Another supplement that I take every other day is vitamin K2, which is found in fermented foods, particularly natto, but also an organ meat. This is thought to be a good one to take with vitamin D since both are involved in calcium homeostasis. I usually take around 100 micrograms in the form of menaquinone, otherwise known as MK4.

Lastly is the part of the core supplements I take daily is fish oil, which I actually take a lot of. I usually take two omega 3 phospholipid gel capsules by Nordic Naturals, which is omega 3 isolated from herring row because the DHA is in a specific form known as lysophosphatidylcholine DHA. This form has been shown to be taken up by the brain best by the MFSD2A transporter. This is also the form you can get if you get krill oil as well.

In addition to this, I also take four capsules of ProMega 2,000 fish oil by Nordic Naturals. One of the key things to know about fish oil is that it's one of the supplements that you really need to watch out for quality on. It should be kept refrigerated and you ideally want a brand that's trustworthy and not arriving too already oxidized. In fact, varying degrees of fish oil oxidation is of great concern to the scientific community, and scientific study design when it comes to fish oil because if researchers fail to ensure the fish oil that they use in their study as high quality weird mixed results surrounding supplementation can very well be expected. This is a characteristic that is sort of unique to fish oil unfortunately.

What I like about Nordic Naturals is that they are NSF certified, which is one of the certifications for quality I mentioned when responding to an earlier question. In addition to that, my understanding from having inquired is that they also isolate their fish oil under nitrogen conditions, meaning no oxygen present, so as to minimize any oxidation during the isolation process. They are by no means the only option out there, but I felt pretty good about using their products and I've used them for many years.

A little bit more about the fish oil habit. I've taken fish oil daily for about nine years now. Some of the studies that have kept me taking fish oil have to do in particular with brain health. For example, supplemental fish oil in the form of DHA, two grams a day, has been shown to increase the clearance of amyloid plaques in people with mild cognitive impairment after four to 17 months. I also take it because it has been shown to slow the process in general. For example, supplemental fish oil of 2.5 grams a day has been shown to slow telomere shortening, again, which is a biomarker for aging, and lowers biomarkers of oxidation in blood cells in overweight, middle age and older adults.

In another study supplemental fish oil of one gram a day increased muscle mass, hand grip strength, upper and lower body muscle strength and leg power in older women after six months. Another study showed that high dose supplemental fish oil of three grams a day increased resting metabolic rate by 14%, energy expenditure during exercise by 10%, and the rate of fat oxidation during rest by 19%, and during exercise by 27%. It lowered triglyceride levels by 29% and increased lean mass by 4%, and functional capacity by 7% in healthy older females. There's also been studies that even show it can effect the metabolic activity of brown fat. There are hundreds of studies like these that have convinced me to take fish oil daily, but you get the point.

Moving on from fish, I also take the probiotic VSL number 3 sachets either once a week or once every two weeks. I'll talk a bit more about probiotics, and this one in particular, when following up on another question.
I mix in some other supplements like the meriva formulation of curcumin, which I already talked about earlier. I’m also just starting to mix in a little bit of nicotinamide riboside into the mix. Nicotinamide riboside is a form of vitamin B3 that gets converted into NAD which I already explained the importance of when I talked about fasting, but a brief recap.

NAD status improving is generally perceived as one of the benefits of fasting that improved mitochondrial and metabolic function. Declining NAD status can be one of the unfortunate negatives of the inflammatory process. Nicotinamide riboside supplementation, 100 milligrams up to 1,000 milligrams, has been shown to be safe in humans and increased NAD levels in a dose dependent manner with 1,000 milligrams per day raising NAD levels up to 2.7 fold over baseline.

There have been several animal studies showing nicotinamide riboside improves mitochondrial function, improves mitochondrial biogenesis, muscle mass and metabolism, but this is an important easy to miss point. The doses that were given to animals involved in studies were so high that I’m afraid that the supplement I’m taking right now, which is by thorn and only has around 125 milligrams per capsule, won’t quite cut it to meet some of the robust results being seen in these animals studies. I think there’s still potential here, but more studies in humans definitely need to be done at this point. I’m still interested though.

The last part of my weekly health routine has to do with exercise. I like to mix up my weekly exercise routine with aerobic exercise, high intensity training, strength training and yoga and ballet exercises. I usually do some form of exercise every day, even if it’s only 15 minutes. I usually like to do a 20 to 30 minute sauna session three times a week, but I recently moved and have not gotten back into the sauna routine, but I hope to change that soon.

Usually I go for about a three mile run about three times a week. I’m not really an endurance athlete clearly, but I do enjoy it for the quick cognitive boast it gives me. Whenever I have a big decision to make or something that’s causing me anxiety, these are times I’m especially enthusiastic about going for a run. Aerobic exercise has been shown to increase the growth of new neurons in the brain by two-fold. Aerobic exercise even starting in mid-life has been shown to almost completely reverse the structural changes that occur in the brain with the aging. It has been shown that 20 to 40 minutes of aerobic exercise can increase serum drive, brain-derived neurotrophic factor in healthy men by up to 30%, and similarly even 15 minutes of aerobic exercise can increase some brain-derived neurotrophic, albeit to a lesser extent.

Brain-derived neurotrophic factor robustly increases the growth of new neurons in the brain and sort of interestingly in the muscle. It plays a role in repairing damaged muscle. It combats brain atrophy which actually begins at 20 years of age and by the time a person reaches 100, if they do, they usually have lost on average about 20% of their brain mass. Brain-derived neurotrophic factor is also good for combating brain atrophy by growing new neurons. It also has been shown to help prevent neuropsychiatric disorders like bipolar disorder, schizophrenia, depression, good stuff that you don’t want in short supply.

