Independent Research & further reading

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Contents

Lifestyle as the Primary Driver of Ageing

> *“genetics does play a role in the way you age, but it's a small role. In fact, 70% or more of the way you're aging is actually due to your lifestyle.”*

While genetic factors do influence aging, current research suggests they account for only about 20–25% of the variation in human lifespan. The remaining 75–80% is largely determined by lifestyle choices, including diet, exercise, smoking, alcohol consumption, and social engagement. These modifiable behaviors play a significant role in shaping both the quality and length of life. Even among individuals with a high genetic risk for age-related diseases, adopting healthy habits can substantially reduce the likelihood of poor outcomes. Lifestyle can also influence gene expression through epigenetic mechanisms, underscoring the dynamic relationship between environment and biology. Overall, while genetics set the baseline, lifestyle exerts the greater and more actionable influence on how we age.

References 1-3.

Obesity and Life Expectancy

> *“there's studies that show even like a 14 year difference in life expectancy for someone who's morbidly obese versus lean.”*

Research consistently shows that severe obesity is associated with a substantial reduction in life expectancy compared to lean body weight. In young adults, particularly men, morbid obesity can shorten life by as much as 13 years. Women with severe obesity may lose up to 8 years of life. These differences are most pronounced when obesity begins early in life and are largely driven by increased risks of cardiovascular disease, diabetes, and certain cancers. Even individuals classified as “metabolically healthy” but obese face higher mortality risk than lean counterparts. While overweight and moderate obesity reduce life expectancy to a lesser degree—by about 3 to 7 years—severe obesity has the most significant impact, reinforcing the importance of maintaining a healthy weight to support longevity and long-term health.

References 4-7.

Partial Reprogramming and the Reversal of Cellular Ageing

"Shaya Yamanaka (…) had shown that you could take a cell that's old and it could be a any cell. It could be from an 85-year-old person with Parkinson's disease, for example (...) and add four different proteins to them. They're called transcription factors (...) you can make it into what's called an embryonic stem cell. And it does that by sort of wiping out what's called epigenome (…) And it sort of brings it back, reprograms it to this youthful state where it becomes an embryonic stem cell. And then that embryonic stem cell can then form any type of cell in the body (...) And so this is called induced pluripotent stem cells (...) A whole handful of brilliant aging scientists have discovered (...) what I call pulse, it's partial reprogramming. You're kind of putting it on for like a shorter period of time, and then that cell keeps its identity, but it's youthful. It wipes out all the damage (...) this has been shown in animal studies and rodents that if you, if you add these four different transcription factors and you give them to mice, you can rejuvenate many of the different organs. So essentially turning back the aging clock in different organs in these mice."

In animal studies, partial cellular reprogramming using Yamanaka factors has shown promising potential to reverse biological signs of aging and restore tissue function. Yamanaka factors—Oct4, Sox2, Klf4, and c-Myc—are a set of transcription factors originally used to convert adult cells into pluripotent stem cells. When applied transiently in short cycles, these factors can reset age-related molecular changes without fully erasing a cell's identity or triggering uncontrolled growth. This approach has been found to rejuvenate multiple organs in mice, including improved regeneration in the liver, enhanced neurogenesis and cognitive function in the brain, and restored vitality in kidney and skin tissues. At the cellular level, partial reprogramming reduces markers of senescence (the condition or process of deterioration with age), improves DNA repair, and resets the epigenetic "clock." While the long-term safety and effectiveness in humans are still unknown, these findings suggest that partial reprogramming may hold future therapeutic potential for age-related decline.

References 8-11.

Sedentarism as a Stronger Predictor of Mortality than Smoking

> *"sedentarism is a disease because it's actually been shown to increase the risk of early mortality, even more than diseases that we know of, like type two diabetes, cardiovascular disease, or even terrible habits like smoking. So being sedentary actually could predict early mortality even more than those diseases."*

Prolonged inactivity—commonly referred to as sedentarism—has been consistently linked to an increased risk of early death, particularly from cardiovascular disease and all causes combined. The risk begins to rise when daily sitting exceeds 6–8 hours and becomes more pronounced above 12 hours, especially in individuals who are otherwise physically inactive. While regular physical activity can partially offset this risk, it does not eliminate it entirely. However, when comparing risk levels directly, sedentarism is associated with a smaller increase in mortality than other well-established factors such as smoking, type 2 diabetes, or cardiovascular disease. For example, smoking and unmanaged diabetes are typically associated with a 50–200% higher mortality risk, compared to a 4–49% increase from sedentarism depending on the amount of sitting. Nonetheless, reducing sedentary time remains an important and modifiable factor in preventing premature death and improving long-term health outcomes.

References 12-15.

The Dallas Bedrest Study: Three Weeks Worse Than 30 Years of Ageing

> *"there's this amazing study, it's called the Dallas Bedrest Study (...) they took five college students and they put them on bedrest. And this is like three weeks of legitimate bedrest (...) and the researchers wanted to find out what happens to your cardiovascular system if you are not moving around for three weeks (...) And what was found is after that three weeks, their cardiovascular system was just tanked. And one of the biggest factors that was measured was their cardio respiratory fitness (...) it tanked (...) they found these five men from 30 years earlier and they measured their cardio respiratory fitness in a variety of other parameters that they had measured at the time. And what they found was that three weeks of bed rest was worse on their cardio respiratory fitness than 30 years of aging."*

The Dallas Bed Rest and Training Study, first conducted in 1966, demonstrated that three weeks of complete bed rest in healthy young men led to a 27% decline in cardiorespiratory fitness, measured by VO_2max. This reduction was primarily due to decreased cardiac output from lowered stroke volume. When the same participants were re-evaluated 30 years later, their VO_2max had declined only 12% with aging—indicating that short-term inactivity at age 20 had a more profound effect on cardiovascular fitness than three decades of aging. The study's follow-ups also showed that endurance training could reverse much of this decline, restoring cardiovascular capacity close to baseline levels. At the 40-year mark, VO_2max had fallen further, but the long-term data emphasized a striking conclusion: bed rest in early adulthood can have more acute effects on cardiovascular function than aging itself. This work helped transform clinical practices, shifting away from prolonged bed rest in medical care and toward early mobilization and rehabilitation.