To try to get a little bit of high intensity workout I’ll do squat jumps for a few minutes at a time. High intensity training has been shown to improve learning and memory and when done for eight to 20 minutes it increases the production of neurotransmitters glutamate by 5% and gaba by 7%, as well as norepinephrine, which again, is a catecholamine involved in focus and attention. Interestingly the production of norepinephrine is also associated with the amount of lactate generated from the high intensity workout.

A highly vigorous exercise causes demand for energy to become too high for the mitochondria to use
glucose or fatty acids to generate energy, so glucose is used as energy without the mitochondria via a
process called glycolysis. Lactate is then produced as a bi-product. Lactate is very similar to ketone
bodies in that it is transported to other tissues including muscle, brain, heart, liver, utilizing the same
transporter known as the monocarboxylate transporter, which is used by ketones. Then lactate is able
to shunt into the mitochondria to be used as an energetically favorable source of energy, such as in
the brain where it then can be used preferentially as a source of energy by norepinephrine -producing
neurons.

This idea that we can use lactate possibly produced by our muscles to help out brain tissue or other
tissues not responsible for its generation is known as the Lactate Shuttle Theory, which is an idea that
was pioneered by Dr. George Brooks, that lactate produced by the muscles might be used or shuttled
elsewhere.

In addition to squat jumps and running, I also lift some weights and do lunges and squats with
weights either two to three times per week. It is really important to maintain muscle mass. Starting in
middle age, people lose between .5 to one percent muscle mass per year.

One study involving over 300 twins speaks to the importance of legs in particular. Greater strength
and power in the legs, in particular, was associated with an increased brain volume 10 years later and
less brain aging in over 300 twins. Other fitness measures, besides that of legs, such as forced
expiratory volume or grip strength, were not associated with brain aging when leg power was
excluded. Other lifestyle and health measures, such as frailty telomere length also indicated that
reverse causation was not likely. To get right down to it, don’t skip leg day.

Lastly, I do some yoga and ballet exercises three to four days a week. I really like to do these
exercises because they increase my flexibility and tone very specific muscle groups. I like it, but your
mileage may very.

We’re finally moving onto the next question.

**Russ Thalheimer @ 1:58:39:**
What small change can you make in your lifestyle that leads the biggest impact on your health and
wellbeing? Essentially, what is the 80-20 of lifestyle changes?

**Rhonda @ 1:58:47:**
To summarize Russ’s question, what 20% of lifestyle inputs are leading to 80% of the positive effects?
I think for people starting from ground zero, one of the easiest lifestyle changes to make with the
biggest impact on health is to cut out refined sugar, meaning any processed cookies, cakes, candies,
 crackers, drinks, et cetera. Refined sugar intake in the United States is a big problem. Around 10% of
adults in the United States get around 25% or more of their daily calories from added sugar, and over
70% get at least 10% of their daily calories from added sugar.

It has been estimated that consumption of sugar sweetened beverages in 2010 may have been
responsible for approximately 133,000 deaths from type II diabetes, 45,000 deaths from
cardiovascular disease, and 6,450 deaths from cancer worldwide. Let that sink in. We’re not talking
about smoking or alcoholism. We’re not even talking about just sugar in general. We’re talking about
sugar sweetened beverages by themselves. To give an idea of some of the magnitude effects that
sugar consumption can have in terms of sodas, associative studies have shown that adult Americans
that consumed roughly one can of soda per day had a 46% higher risk of developing pre-diabetes
compared to low or non-consumers over the same 14 year period.

In a similar vein, another study showed that replacing one sugar sweetened beverage such as soda
or sweetened juice with water or unsweetened coffee or tea reduces the type II diabetes risk by up to 25% over an 11 year period followup. Dropping refined sugar seems to also take effect pretty quickly too. In another study in obese children that were put on a diet with no added sugar for just 10 days it was shown to decrease fasting blood glucose by 5 points, reduce insulin levels by a third, and also improve cholesterol and blood pressure. Cutting out the refined sugar maybe the single easiest thing a person can do to dramatically improve their health.

Not only is refined sugar associated with higher risk of many diseases, refined sugar literally accelerates the aging process itself. Healthy adults that drink 12 fluid ounces, or roughly one can of soda, per day had much shorter telomeres in their white cells than people the same age but that do not drink soda every day. A reduction in telomere length roughly equivalent to 4.6 years of the biological aging.

Telomere length, again, is a well established biomarker for aging since our telomeres get shorter every year, and for that reason it should be at least a little alarming when you see an amount that is equivalent to 4.6 years of aging getting trimmed off.

Inflammation, one of the factors that are very important to aging, may also be at play here. One trial found that giving healthy normal weight young men 20 ounces of a sugar sweetened beverage that was more or less similar to drinking a similar amount of soda daily for three weeks was enough to trigger an increase in the biomarker of inflammation C-reactive protein between 60 to 100 percent higher than levels that they started with.

What about hormones? In one study men experienced a 25% decrease in testosterone for up to two hours after 75 grams of sugar intake. There is nothing good about consuming refined sugar, except for that short lived dopamine hit you experience, which by the way, is also been shown that refined sugar increases dopamine and activates the brain’s reward pathway in a way that in some respects is very similar to drugs like tobacco, cocaine, and morphine.

It also effects the opioid system. The effects in terms of magnitude are smaller than these substance abuse drugs, but the pattern ultimately follows a similar trajectory. You continually activate the brain’s reward system. You begin to lose self-control, you start to crave it, and eventually build up a tolerance to it so you need more and more.

The same mechanisms are at play when we talk about sugar addiction too. In my opinion the best thing you can do is cut it out. You’ll be so much healthier by just cutting out this one thing. Once you stop eating refined sugars foods begin to actually taste sweeter. That’s a real effect that’s been shown in clinical studies.

Moving on, the second easiest thing that you can do that will have a big impact on health is to begin doing time restricted eating within a nine to 12 hour timeframe in accordance with circadian rhythm, where unless you are a night shift worker you try to eat your meals earlier in the day as possible like I discussed earlier. If you’re looking to start out, I think 10 hour is a very good middle of the road approach.

A fact I mentioned earlier does a great job at establishing magnitude of impact. Women that previously had breast cancer and ate all their food within an 11 hour time period in changed nothing else in terms of their dietary composition reduced their breast cancer recurrence by 36%. Mice that were fed a high sugar, high fat diet but could only eat within a 12 hour window and still ate the same number of calories as mice that were allowed to eat within a 15 hour window ended being 28% leaner, had 70% less body fat, did not get fatty liver compared to the mice splitting their meals over a longer period of time, which did end up with fatty liver. The time restricted mice also had better blood
glucose levels, cholesterol profile, and were more active and could do more complex motor tasks better. This even included two cheat days per week in which time restriction wasn’t in place to sort of simulate a human weekend off.

It’s really important to drive home the fact that the impact of time restricted eating was made without other improvements in food quality. The versatility factor is a huge benefit here and what makes it appealing is it’s broadly applicable for people, so that’s two.

So far to answer this question, the big lifestyle inputs I’ve suggested are remove all refined sugar as much as humanly possible, especially sodas, and implement time restrictive eating regardless of diet, preferably earlier in the day.

The huge third lifestyle input that I think can make a big, big difference is simply doing whatever it takes to potentially triple the amount of vegetables you take in on a daily basis. For me, the way I’ve gone about this has been to make a habit out of creating a micronutrient smoothie, as I’ve termed it. Basically I grab various combinations of vegetables and sometimes a few fruits to balance it out, drop them all into a powerful blender or food processor, and drink it down. Going about it this way means that all that hugely beneficial fiber still gets ingested. This is important because commercial juicers remove the fiber, which is problematic since fiber is highly beneficial for the microbiome, important for health and the regulation of blood glucose levels, and often in short supply in the diet in the typical westerner. We’ll talk about the implications of that in another question that comes up later.

One important tip is that using an especially powerful blender, make sure that the smoothie has a consistent texture enhancing the palatability of it, which maybe a drawback for some folk that may otherwise have preferred juicing. You learn over time adding certain things like an avocado can greatly change the texture, usually improving it. Having done this micronutrient smoothie hack four to five times per week for the past six years, often without regard of where it may fit in with the rest of my diet, even adding it on top, I noticed something pretty interesting early on. I noticed that the amount of vegetables I was buying almost quadrupled.

Vegetables are a rich source of many important micronutrients and other compounds like lutein and zeaxanthin that have important functions that I mentioned earlier when talking about the foods I eat. The smoothie that I make at the very least usually has kale, berries, and avocado, but I also like to add chard and some other veggies like carrots and a tomato.

In United States, micronutrient deficiencies are especially common, but this probably is true elsewhere aborad as well. RDAs have been set to make sure people meet their daily intakes, but even still people don’t meet them. Some micronutrients that are abundantly found in greens just happen to be ones that people in the United States are the most deficient in. Somewhere around 45% of people are deficient in magnesium, 35% in vitamin K, 24% in vitamin C, 34% in vitamin A, 38% in calcium, and 8% in folate. Magnesium, because of it’s location at the center of a chloroform molecule, is especially telling when it comes to the root cause of the problem. A lack of consumption of green leafy’s.

Earlier I mentioned that around 22% of all enzymes require a micronutrient to function. These micronutrients are necessary for metabolic pathways that are essential for short-term survival and metabolic processes that are important for long-term health. Sometimes these different processes both require the same micronutrient to function. What happens in a person that happens to be inadequate or deficient in that particular micronutrient?

My former post-doctoral mentor, Dr. Bruce Ames, proposed that those metabolic processes that are required for short-term survival will get their share of the micronutrient first because nature wants you
to survive long enough to reproduce and pass on your genes, whereas processes that are more concerned with the long-term maintenance, processes involved in mitigating aging in the long term ultimately get neglected. Bruce calls this evolved strategic rationing of micronutrients the triage theory. It’s a helpful way to think about how the body deals with micronutrient inadequacies and deficiencies, and he’s published a couple of studies providing the theoretical backing to support the idea.

While nature has devised this elegant way of allocating vitamins and minerals to ensure survival during periods of food scarcity, which has occurred throughout evolution, the trade off is it results in insidious types of damage that accumulate with age, accelerates the aging process, and leads to cancer and nerve degeneration. In the case of magnesium, over 300 different enzymes in the body require magnesium, including all the enzymes that use and produce ATP, the energetic currency of the cell. ATP must be bound to a magnesium ion in order for it to be biologically active. These functions of magnesium are required for short term survival. If you can’t make ATP you simply can’t live.

The enzymes that are involved in the generation of ATP are not the only enzymes in the body that require magnesium. Magnesium is also required for enzymes that repair damage to DNA, which has been shown to lead to cancer and damaged mitochondria, which can accelerate the aging process. Optimal DNA repair function is not critical for short term survival, so those enzymes, it would logically follow, would not get their first pick of magnesium. Putting aside the micronutrients for a moment, of course, along with the kale you also get some isothiocyanates like sulforaphane, which we talked quite a bit about earlier.