Reference 16.

Cardiorespiratory Fitness as a Marker of Longevity

> *"We know that cardiorespiratory fitness is one of the best predictors of longevity. So there are studies that have shown that people with a high cardiorespiratory fitness live five years longer than people with a low cardiorespiratory fitness (...) they're basically 80% less likely to die of many different causes of death."*

Cardiorespiratory fitness (CRF) is one of the most powerful predictors of longevity and all-cause mortality. Research consistently shows that adults with high CRF levels have a 45–55% lower risk of dying from any cause compared to those with low fitness levels. This translates into a life expectancy advantage of up to five years. Even small improvements in CRF are beneficial—each 1 MET (metabolic equivalent) increase is associated with an 11–17% reduction in mortality risk, roughly equating to 45 extra days of life per MET. These effects are observed across age groups, sexes, and racial backgrounds, and remain significant regardless of other risk factors such as smoking or obesity. .

References 17-19.

High Intensity Interval Training (HIIT) for Cardiorespiratory Improvement in Non-Responders

> *"now what we really understand is that you want to do and engage in what's called vigorous intensity exercise (...) multiple studies that have shown people that engage in moderate intensity exercise (...) even people that are engaging in that type of exercise for two and a half hours a week (...) 40% of those people can't improve their cardio respiratory fitness (...) you take those people and then you have them engage in high intensity interval training and they're able to improve their cardio respiratory fitness (...) because you're putting a stronger stress on your cardiovascular system. And so the adaptations are greater."*

High-intensity interval training (HIIT) appears to be particularly effective for improving cardiorespiratory fitness (CRF), especially in individuals who do not respond to moderate-intensity continuous training (MICT). While MICT can improve CRF in many people, studies show that a substantial portion—up to 60% in some populations—may see little or no improvement. In such cases, switching to HIIT can yield meaningful gains. For example, in one study, individuals who failed to respond to 12 months of moderate exercise showed significant increases in CRF after just three months of HIIT. More broadly, meta-analyses have found that HIIT is generally equal to or more effective than MICT for improving CRF across diverse populations, including healthy adults, older individuals, and those with chronic conditions. HIIT's benefits are thought to stem from its higher metabolic demands, which trigger stronger physiological adaptations. Moreover, HIIT is time-efficient, often requiring less total exercise time than moderate approaches, and is well-tolerated in supervised settings.

References 20-24.

The Norwegian Four-by-Four Protocol

> *"I would say the Norwegian four by four is the gold standard (...) being part of an exercise protocol was shown to reverse the structural changes that occur with age In the heart by 20 years (...) this was done by Ben Levine (...) He took these 50 year olds and put them on a pretty intense exercise routine for two years, or a stretching routine."*

A landmark randomized controlled trial by Howden et al. (2018) demonstrated that a structured, high-intensity exercise regimen—specifically the “Norwegian 4x4” protocol—can reverse some of the age-related structural changes in the heart when initiated in middle age. In the study, sedentary adults aged 45–64 were assigned either to a control group (stretching and balance exercises) or to a two-year exercise training program involving four weekly sessions, including two sessions of high-intensity interval training (4 minutes at 85–95% max heart rate, repeated 4 times). The results showed that participants in the high-intensity group significantly increased their left ventricular end-diastolic volume and maximal oxygen uptake (VO_2max), both key indicators of cardiac youthfulness and function. Importantly, this reversal of sedentary cardiac aging was not observed in the control group, suggesting that intensity, not just activity, is critical. These findings support the idea that specific exercise protocols can restore cardiovascular health even decades into adulthood, potentially turning back the biological clock of the heart by as much as 20 years.

Reference 25.

Heart Stiffness, Glycation, and Glucose Exposure

> *“as we age, our hearts shrink and they get stiffer. And that plays a role in causing cardiovascular disease. I mean, that's the number one killer in the United States (...) it has a lot to do with actually being exposed to a lot of glucose (...) This causes a chemical reaction called glycation. So you get these advanced glycation end products that sort of react with your collagen that's lining your heart and your myocardium, and it causes it to stiffen.”*

Glycation—the process by which sugars react with proteins to form advanced glycation end-products (AGEs)—is a well-established contributor to age-related stiffening of the heart and blood vessels. As we age, AGEs accumulate in tissues like the myocardium and arterial walls, where they bind to long-lived structural proteins such as collagen. This cross-linking reduces elasticity, making the heart and arteries stiffer and less able to respond to changes in pressure or demand. In addition to structural changes, AGEs trigger inflammation and oxidative stress, further impairing cardiovascular function. Research in both humans and animal models consistently shows that higher levels of AGEs are associated with increased arterial stiffness, a greater risk of heart disease, and higher rates of stroke and cardiovascular events—even in people without diabetes. These findings support the idea that glycation

plays a central role in cardiovascular aging and may be a promising target for prevention and treatment.

References 26-30.

Mitochondria, Oxygen, and Cellular Energy Production

> *"the way that most of our cells make energy, like our muscles, is by using our mitochondria. These are tiny organelles inside of our cells that produce energy, but they need oxygen to do it."*

Mitochondria are the primary structures responsible for energy production in human cells. These small organelles generate most of the cell's energy in the form of ATP (adenosine triphosphate) through a process called oxidative phosphorylation, which requires oxygen. By breaking down nutrients like glucose and fatty acids, mitochondria convert chemical energy into a usable form that powers cellular functions—particularly in energy-demanding tissues like muscle. In addition to producing ATP, mitochondria play key roles in regulating metabolism, cell signaling, and cell survival. When mitochondrial function is impaired, it can lead to a range of health problems, including metabolic and neurodegenerative diseases. Overall, healthy mitochondrial activity is essential for sustaining life and maintaining cellular health.

References 31-34.