Finally, for lifestyle input number four, the other really, really easy lifestyle change that I think has a potentially big impact for many, many people is probably taking a Vitamin D supplement. Vitamin D is actually converted into a steroid hormone in the body and regulates around 5% of the human genome. Let that sink in and recall back to the fact that approximately 70% of the United States population does not have adequate levels of Vitamin D, which is an amount of around 30 ng/ml or greater, or 75 nmol/L if your test uses that unit. That means around 70% of people in the United States are experiencing some dysregulation of their genes due to poor Vitamin D status. As I mentioned earlier, this is largely due to the fact that people are spending more time indoors, wearing sunscreen, which blocks out the ability of your skin to make Vitamin D, people with darker skin pigmentation moving to more northern latitudes, age, etc.

Earlier when discussing Vitamin D in the context of serotonin production as a nootropic, I mentioned that I like my Vitamin D levels to be between 40 and 60 ng/ml. Here’s part of the basis of that. A meta-analysis including around 30 studies from 1960 - 2013 showed that people with Vitamin D levels between 40-60 ng/ml had the lowest all cause mortality. Another study found that people with those same Vitamin D levels had the longest telomeres compared to age-matched controls with lower Vitamin D levels. Sort of just generally establishing again the importance of Vitamin D, yet another study involving a couple of thousand twins found that those with the lowest Vitamin D levels had shorter telomeres that corresponded to five years of accelerated aging. Vitamin D activates the expression of DNA repair genes, anti-inflammatory genes and thus lowers DNA damage and inflammation, both which accelerate the attrition of telomeres. I think having adequate Vitamin D levels definitely has an effect on long term health.

It also affects short term health as well. A meta-analysis of 25 randomized controlled clinical trials conducted in 14 countries showed that Vitamin D supplementation cut infection risk by 50% in people that were deficient and by 10% in people with normal Vitamin D levels.

It also affects muscle mass and exercise performance. For example, 2,000 IU of Vitamin D per day for two weeks increased exercise performance by 30%, while lowering physical exertion. Post-
menopausal women receiving a Vitamin D supplement had a significant increase, about 25%, in muscle strength, while those receiving the placebo actually lost an average of around 7% of muscle mass.

There are so many studies showing that Vitamin D improves health, including brain health. You do not want to be deficient in it, and yet so many people are. The solution is to take a Vitamin D supplement. Generally speaking, as a rule of thumb, 1,000 IU's of Vitamin D3 usually raises serum levels of Vitamin D by 5 ng/ml. This is sort of useful as a course correction when you've got a Vitamin D test coming back outside of the range you want to see it. It really is important, however, to measure your blood levels of Vitamin D after supplementing as well.

With that last one, I think that sort of wraps up my high level thoughts on lifestyle strategy choices that might drive big changes in a Pareto's principle sort of fashion.

To recap, number one: eliminate refined sugar from the diet to the greatest extent possible. Number two: Practice time-restricted eating and eat generally in accordance with your circadian rhythm. Number three: do everything in your power to maximize vegetable intake, possibly using the micronutrients smoothie method as a way to jump start the habit. Number four: enlist your physician in helping you to monitor your Vitamin D blood status and then attempt to titrate your dose to an above 30 ng/ml range, possibly trying to land between 40 and 60 ng/ml. Then, to sort of quickly add a number four and a number five. Number four: try to get some form of meaningful vigorous cardiovascular exercise, at least 30 minutes, a few times a week. Number five: get bright blue light during the day as early as possible, and avoid that same blue light as much as you can in the evenings.

All right. If you’re still with me, we’re moving onto the next question.

Shawn Ballard @ 2:12:46:
Rhonda, have you considered taking meat completely out of your diet? Also, which meats do you consume, where do you get them, and how frequently do you consume meats?

Rhonda @ 2:12:56:
The truth of the matter is that there have been many many correlative studies that have found that higher meat consumption is associated with a significantly higher risk of cancer and cancer mortality. This fact alone should be enough to at least make a person give thought to their position on this subject, especially when it's a relationship that keeps showing up.

That said, one of the largest studies to date, which was published in JAMA Internal Medicine in 2016 looked at meat consumption and all cause mortality and cancer related mortality, found something very interesting that is very important to this narrative. Specifically, it found that a high intake of meat from animal sources was only associated with a higher mortality rate and cancer mortality rate in people that had at least one other factor associated with an unhealthy lifestyle, such as being obese or having a history of smoking, or being physically inactive, or being a heavy consumer of alcohol. Meat consumers that were healthy by not having any of these aforementioned unhealthy lifestyle factors did not have a higher mortality rate or cancer mortality rate.

Critical to the meat consumption and cancer link is the fact that protein increases IGF-1, something that research suggests may be an important link in this meat-cancer relationship. Earlier we talked a little bit about the importance of IGF-1 and its beneficial context for muscle hypertrophy, but this cancer link is a trade off that's worth paying attention. Amino acids, and particularly essential amino acids such as leucine, which are more abundant in meat, are the most potent dietary activators of the IGF-1 pathway. IGF-1 does a lot of stuff. It's a growth factor that plays a very important role during
early growth development, and also is important in promoting and maintaining muscle mass, as we discussed, and also neuronal function.

There are many positive benefits to IGF-1, but there's also a trade off, as there so often is in biology. IGF-1 is a potent growth factor that allows cells that have been damaged to survive when they otherwise would die. It is important to understand that IGF-1 does not cause damage to the cell, rather it allows damaged cells to live and reproduce so that they can make more copies of the damaged cells. IGF-1 is known as a tumor promoter because it promotes the growth of cancer cells.

Other factors that cause DNA damage, such as reactive oxygen species, which are by-products of normal metabolism, and inflammatory cytokines, which are by-products of immune activation, can initiate cancer by causing DNA damage, which is the initial insult that can lead to a damaged cell. Our body has a protective mechanism that can sense that damage and kill the cell, but the presence of an abundance of IGF-1 overrides this mechanism and can allow that damaged cell to survive. This is why IGF-1 can be fuel for cancer growth, not initiation, but growth. That distinction may be important.