Lactate: A Signaling Molecule for Brain and Gut Health

> *lactate is a way for your muscles to communicate with other organs, like the brain. And it's called the signaling molecule (...) so what happens is the lactate (...) gets consumed a lot by the brain. And in the brain it, it activates something called brain derived neurotrophic factor BDNF. And this is kind of like a miracle grow for your brain. So essentially it's able to increase the growth of new neurons, which is amazing. It's called neurogenesis. It increases the connections between neurons, so it improves memory, cognition (...) its involved in what's called neuroplasticity (...)*

it's been shown that high levels of lactate are correlated with improved cognition scores, improved impulse control (...)

there have been studies that have been done looking at, for example, traumatic brain injury patients. So people that have undergone some sort of head trauma and they've infused sodium lactate through like an IV into their system. And the lactate immediately gets consumed by the brain and it's been shown to improve their recovery. So it's called the Glasgow score (...)

Lactate is really beneficial for the gut epithelial cells. And in fact, if you think about it, all these sort of beneficial probiotic bacteria, like bifido bacterium for example, they're producing lactic acid and that lactic acid does get converted into lactate (...) And the reason it's so good is because it is an very easily utilizable source of energy for the gut cells."

Brain-Derived Neurotrophic Factor (BDNF) and Neuroplasticity

Lactate, a substance produced by muscles during intense exercise, has been shown to play an important signaling role in the brain. Rather than simply being a waste product, lactate crosses the blood-brain barrier and stimulates the production of brain-derived neurotrophic factor (BDNF)—a protein that supports the growth, survival, and connectivity of neurons. This effect is particularly evident in the hippocampus, a region involved in learning and memory. Lactate promotes BDNF expression through molecular pathways such as SIRT1 and can enhance the brain's readiness for plastic changes, including the formation of new neurons and stronger connections between existing ones. However, lactate alone may not be sufficient to fully drive neuroplasticity without concurrent brain activity. Together, these findings highlight lactate's role as a metabolic signal that links physical activity to cognitive and neurological benefits.

Cognition and Impulse Control

Research shows that elevated lactate levels—particularly those produced during exercise—are associated with improved cognitive function. Lactate acts as both a fuel source and a signaling molecule in the brain, supporting memory, learning, and synaptic plasticity. These benefits are primarily mediated by the upregulation of brain-derived neurotrophic factor (BDNF) and activation of pathways such as SIRT1 in key brain regions like the hippocampus. Lactate has also been shown to reverse certain types of cognitive impairment in animal studies. However, while lactate's role in enhancing cognition is well supported, there is currently no clear evidence linking high lactate

levels to improvements in impulse control. More research is needed to understand whether lactate influences this aspect of behavior.

Intravenous Sodium Lactate and Traumatic Brain Injury Recovery

Sodium lactate infusion has been investigated as a treatment for traumatic brain injury (TBI), particularly for its potential to support brain metabolism and reduce intracranial pressure (ICP). In both animal models and human studies, lactate appears to serve as an alternative energy substrate for the injured brain, improving cerebral metabolism, reducing glutamate accumulation, and enhancing ATP (adenosine triphosphate) production. Some human trials report improved cognitive function following mild TBI, while microdialysis studies in severe TBI patients have shown enhanced metabolic efficiency and fewer episodes of raised ICP with lactate infusion. However, larger randomized trials have not consistently demonstrated clear improvements in long-term neurological outcomes when compared to standard fluids like saline. Although promising in the acute phase, further research is needed to establish the long-term benefits and optimal clinical use of sodium lactate in TBI care.

Lactate Supports Gut Epithelial Health and Barrier Integrity

Lactate is produced by gut bacteria such as Lactobacillus and Bifidobacterium and plays a beneficial role in maintaining and repairing the gut epithelium. It promotes the proliferation of intestinal stem cells and the development of key epithelial cell types by activating the Wnt/β-catenin pathway through GPR81 signaling. Lactate also supports epithelial barrier integrity by preserving tight junctions, reducing oxidative stress, and suppressing inflammation. In both experimental models and in vitro studies, lactate has been shown to enhance epithelial repair following injury from radiation or chemotherapy, and to promote anti-apoptotic gene expression. These findings highlight the importance of lactate as a signaling molecule in gut homeostasis and suggest that lactate-producing microbes contribute meaningfully to intestinal health.

References 35-45.

Heat Shock Proteins and Neurodegeneration Prevention

> *“heat shock proteins [that] are important for preventing neurodegenerative disease.”*

Heat shock proteins (HSPs) are molecular chaperones that maintain cellular protein quality, especially under stress. In the context of neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's, HSPs play a critical protective role by preventing the buildup of toxic protein aggregates—a hallmark of these conditions. Proteins like Hsp70 and Hsp90 assist in refolding misfolded proteins or targeting them for degradation, reducing cellular damage. HSPs also help shield neurons by limiting oxidative stress, modulating inflammation, and interfering with cell death pathways. Experimental studies show that increasing HSP activity can slow neurodegeneration and improve neuronal survival, making these proteins a promising focus for therapeutic development.

References 46-48.

Aerobic Exercise Reverses Brain Atrophy in Older Adults

> *"this study is so profound (...) done in older adults. So we're talking 60 year olds or a little bit older. And these individuals were put on a aerobic exercise training program for one year that was more of like a 70 to 75% max heart rate. So it wasn't so vigorous, but it was pretty, pretty vigorous for them (...) and the basis of this study was to look at brain aging (...) Our brain also shrinks with age. It's called atrophy. And as we age, especially starting in midlife, so around the age of 50, your brain in certain areas of the brain, like the hippocampus, which is involved in learning and memory, starts to shrink by about one to 2% per year (...) in this study, after a year of this sort of aerobic exercise training program, they were doing three times a week, about 30 minutes a day (...) And then there was a control group that was kind of the stretching (...) the stretching group did lose about one to 2% in terms of the size of the hippocampus. It shrunk one to 2% after that year, which is what you would expect normally. However, the group that was training, not only did they not have their hippocampus shrink by one to 2%, it actually grew by one to 2%, which comes down to that neurogenesis, that growth of new neurons."*

A landmark randomized controlled trial published in *PNAS* investigated the effects of aerobic exercise on hippocampal volume in older adults. Participants aged 55 to 80 were randomly assigned to either a moderate-intensity aerobic training group or a stretching and toning control group. Over the course of one year, the aerobic exercise group—engaging in walking at 60–75% of their maximum heart rate three times per week—showed a 2% increase in hippocampal volume, effectively reversing age-related atrophy typically seen in this region. In contrast, the control group experienced the

expected 1–2% decline. These changes were associated with improvements in spatial memory and were mediated in part by increased serum levels of brain-derived neurotrophic factor (BDNF), a key regulator of neurogenesis. The findings provide compelling evidence that even moderate aerobic exercise can promote structural brain plasticity and counteract cognitive aging in later life.

Reference 49.

Cardiorespiratory Fitness and Dementia Risk Reduction

> *"There's also studies showing that (...) women with the highest cardiorespiratory fitness were 80% less likely to come down with dementia over the follow up period time."*

A 2018 prospective cohort study published in *Neurology* examined the relationship between cardiorespiratory fitness (CRF) and dementia risk in a population of Swedish women. The researchers followed 191 women with a mean age of 50 over a 44-year period, assessing their fitness levels using a submaximal cycling test and tracking dementia incidence. Women with the highest CRF were found to have an 88% lower risk of developing dementia compared to those with moderate fitness levels. Notably, the onset of dementia was delayed by approximately 11 years in the high-fitness group..

Reference 50.

Multifactorial Causes of Alzheimer's: Genetics, Sleep, Trauma

> *"the causes of Alzheimer's (...) it's multifactorial (...) What happens is the aggregation of a protein on our brain called amyloid that typically is cleared from our brain (...) you're not clearing the amyloid, and so it starts to kind of form these clumps and aggregates with the amyloid proteins that are not being cleared. And that essentially is happening outside of your neurons, but it's happening where the synapses are formed between neurons. And so what happens is it kind of disrupts the synaptic connection between neurons, which is essentially forming a memory (...)*

That glymphatic system is activated during sleep, and it's one of the reasons why people that don't get good sleep over the course of decades have a higher risk of Alzheimer's disease is because they're getting these amyloid plaques built up in their brains (...)

And glucose metabolism is disrupted in the brains of Alzheimer's disease (...) And so that's another sort of metabolic, underlying cause of Alzheimer's disease (...)

there's also genetic causes as well (...) some people have genes that can increase the risk of Alzheimer's disease because they're not able to clear amyloid as well, because they're not able to repair damage as well. So the, the blood brain barrier, which is really important for filtering out toxic things from getting into the brain, it starts to break down. And that's one of the, I would say early signs of Alzheimer's disease (...) And that happens in people that have a genetic risk factor called APOE4 (...) this is probably one of the biggest genetic risk factors for Alzheimer's disease. About 25% of the population has one copy of this gene. That increases the risk of Alzheimer's disease by twofold. If you have two copies of it, it increases the risk of Alzheimer's disease by tenfold (...)

People that have any one or two of the APOE4 genes (...) if they get a TBI (...) then you talk about like going up to a tenfold risk for Alzheimer's disease when you get like an injury because people with those genes don't repair damage as well."

Alzheimer's disease is a multifactorial neurodegenerative disorder characterized by the accumulation of amyloid-beta plaques and tau tangles, which progressively damage the brain. A central feature of the disease is the impaired clearance of amyloid-beta, a protein that normally functions in the brain but, when not properly removed, begins to aggregate in extracellular spaces—particularly at synapses, where neurons communicate. These amyloid plaques disrupt synaptic function, undermining the neural connectivity that supports memory and cognition. Over time, this leads to widespread neuronal loss, brain atrophy—especially in memory-related regions like the hippocampus—and profound cognitive decline. While amyloid aggregation is a key initiating factor, Alzheimer's pathology also involves tau protein dysfunction, neuroinflammation, neurotransmitter deficits, and vascular impairment, reflecting the disease's complex and multifaceted nature.

Sleep, the Glymphatic System, and Alzheimer's Risk

Emerging research indicates that poor sleep significantly increases the risk of Alzheimer's disease by impairing the glymphatic system—a cerebrospinal fluid-dependent clearance pathway active primarily during sleep. This system is most efficient during slow-wave (deep) sleep, facilitating the removal of metabolic waste products such as amyloid-beta, a protein whose accumulation in the brain is a defining feature of Alzheimer's pathology. Studies in both animals and humans show that sleep deprivation impairs this clearance process, leading to increased amyloid-beta deposition and associated neuroinflammation. Remarkably, even a single night of sleep deprivation has been shown to raise brain amyloid levels. Chronic sleep disruption over decades is strongly correlated with greater amyloid burden and elevated Alzheimer's risk. Genetic variants, including polymorphisms in AQP4, which regulates glymphatic function, may further influence this relationship. Thus, consistent, high-quality sleep is not merely restorative—it is neuroprotective.

Glucose Metabolism and Alzheimer's Disease

Impaired glucose metabolism is a hallmark feature of Alzheimer's disease and may contribute directly to its onset and progression. The brain's reduced ability to use glucose for energy—known as glucose hypometabolism—can be detected before symptoms appear and worsens over time, leading to cognitive decline and neuronal dysfunction. This energy deficit contributes to mitochondrial impairment, increased oxidative stress, and ultimately neuronal death. In addition, insulin resistance in the brain further limits glucose uptake and is associated with more severe Alzheimer's pathology. Disrupted glucose metabolism has also been linked to the accumulation of amyloid-beta and the abnormal phosphorylation of tau protein, both of which are central features of the disease. These insights have diagnostic significance, as reduced brain glucose uptake is measurable via FDG-PET imaging, and therapeutic relevance, with metabolic pathways now being explored as targets for intervention.

APOE4 and Genetic Risk for Alzheimer's Disease

The APOE4 allele is the strongest known genetic risk factor for late-onset Alzheimer's disease, with both risk and severity increasing in a dose-dependent manner. One copy (heterozygous) raises the risk of developing Alzheimer's by 2–4 times compared to non-carriers and is associated with symptom onset in the mid- to late 70s. Two copies (homozygous) increase the risk up to 10–15 times, with a lifetime probability of over 50%, and often lead to disease pathology by age 65–70. APOE4 increases vulnerability through several interrelated mechanisms: it impairs clearance and

promotes aggregation of amyloid-beta plaques, exacerbates tau pathology, contributes to synaptic and neuronal loss, and disrupts lipid metabolism and cholesterol transport. It also alters inflammatory responses in glial cells, weakens the blood-brain barrier, and interferes with cellular waste clearance. These overlapping pathways contribute to earlier and more severe neurodegeneration, particularly in memory-related regions, and may be intensified by chronic inflammation.