As a pathway, IGF-1 is actually of great interest in both cancer and longevity research. We know from animal evidence that growth hormone and IGF-1 deficient mice are resistant to cancer. Interestingly, this evidence isn't limited to animal research. Some humans also have polymorphisms in the gene that encodes for the IGF-1 receptor which leads to a decrease in IGF-1 activity in these individuals. Similar to animal research, we see a decreased incidence in cancer and also longer life spans in these people.

Human evidence also exists for the exact opposite, where people that have genetic polymorphisms that cause them to have increased IGF-1 also have an increased cancer risk. If we get away from genetic polymorphisms and look just at people with higher circulating IGF-1 in their serum, something that actually can be quantified, this also has been associated with an increased risk of several different common types of cancers, including breast, colon and prostate. High IGF-1, higher cancer risk. Low IGF-1, reduced cancer risk, and even longevity.

With this new understanding of the relationship of meat consumption to IGF-1 production and IGF-1’s relationship with cancer and longevity, where it even inhibits the longevity gene FOXO3, it would be very tempting and very easy to take an absolutist position and never touch meat again, putting aside all the other reasons why someone might make such a choice.

As I mentioned earlier, there are good aspects to IGF-1. IGF-1 has been shown to increase muscle and reduce adipose tissue simultaneously. It acts as a neurotrophic factor, increasing the growth of new brain cells. It prevents brain cells from dying. It's pretty clear that I actually want some IGF-1 activity. I think this is a really important take home with respect to IGF-1, because IGF-1 has a good and a bad side. I think exercise is the way to tip the balance toward the good. Exercise, whether we're talking about aerobic or resistance training, has been shown to lower serum IGF-1 levels because exercise causes our muscles to take up IGF-1. Additionally, IGF-1 has been shown in rat studies to cross the blood-brain barrier in response to exercise and increases neurogenesis. This also means the exercise lowers circulating concentrations of IGF-1, which means it has less of a chance to promote the growth of damaged cells or inhibit FOXO3 in other tissues.

If we circle back to the original study I mentioned where meat consumption was only associated with a higher all cause mortality and cancer mortality, if one other unhealthy lifestyle factor was present this makes perfect sense if most of the bad effects are mediated through IGF-1. Since I do not have any of those unhealthy lifestyle factors, and I understand what I perceive to be the mechanism behind the relationship between cancer and meat consumption, I have decided to keep some meat in my diet.
Since I already got into a meal breakdown where I talk about the meals I eat in a typical week in another question, I'll skip to the last part of this question, which is where do I get my meat from? I usually get them from a local grocery store or the farmer’s market. I buy wild fish, mostly Alaskan salmon, grass fed beef, and pasture raised chicken with no antibiotics or hormones.

Onto the next question.

Andrea Curlin @ 2:18:35:
I would like to hear your thoughts on some of the fad diets that have been circulating, paleo, ketogenetic, vegetarian?

Rhonda @ 2:18:41:
Advocates of each of these often claim that their diet is the best for inflammation, yet they are all different. I think there are benefits to the perspectives that are brought by each of these various philosophies, though there might be context that make one or another make more sense. I personally choose a more middle of the road route and eat what might be loosely termed a paleoish-type of diet. The good news is that some of these diets have aims at sort of overlap with one another.

For example, both paleo and ketogenic style diets emphasize cutting out refined carbohydrates and refined sugar, which in and of itself has a dramatic effect on lowering inflammation, lowering cancer risk, cardiovascular disease risk, dementia risk, and delays aging, all of which we talked about in a more detail a minute ago when discussing how cutting out refined sugar is one of the big changes a person can make to have a rapid impact on personal health.

The paleo diet in contrast to some of the popular cultures flavors of keto emphasizes eating a lot of vegetables and fruits, which also comes with the package in vegetarian diets as well. As I mentioned earlier, fruits, and particularly vegetables, are a great source of micronutrients and other important compounds such as folate, magnesium, vitamin K1, calcium, vitamin A, vitamin E, vitamin C, potassium, lutein, xanthin, pterostilbene, anthocyanins, and other polyphenols and flavonols.

I already mentioned how incredibly important these micronutrients are, how 22% of all enzymes require some micronutrient to work properly and how important they are for metabolism, mitochondrial function, neurotransmitter production, antioxidant and anti-inflammatory pathways, immune function, brain function, repair enzymes, basically everything important for preventing disease and healthy aging.

One of the problem with certain variations of the ketogenic diet is that without a great deal of care to avoid this pitfall it can lead to inadequacies or deficiencies in some of these micronutrients, and you may not get as many of the other beneficial compounds present in plants as well. A great example of this might be the flavonols in blueberries, just by way of example.

Fruits and vegetables, which again, it seems the paleo diet and vegetarian diet focus a bit more on, are also a great source of various types of fiber, including fermentable fiber and non-fermentable fiber. Fiber is not a single nutrient, which is why fiber supplements are no magic bullet either. It’s not just about quantity but also diversity of complex carbohydrates. There are hundreds of different polysaccharides, which are complex carbohydrates in plants. Gut microbes reflect this same diversity, specializing in using different types of complex carbohydrates, and even the metabolic by-products of the microbes.

These microbes then produce short chain fatty acids that impact our health in a variety of ways. This is why eating only one type of fiber as in from supplementation is ultimately a failed strategy. The best
way to increase your microbial biodiversity is to actually eat a variety of polysaccharides from a
diverse diet of plants and vegetables as well as fruits.

For example, lignans and cellulose, which are found in plant cell walls, are non-fermentable fiber that
help move food and other by-products through the intestines. Examples of fermentable fiber that are
eaten by a wide variety of commensal bacteria in the gut include pectins, which are found in fruits and
berries, gums, which are found in seeds, inulin, which are found in onions, garlic, artichoke, resistant
starch, which is found in bananas and legumes, green leafy vegetables also contain a pre-biotic
known as sulfoquinovose, which also feeds beneficial gut bacteria in the gut.

In addition to diversity, however, we also need volume of dietary fiber. Figuring out what this golden
amount is to keep our microbes metabolically satisfied and not literally starving is tricky. The Institute
of Medicine recommends men 50 years of age and younger get at least 38 grams of fiber per day, and
women 50 years of age and younger get 35 grams of fiber per day. Those numbers drop slightly for
adults older than 50. Traditional societies, for example, those that exist in places like Tanzania, they’re
living a hunter-gatherer lifestyle can get around 200 grams of fiber, compared to the norm for US,
which is shockingly only about 15 grams per day on average.

Either by comparing to traditional societies or just taking The Institute of Medicine’s recommendation,
most people miss the mark. It is therefore important that whatever diet you do choose you ultimately
ensure your microbiome has adequate substrate which survives digestion to make it toward the end
of the digestive tract where the majority of these microorganisms live and interact with our immune
systems and also our brains.

The big problem with a low fiber diet, which in the context of this discussion may possibly be a version
of the ketogenic diet, again, unless special care is taken, is that it may not provide this substrate. Fats,
proteins, and sugar are all absorbed in the small intestine earlier on, but all of the hundreds or trillions
of bacteria that are in our gut and regulate our immune systems, brain function, are more at the end
or the distal part of our large intestine called the colon. When we eat fiber deficient foods our gut
microbes starve, but to keep from starving they eat and cannibalize the gut barrier, which is made of
carbohydrates and mucin.

In terms of magnitude, low fiber has the largest negative effect on breaking down the gut barrier.
Additionally, one study showed that a low fiber diet cause up to a 75% depletion in half of the gut
bacterial species. That's a magnitude of effect that sounds almost on par with actually taking a round
of antibiotics if you think about it.

I've voiced some real concerns about possible implementations of certain variations of ketogenic diet,
but there are also many other benefits of a ketogenic diet. In my opinion, one of the main benefits
from the ketogenic diet is a steady stream of ketone body production, particularly beta
hydroxybutyrate. Beta hydroxybutyrate is a fascinating, mostly antiinflammatory compound that also
plays an antioxidative role as well. Altogether most studies in animals link to production of beta
hydroxybutyrate to lower oxidative stress, lower inflammation, improvements in mitochondrial
respiration and ATP production, and improved brain function. It also may change gene expression in a
positive way by regulating class II histone deacetylases.

As I mentioned earlier in another question, the ketogenic diet has also been shown to lower blood
glucose levels and improve insulin sensitivity, and lead to weight loss in some individuals. This is not
true for everyone, as some people do experience negative metabolic effects likely due to genetic
variation, which is why it maybe helpful if you experiment with this diet to keep an eye on some of the
blood biomarkers mentioned earlier to make sure that if you do experiment with it you’re not one of
the folk that it may not be ideal for it in the long term. It's also possible to ramp up ketone body
production for short burst by kicking off evening fast a bit earlier, playing it strict and following some of the time restricted eating or intermittent fasting protocols out there.

Going back to the paleo and vegetarian diets, why they both focus on eating whole vegetables and fruits, they obviously differ in that vegetarian diets lack meat and have even heavier emphasis on plants, obviously. One potential drawback from the vegetarian diet is that people on this type of diet must put in a little more effort to get some of the micronutrients that are found in meat, such as the marine omega 3 fatty acids, EPA and DHA, iron, zinc, vitamin B12, selenium, for example. Iron, which in addition to being important for red blood cells to carry oxygen to all tissues, is also required to produce neurotransmitters in myelin. Non-meat sources of iron, such as kidney beans or lentil beans, contain iron that is bound to something called phytate.

There are large bioavailability differences between iron that is in heme, which is how it is found in meat compared to iron that is in phytate from a plant source. The bioavailability of iron in phytate is about 1.8 times lower than the iron and bioavailability from heme. The poor bioavailability of iron that is bound not phytate has to do with the fact that humans cannot digest phytate, so most of that iron does not get absorbed. For this reason the RDA for iron for vegetarians should be 1.8 times higher. The RDA for adult males is about eight milligrams a day, and for pre-menopausal woman about 18 milligrams a day.

A lot of iron is lost during menstruation, which is why menstruating women are at high risk for deficiency in iron. In fact, approximately 16% of all menstruating women are iron deficient. Too much iron, however, can cause serious oxidative damage and other problems, which is why it’s a good idea to get iron levels measured instead of blindly supplementing. This is just one example of what I mean by vegetarians having to work a little harder and think about the complexities like this to make sure they get all of their micronutrients.

There are other examples. A great one I mentioned earlier are the omega 3 fatty acids. It maybe tempting for vegetarians to just dose up on conventional plant sources like flaxseed. Some people have a gene polymorphism in a gene that encodes for the enzyme that converts the plant omega 3 ALA into EPA and DHA, the ones I refer to as marine omega-3 fatty acids a moment ago. This can cause them to not convert as well as others. This can be circumvented by supplementing with something like microalgae oil and possibly eating higher concentrations of ALA however or you may just be lucky and have a highly efficient converter of ALA in which case it may not be a problem. Similarly, essential amino acids are much more abundant in meat and maybe something that vegetarians may need to work a little harder to make sure they’re getting enough of particularly in older age. One study looking at people over 65 years of age found that there was an increase mortality rate with low protein intake likely due to frailty.