APOE4, Traumatic Brain Injury, and Alzheimer's Risk

Both the APOE4 allele and a history of traumatic brain injury (TBI) are independent risk factors for developing Alzheimer's disease at an earlier age. When combined, these factors appear to further lower the age of onset, although their interaction is complex and not strictly additive. APOE4 carriers with a history of TBI tend to show the earliest mean onset of Alzheimer's symptoms, but the effect is not always statistically significant, and APOE4 generally exerts a stronger influence than TBI alone. Mechanistically, APOE4 may worsen outcomes after brain injury by increasing neuroinflammation, impairing brain repair, and exacerbating tau pathology, which can accelerate neurodegeneration.

References 51-59.

Multivitamins Improve Cognitive Aging

> *"three large clinical trials have been done. These are randomized controlled trials where older adults were given either a multivitamin and this was just your standard run of the mill multivitamin, Centrum silver, or they were given a placebo and they were given this for a couple of years. And what three different studies showed was that a multivitamin improved cognition, improved processing speed. It improved what's called episodic memory (...) And not only did it improve it, it improved it so much that it was equivalent to reducing the aging of the episodic memory by five years."*

Recent large-scale randomized controlled trials and meta-analyses indicate that daily multivitamin supplementation offers modest but statistically significant benefits for episodic memory and global cognitive function in older adults. In particular, improvements in delayed recall tasks have been observed, with one major study—the COSMOS-Web trial—reporting memory gains equivalent

to reversing approximately three years of age-related memory decline. A meta-analysis of over 13,000 participants also found significant effects on delayed free recall. While benefits for global cognition were smaller, they were still meaningful, corresponding to a reduction in cognitive aging of around two years. However, no consistent improvements were found in other cognitive domains. Overall, multivitamin use appears to be a safe and accessible strategy for supporting memory in aging populations.

References 60-62.

Folate Deficiency and DNA Damage

> *"if you decrease folate and make someone deficient in it, it essentially causes double stranded breaks in your DNA that essentially is like being under ionizing radiation. And that experiment was done, like you could take a mouse, make it like, put low folate in the, in, you know, the mouse's food, and then take another mouse and put it under an ionizing radiation machine. And the amount of double stranded breaks in their DNA, which cause cancer, which accelerate aging, which affect how your cells are functioning. It was just the same."*

Both folate deficiency and ionizing radiation can cause DNA double-strand breaks (DSBs), one of the most severe forms of genomic damage. Research has shown that physiological levels of folate deficiency can induce DNA damage in human cells comparable to that caused by a relatively high dose—1 gray (Gy)—of ionizing radiation, a level considered significant in environmental and occupational contexts. While both stressors reduce cell proliferation, increase DNA breaks, and trigger apoptosis, they do so through distinct biological mechanisms. Ionizing radiation directly induces DSBs and activates repair pathways like non-homologous end joining, whereas folate deficiency disrupts nucleotide synthesis and replication, leading to DNA instability without engaging the same DSB-specific repair responses..

References 63-65.

Vitamin D as a Hormonal Regulator of Brain Health and Mortality

"What's gonna help prevent dementia? Vitamin D is, it's actually more than a vitamin. Vitamin D gets converted into a steroid hormone. So a steroid hormone, essentially what it does is it goes into the nucleus of a cell where all your DNA is, and it's activating genes and deactivating 'em. It's affecting your genome. And it's actually over 5% of your genomes being affected by vitamin D (...) being deficient or insufficient in vitamin D can increase dementia risk by 80% (...) People that supplement with vitamin D three have a 40% reduced risk of dementia (...) there's actually even been studies in people with dementia, in people with Alzheimer's disease that were giving a vitamin D supplement or a placebo control. And those individuals, given the vitamin D supplement, had improved cognition. They had lower markers of amyloid plaques (...)

70% of the US population has insufficient levels of vitamin D. The reason for that is because vitamin D three is actually made in the skin from UVB radiation from the sun. And so if you're not outside, then you're not really making a lot of vitamin D3 in your skin. And vitamin D3 then gets converted into this steroid hormone that regulates everything (...)

People that are closer to the equator usually have more melanin. it's an adaptation to prevent you from burning from the UV rays of the sun. Well this University of Chicago study found that (...) people that are African American had to stay in the sun six to 10 times longer than people with fair skin, the Caucasians, to make the same amount of vitamin D three (...)

People that have blood levels of vitamin D between 40, 60, maybe 80 nanograms per milliliter have the lowest all cause mortality (...)

it's been shown that for every 10 nanograms per milliliter decrease in vitamin D blood levels, there's an increase in brain damage. It's called white matter hyperintensities. It's basically damage to the white matter in your brain"

Vitamin D as a Steroid Hormone and Gene Regulator

Vitamin D functions as a steroid hormone by binding to the vitamin D receptor (VDR), a nuclear receptor that regulates gene expression in numerous tissues. The active form, 1,25-dihydroxyvitamin D_3, enters cells and binds to VDR in the nucleus, where it interacts with specific DNA sequences known as vitamin D response elements (VDREs). This process recruits

chromatin remodeling proteins and coregulators to modulate gene transcription, much like other steroid hormones such as estrogen and glucocorticoids. Through this mechanism, vitamin D influences a wide range of physiological functions—including immune regulation, cell growth, and calcium metabolism—and is estimated to regulate approximately 3% of the human genome.

Vitamin D Deficiency in the U.S. Population

Vitamin D deficiency is widespread in the United States, with estimates indicating that approximately 18% to 20% of Americans have moderate to severe deficiency, and up to 41.6% have levels considered insufficient when broader thresholds are applied. Deficiency rates are notably higher among non-Hispanic Black Americans, Hispanics, younger adults, women, and individuals with lower socioeconomic status. UVB radiation from the sun is essential for the natural production of vitamin D3 in human skin. When skin is exposed to UVB rays (wavelengths ~290–315 nm), it triggers a chemical reaction that converts 7-dehydrocholesterol to previtamin D3, which is then transformed into vitamin D3. This process is the primary source of vitamin D for most people.

Skin Pigmentation and Vitamin D3 Synthesis

Skin pigmentation significantly affects the body's ability to produce vitamin D3 from sunlight. Melanin, the pigment responsible for darker skin tones, acts as a natural sunscreen by absorbing and scattering UVB radiation, which reduces the conversion of 7-dehydrocholesterol to vitamin D3 in the skin. As a result, individuals with darker skin require substantially more sun exposure to generate the same amount of vitamin D3 as those with lighter skin. Empirical studies show that after standard UVB exposure, light-skinned individuals experience a large increase in vitamin D3 levels, while dark-skinned individuals show little to no increase unless exposed to much higher doses. Estimates suggest that people with very dark skin may need up to five times more sun exposure to achieve similar vitamin D3 synthesis. This disparity contributes to a higher risk of vitamin D deficiency in darker-skinned populations, especially in regions with limited sunlight. A study led by researchers at Northwestern University found that African-American men were up to 3.5-times more likely to be deficient in vitamin D and required approximately six times more sun exposure (about 90 minutes three times a week) to produce sufficient vitamin D, compared to Caucasian men (~15 minutes three times a week).

Vitamin D Deficiency and Dementia Risk

Vitamin D deficiency has been consistently associated with an increased risk of developing dementia, with the magnitude of risk rising as vitamin D levels decline. Meta-analyses and large cohort studies report that individuals with vitamin D deficiency—typically defined as blood levels below 50 nmol/L—face a 25% to 42% greater risk of dementia compared to those with sufficient levels. Severe deficiency, with levels below 25 nmol/L, is linked to a 33% to 79% higher risk. For Alzheimer's disease specifically, recent studies have found relative risk increases of up to 57% in those who are deficient. These findings suggest a dose-dependent relationship, in which the lowest vitamin D levels carry the highest risk, highlighting the importance of maintaining adequate vitamin D status to support long-term cognitive health.

Optimal Vitamin D Levels for Lowest Mortality

The lowest all-cause mortality is consistently observed at serum 25-hydroxyvitamin D [25(OH)D] levels between 50 and 75 nmol/L (20–30 ng/mL). Levels below 50 nmol/L are linked to increased risk, while higher levels do not provide additional benefit and may carry some risk if excessively high.

Vitamin D Levels and White Matter Hyperintensities

Lower vitamin D levels have been generally associated with a greater burden of white matter hyperintensities (WMH)—a marker of brain tissue damage—particularly in older adults and those with cognitive impairment. One meta-analysis reported an 83% increase in the odds of WMH for every 25 nmol/L decrease in serum vitamin D. While deficiency (typically defined as levels below 25–30 nmol/L) is most consistently linked to elevated WMH burden, findings across studies vary, and some well-controlled research has found no significant association. Overall, the evidence suggests a trend toward increased WMH with lower vitamin D levels, though it does not confirm a specific threshold or establish a direct causal relationship.

References 66-78.

Ketogenic Diet, Ketones, and Brain Health

“it takes about 12 hours on average to deplete all your glycogen levels. Now you can accelerate that if you're doing a lot of physical activity, but once you deplete that liver glycogen, that is when you shift into burning fatty acids and then eventually ketosis (...)

There have been studies [on ketogenic diet and longevity] by Dr. Eric Verdin out of the Buck Institute for Aging in Novato, California (...) with a ketogenic diet and rodents. And it did seem to extend life expectancy, but more importantly, the health span (...)

This ketone called beta hydroxybutyrate gets into the brain (...) then activates brain derived neurotrophic factor (...)

what's happening [with exogenous ketones] is you are essentially giving your body the beta hydroxybutyrate ketone that it would make normally if you were undergoing ketosis and using fatty acids only as energy (...) there's also some potential therapeutic effects. So people that have mild cognitive decline, maybe like the first stages of dementia or Alzheimer's disease, can kind of perk up and perform better when they're given an exogenous ketone (...) on the Deltaagketones.com website it says that in the studies they found an 87% improvement in brain network stability. A study from 2020.”

Glycogen Depletion and the Onset of Ketosis

Liver glycogen depletion and the metabolic shift to fat burning and ketone production can begin much sooner than often assumed. In healthy individuals, ketone production may start within 3 to 9 hours of fasting or carbohydrate restriction, with the process accelerated by low insulin, elevated glucagon, and physical activity. Exercise, particularly at high intensity, can significantly hasten glycogen depletion—sometimes within an hour—compared to 12–24 hours during rest or fasting alone. The rate of depletion depends on factors such as exercise intensity, training status, and metabolic health. Once liver glycogen is depleted, the body increases fat oxidation to meet energy demands, initiating the transition toward ketosis.

Increased Health Span in Rodents

Roberts et al. (2017) conducted a study published in *Cell Metabolism* that found a ketogenic diet (KD) significantly extended median lifespan and improved healthspan in adult male mice. Mice fed a KD from midlife showed enhanced memory, motor coordination, and muscle mass preservation into old age compared to controls. Mechanistically, the KD elevated protein acetylation—particularly acetylation of the tumor suppressor p53—and modulated mTORC1 signaling in a tissue-specific manner. The study also reported reduced cancer incidence and suggested that ketone bodies may function as neuroprotective and muscle-preserving signaling molecules.

Newman et al. (2017), in a companion study published in *Cell Metabolism*, found that administration of the ketone body β-hydroxybutyrate (BHB) extended lifespan in mice, even without altering macronutrient intake. The study proposed that BHB acts as an endogenous signaling metabolite, promoting stress resistance, reducing inflammation, and inhibiting histone deacetylases (HDACs)—mechanisms thought to mimic caloric restriction. These findings support the view that ketone bodies themselves may mediate key anti-aging effects.