As I mentioned earlier, starting in middle age we lose about .5 to 1% of muscle mass a year and essential amino acids are important for maintaining muscle mass along with putting those muscles to work of course. If you recall earlier, there maybe a flip side to that. Folks on a paleo or keto diet do include meat. This means that they may need to take special care to be active and not sedentary to put that IGF-1 to use. Remember that eating meat increases IGF-1 and for people that have even one component of an unhealthy lifestyle such as being sedentary, smoking or excessive drinking or obesity without trying to lose weight, for example paleo and keto diets both have been shown to result in weight loss, this may increase all cause mortality and cancer mortality.

That is my sort of high level general summary of these three diets. Like I said, I personally choose to try to get the best of all worlds. I eat paleo-ish including fish and other meats, but with a big emphasis on plants that otherwise might be more common among vegetarian eaters. I am very vigilant about avoiding refined or processed foods especially refined sugar. I practice time restricted eating and
intermittent fasting to get the occasional dose of the ketone body beta-hydroxybutyrate. I do not smoke or drink excessively. I make sure to exercise. This protocol works really well for me, but there may be life context being honest to God sedentary for example or possibly even genetic backgrounds in which we need to emphasize one philosophy over the other.

Similarly, a person might have an important clinical reason for pursuing a ketogenic diet in which case avoiding pitfalls like poor micronutrient intake can become especially important. Either way I think there’s a rich future in figuring out where individual variation and genetic polymorphisms come into play in the pursuit of a healthy lifestyle and conversely, what approaches are more broadly applicable like time restricted eating.

Okay. Onto the next question.

**Luke Hoskovic @ 2:29:48:**
Do probiotics need to be taken forever or do the different strains of bacteria gain a foothold at some point? If I take probiotics for six months and stop, will introduced colonies survive?

**Rhonda @ 2:29:58:**
Your question actually highlights one of the important drawbacks of taking supplemental probiotics.

In order for probiotics that are introduced to actually remain in the colon which is where the majority of our gut microbiome resides, there has to be space for these tiny microbes to stay. The predominant way bacteria take up residence long-term in the large intestines is by sticking to the mucus which is the mucus-like material that makes up the gut barrier and lines the interior of the gut. The problem is that unless a person has just taken a course of antibiotics that mucus is already effectively colonized with bacteria that already reside there which can be a limiting factor that reduces the foothold that new species are able to gain.

What this effectively means is that often probiotics that actually make it to the colon if they were alive when you took them end up being flow through instead of sticking around. What's interesting however is that probiotics can while passing through facilitate population shifts that maybe otherwise less than straightforward while they pass through. Sort of like you introduce population A and B, but the resident populations X is diminished and resident population Y is increased. Alternatively the probiotics may also interact more directly with our immune system while they pass through. Basically there's still a ton of research to be done on probiotics.

It's clear that in some cases they can be highly, highly effective for a variety of purposes, but sometimes the exact mechanism is a bit elusive and may not be strictly intuitive. This issue of already being colonized and existing bio taking up space does however come with certain obvious conclusions. The first of which is that if you're perhaps most advantaged in taking probiotics, shortly after you wiped out your existing population with antibiotics. It’s important to note however that the cumulative effect of repeated use of antibiotics is pretty much unambiguously negative from the perspective of the gut microbial communities with each additional course causing even greater changes that shifts the community further away from its natural starting state.

It would not be prudent to seek out antibiotic strictly to try to liberate a little space in the gut. Interestingly, another time to take them maybe while taking antibiotics too. Clinical studies have shown that this can reduce the potential of later C. diff infections among other things. Gut researcher Dr. Justin Sonnenburg out of Stanford has characterized probiotics as potential placeholders that prevent pathogens from gaining a foothold during recovery, which maybe an interesting way to look at it. However with that said, it is possible that with repeated use as is the case with six months, that some can get a foothold in the mucus and stick there.
To have a better chance of that happening or having any sort of therapeutic effect at all, it's helpful to first have a product that you're confident is alive when it arrives to you and also has a sufficient quantity of bacterial cells that can actually make an impact. There's one particularly product that stands out for this reason and also because the sheer volume of clinical evidence that you can find by just searching its name in Google Scholar or PubMed. The product which I’m referring to is known as VSL#3, particularly the unflavored sachets which has 450 billion probiotics per serving packet. They also get shipped in an actual cooler with ice packs to ensure they’re viable when they get to you.

By way of comparison, you might be lucky to find a probiotic with a 100 billion, but most contain more like 10 billion or sometimes even less. The viability of those bacterial cells by the time it makes it off the shelf or out of the warehouse into your refrigerator may or may not be effectively zero. There are also dozens of publications showing the effectiveness of VSL#3 both in humans and animals, looking at its effect on a wide variety of conditions ranging from the most obvious like antibiotic induced diarrhea, but also its effect on insulin signaling, atherosclerosis, food allergy colitis, liver dysfunction, lipid profiles, blood pressure and more.

To speak to Luke’s question about whether species in probiotics are able to gain a foothold, I have anecdotally measured in both mine and my husband's microbiome species using a consumer service both before and after taking VSL#3 for several months and did find that the VSL#3 cause new species of a commensal bacteria to crop up that were not quantifiable at my baseline and were not even species necessarily found in VSL#3. I think it is possible that some of the probiotic strains that were in the VSL#3 produced what are known short-chain fatty acids. Small molecules like lactate which then ultimately provide fuel for other neighboring strains of bacteria that I may have had in very small quantities already present in my gut which then became more detectable once they sufficiently increased in quantity. This sort of feeds into that earlier discussion about how probiotics can have positive effects, but then when you go and actually look at the changes from the probiotics, they maybe somewhat unexpected. Additionally in my experience some of the strains actually present in the super probiotic VSL#3 did begin to show up as well.