Beta-Hydroxybutyrate and BDNF Expression

Beta-hydroxybutyrate (BHB), a ketone body produced during fasting, exercise, or ketogenic diets, has been shown in animal and cellular studies to increase expression of brain-derived neurotrophic factor (BDNF), a protein critical for neuroplasticity, learning, and mood regulation. This effect is mediated through signaling pathways such as CREB activation and epigenetic modifications, including inhibition of histone deacetylases and changes to histone marks that enhance BDNF gene transcription. While BHB consistently upregulates BDNF in animal models, evidence from human studies is mixed. Increases in BHB sometimes raise blood levels of proBDNF, but not always mature BDNF, and the effects vary depending on factors like metabolic health and intervention type.

Beta-Hydroxybutyrate Improves Cognitive Function

Exogenous ketones, particularly beta-hydroxybutyrate (BHB) delivered via supplements like medium-chain triglycerides (MCTs) or ketone esters, have shown potential in improving cognitive function in individuals with mild cognitive impairment (MCI). Clinical trials report that sustained daily supplementation—such as 30g of MCT oil over six months—can lead to significant improvements in episodic memory, language, executive function, and processing speed. Neuroimaging studies also demonstrate enhanced ketone uptake in the brain and improved connectivity in attention networks,

which correlates with cognitive gains. While the effects are most pronounced in individuals without the APOE ε4 allele, the intervention is generally safe and well-tolerated. These findings suggest that consistent exogenous ketone supplementation may support brain function in early cognitive decline.

Ketogenic Supplement Increases Brain Network Stability

A 2020 study by Mujica-Parodi et al. investigated how dietary interventions influence brain network stability—a proposed biomarker of brain aging. Using functional MRI and advanced network analysis, the researchers found that brain network stability declines with age but can be improved through nutritional ketosis. In a randomized crossover design, young adults who consumed a ketogenic supplement (containing ketone esters) showed an average 87% increase in brain network stability compared to when they consumed a standard glucose-based meal. These findings suggest that acute nutritional ketosis may enhance brain function by stabilizing large-scale neural networks, offering a potential strategy to counteract age-related cognitive decline even in younger individuals.

References 79-85.

High-Normal Blood Glucose and Brain Atrophy

> *"There's studies showing that people, even on the high end of normal, in terms of their blood glucose levels, so they're normal, but they're kind of on the high end of normal. They had more brain atrophy than people on the low end of normal."*

Emerging evidence suggests that even high-normal blood glucose levels—within the non-diabetic range—may contribute to greater brain atrophy. Studies in older adults without diabetes have found that fasting glucose levels below 6.1 mmol/L, but at the higher end of this range, are associated with reduced gray and white matter volumes in the frontal cortex, hippocampus, and amygdala—regions critical for memory and executive function. Similar patterns are observed in middle-aged and even younger adults, where elevated glucose correlates with thinner parahippocampal gyri and decreased white matter integrity. These structural changes are often linked to poorer cognitive performance and may indicate that subtle brain injury begins early in the course of impaired glucose metabolism. Maintaining fasting glucose at the lower end of the normal range may thus support long-term brain health.

References 86-88.

Cognitive and Cardiovascular Benefits of Blueberries and Polyphenols

"Blueberries are a source of polyphenols (...) polyphenols have been shown even in studies to improve cognition and memory and lower even marker markers of bad cardiovascular disease (...) even a cup of blueberries a day has been shown to improve cognition (...) It increases blood flow to the brain."

Blueberries are rich in polyphenols, particularly anthocyanins, which have been shown to support both cognitive and cardiovascular health. Randomized controlled trials and meta-analyses indicate that regular consumption of blueberries or polyphenol-rich extracts can enhance memory, executive function, and working memory—especially in older adults and individuals experiencing age-related cognitive decline. These effects are thought to arise from increased levels of circulating phenolic metabolites and improved cerebral blood flow.

Cardiovascular benefits include reduced systolic blood pressure, improved endothelial function, and decreased markers of oxidative stress and inflammation. Notably, these outcomes have been observed at dietary doses as low as one cup of blueberries per day, underscoring their potential as a practical, food-based strategy for promoting brain and heart health.

References 89-93.

Omega-3s from Seafood: Longevity, Inflammation, and Heart Health

"salmon because it is a fatty source of fish that is high in Omega-3 fatty acids, EPA and DHA, which are found in marine sources, not plant sources of Omega-3 (...) it resolves inflammation. It's sort of an anti-inflammatory (...)

This Harvard study identified not eating enough seafood as one of the top six preventable causes of death (...)

Omega-3 fatty acid levels in our blood cells, red blood cells, this is called the Omega-3 index. (...) there's been a variety of studies done from Dr. Bill Harris out of the Fatty Acid Research Institute (...) showing that people with what's called a high Omega-3 index (...) They had a five year increased life expectancy compared to people with a low Omega-3 index (...)

there've been some really large randomized controlled trials that have actually given people with cardiovascular disease that are on, you know, some sort of standard of care treatment, like a statin. And they've given them four grams a day of a purified form of Omega-3 called EPA versus a placebo. And the people given the Omega-3, had 25% less cardiovascular related death or events like heart attacks and strokes."

Omega-3s from Salmon Reduce Inflammation

Salmon is a rich source of omega-3 fatty acids—particularly EPA and DHA—which are well-documented for their anti-inflammatory effects. These fatty acids reduce pro-inflammatory cytokines, modulate inflammatory signaling pathways, and generate specialized mediators that help resolve inflammation. Clinical studies show that salmon oil can lower markers such as CRP, IL-6, and TNF-α, with benefits observed in conditions like rheumatoid arthritis, atherosclerosis, and other chronic inflammatory diseases. Maintaining a low omega-6 to omega-3 ratio, such as through regular salmon consumption, supports a balanced immune response and may reduce chronic inflammation.

Low Seafood Intake: A Preventable Causes of Death

A comprehensive study led by researchers at the Harvard School of Public Health identified low seafood intake—specifically omega-3 fatty acids—as one of the top six preventable causes of death in the United States. Published in PLoS Medicine, the study estimated that insufficient consumption of omega-3s from seafood contributed to approximately 84,000 adult deaths per year, placing it alongside more widely recognized risk factors like smoking, high blood pressure, and obesity. The researchers analyzed data from national surveys and epidemiological studies to quantify the mortality burden of twelve modifiable lifestyle and metabolic risks.