All of that said as a person with former gut problems that seem to have been resolved, I no longer take VSL#3 everyday because frankly it is a bit cost prohibitive and probably not even necessary for me at this point. Instead I take a maintenance dose every week or so and generally keep what I consider an airtight diet that promotes a healthy microbiome through the consumption of an abundance of various types of healthy fermentable fiber. If you're listening to this and look up VSL#3 online, again no affiliation here, be aware that it can be bought direct from the manufacturer and shipped to your home without a prescription, but they do advertise it as a medical food with the expectation that you're taking it under the care of a physician.

While I don’t know of any particular risks from taking probiotics, it's always good to follow the prudent podcast listeners rule and consult a physician before trying to treat what maybe a medical condition.

**Mary Maxi @ 2:35:40:**
Are artificial sweeteners bad for gut health or overall health? Should they be avoided?

**Rhonda @ 2:35:45:**
I try to avoid them because they may have adverse effects on gut health and through that overall health too. Once in awhile it's probably fine, but for everyday use as the case with daily diet soda, it’s not a good idea in my opinion. There was a study published in 2015 that showed that artificial sweeteners alter the gut microbiome both in mice and in the small group of human trial participants.

In the mice they tested saccharine, sucralose and aspartame and found that they increase the
population of bacteria that are better at extracting energy specifically glucose from food and then store that energy as fat. This ultimately altered gene expression which then allowed for increased fat storage and decreased fat burning. Similarly, humans that were given a high dose of saccharine showed a rapid alteration of the gut microbiome and also had decreased glucose tolerance. Sort of showing a proof that the same mechanism in mice does seem to crossover when we’re talking about people too.

This sort of hints at a potential bitter irony whereby people having switched to drinking diet sodas for example may actually be affecting their microbiome in such a way as to actually make themselves more obese even if the empty sugar calories they’re taking in have been reduced. In general if we think about overall health, putting aside whether the effects mediated by the microbiome or not, artificial sweeteners in particularly have been linked to metabolic syndrome, coronary heart disease and other cardiovascular events. I’m somewhat optimistic that the effects of the natural nonnutritive sweetener stevia are somewhat more benign especially in light of a 2016 study that showed lipid improvements and even therapeutic potential in a rodent model of obesity.

This sort of hints at the fact that it maybe a totally different can of worms, but even so I still think that it’s worth exercising some degree of caution. In general when talking about artificial sweeteners or even the nonnutritive sweetener stevia, proper randomized controlled trials are lacking. I’m sure the debate will continue until the sort of gold standard trials emerge that can move the conversation forward by firming up the details more. For now I personally avoid artificial sweeteners all together and only use stevia in moderation.

Emily Sinclair @ 2:37:52: Is metformin really damaging to the mitochondria or is it more of a hormedic stressor?

Rhonda @ 2:37:56:
Briefly for those of you that do not know what metformin is, metformin is a drug, specifically a BI-1 derivative that is primarily used for the treatment of type 2 diabetes. It helps control blood glucose levels and restore insulin sensitivity. It decreases the amount of blood sugar that the liver produces mostly through producing gluconeogenesis in the liver via AMP kinase activation. It also reduces the amount of glucose that the intestines or stomach absorb. In addition to affecting blood glucose, metformin affects other pathways involved in metabolism, inflammation and growth.

That said the reason why Emily maybe asking this question if I were to venture a guess is because over the last few decades there have been several hints that metformin in addition to regulating blood sugar and people with type 2 diabetes might also prevent diseases associated with aging. In the late 1990s a study in the UK found that type 2 diabetics taking metformin lowered all diabetes related complications by 32% and also lowered the risk of cardiovascular disease. Other studies have found that taking metformin is associated with the reduced cancer risk and it also preserve cognitive function.

The study that got the most attention and certainly peaked my own interest was a British study involving around 78,000 individuals that found that adults with type 2 diabetes who took metformin on average lived longer than healthy age matched controls. That was kind of mind blowing for me. Oddly enough, among the many compounds that have shown to affect lifespan in animals including metformin, rapamycin, resveratrol and others, metformin has generally not been that impressive, but metformin does have have a long reassuring track records since people with type 2 diabetes have been taking it since the 1960s. Still I don’t take it, but I’m interested for its future and will be keeping an eye on emerging research.

To more directly answer the original question, metformin does inhibit complex one of the
mitochondrial respiratory chain which is a very important complex in the mitochondria that is responsible for energy production and thus inhibits oxygen consumption in the mitochondria. Believe it or not, several researchers actually think that this may be an important mechanism by which metformin affects aging. This is because by inhibiting the mitochondria, this turns down mitochondrial metabolism which may mean the mitochondria accumulate less damage since they aren’t working as hard. The consequence of complex one inhibition by metformin is a decline in ATP production and an increase in ADP and AMP production and this activates AMP kinase.

So far as I am aware, the complex one inhibition in mitochondria does not appear to cause mitochondrial toxicity. Future studies will help better illuminate if and how metformin can reliably extend human health span and whether or not this doesn’t come with some sort of drawback that just hasn’t been teased out yet.

Okay. Onto the last question…

Sarah Fox @ 2:40:47:
For superior health, do you recommend to stay away from any alcohol or are an occasional couple glasses of red wine on the weekends okay?

Rhonda @ 2:40:55:
Sarah, you and indeed probably Tim will be relieved to know that I think a couple of glasses of red wine on weekends are probably okay.

Okay. Having answered my last question, I want to give a big huge gigantic thanks to Tim for having me back on the show.

It’s been an enormous privilege that I am just extremely grateful for. I’d also like to give a special thanks to those of you that have submitted some really fantastic questions that show an amazing amount of attentiveness to some of my pet passions. Of course, thank you, the person listening right now whoever you are, for listening. Your time and attention means something too. All of you, keep being awesome.