Omega-3 Index and Life Expectancy

A large pooled analysis examined data from 17 prospective cohort studies involving over 42,000 individuals across 10 countries to explore the relationship between blood omega-3 fatty acid

levels and mortality. The study found that individuals with higher circulating levels of long-chain omega-3 polyunsaturated fatty acids (specifically EPA, DPA, and DHA)—a profile often summarised as the "Omega-3 Index"—had a 15–18% lower risk of death from all causes compared to those with the lowest levels. This association was independent of factors such as age, sex, smoking status, physical activity, and other health metrics. Based on these findings, the authors estimated that having a high Omega-3 Index could be associated with a longevity benefit of approximately five additional years of life expectancy, a magnitude comparable to the benefits of not smoking. These results suggest that omega-3 status may be a modifiable and meaningful biomarker of healthy aging.

EPA Supplementation Reduces Cardiovascular Risk

A randomized controlled trial known as REDUCE-IT investigated the effects of icosapent ethyl—a purified form of eicosapentaenoic acid (EPA)—on cardiovascular outcomes in over 8,000 patients with established cardiovascular disease or diabetes and elevated triglyceride levels, all of whom were already receiving statin therapy. Participants who received 4 grams of EPA daily experienced a 25% relative risk reduction in major adverse cardiovascular events compared to the placebo group. These events included cardiovascular death, heart attacks, strokes, and the need for coronary revascularization.

References 94-98.

Fish Oil Supplements as a Cleaner Omega-3 Source

> *"fish oil supplements are purified. So you're not getting mercury. Or microplastics or things that are also found in the whole fish. (...) we do have this environmental pollution problem, and fish have been contaminated with heavy metals. They've been contaminated with microplastics (...) And so I do think that fish oil supplements are a good alternative because you're getting those Omega-3 fatty acids and you're not getting some of the other bad things that are in the fish."*

Fish oil supplements are widely regarded as a safer alternative to whole fish when it comes to mercury exposure. Multiple studies have shown that mercury is either undetectable or present at extremely low levels in most fish oil products, well below regulatory safety limits. This contrasts with certain large, predatory fish—such as swordfish or tuna—which can accumulate higher mercury concentrations and pose a risk to frequent consumers. However, while fish oil supplements avoid

many of the heavy metal concerns associated with whole fish, they are not entirely free from environmental contaminants. Recent research has detected microplastics in both fish- and plant-based omega-3 supplements, primarily introduced during manufacturing and packaging processes. Although these microplastic levels are relatively low and not yet linked to known health risks, their presence highlights the need for improved quality control and further study. Overall, purified fish oil supplements may reduce mercury exposure, but they do not entirely eliminate concerns around environmental pollutants.

References 99-103.

Creatine's Role in Muscle, Brain, Mood, and Cancer Risk

"[creatine] can increase muscle mass, it can increase muscle strength in combination with resistance training (...)

any kind of stressful condition, that's where creatine shines in the brain (...)

it's been found that if you take someone and you sleep deprive them for 21 hours and give them about 25 to 30 grams of creatine, it completely negates the cognitive deficits of sleep deprivation. Actually, not only does it negate the cognitive deficits of sleep deprivation, it makes people function better than if they were well rested (...)

I was reading about study in 2025 where they gave creatine to people that had depressive symptoms alongside CBT training and the people that had creatine and the cognitive behavioral therapy training experienced a greater improvement in their depression symptoms than those who just received the cognitive behavioral therapy (...)

There's a new study that came out (...) it did show that giving people with Alzheimer's disease, creatine, I believe it was 20 grams a day, did improve their cognition.

a 2025 study of 25,000 people each found that for each additional 0.09 grams of creatine over a two day average was linked to a 14% reduction in cancer risk."

Muscle Mass and Strength

Creatine supplementation has been extensively studied and is strongly supported as an effective way to enhance muscle growth and strength when paired with resistance training. Research shows that individuals who take creatine while engaging in resistance exercise gain approximately 1 to 1.4 kilograms more lean body mass and experience an 8–14% greater improvement in strength compared to those who train without it. These benefits are observed across age groups, including older adults and women, particularly when supplementation is sustained over time. Strength improvements can begin within just two weeks, and creatine also supports muscle hypertrophy by increasing muscle fiber size and cellular adaptations. Overall, creatine is a well-established and safe supplement for maximizing the results of resistance training.

Supporting the Brain Under Stress

Creatine supplementation has shown potential to support brain function under stressful conditions such as sleep deprivation, hypoxia (low oxygen), and chronic psychological stress. Research indicates that creatine can help maintain or restore cognitive performance when the brain's energy supply is strained. Documented benefits include improved memory, attention, and executive function during sleep deprivation; restored attention and increased corticomotor excitability in low-oxygen environments; and enhanced spatial memory and protection of synaptic plasticity under chronic stress. These effects appear most pronounced in individuals with lower baseline brain creatine levels—such as vegetarians, older adults, or those experiencing acute stress. While creatine's benefits in healthy, non-stressed individuals are less consistent, its ability to support brain energy metabolism makes it a promising option for cognitive support during periods of high demand.

Sleep Deprivation Study

A 2024 randomized, double-blind, placebo-controlled study examined the cognitive effects of high-dose creatine supplementation following sleep deprivation. In the study, healthy male participants were kept awake for 21 hours and then administered a single oral dose of creatine monohydrate at 0.35 grams per kilogram of body weight—equating to approximately 25 to 30 grams for an average adult male. Compared to placebo, creatine significantly improved performance across multiple cognitive domains, including attention, working memory, reaction time, and executive function. In some tasks, participants who received creatine performed better than they had when well rested. These findings suggest that acute high-dose creatine may not only offset the cognitive

deficits caused by short-term sleep deprivation but, under certain conditions, enhance performance beyond baseline levels.

Creatine and CBT for Depression

A 2025 randomized controlled trial investigated whether creatine monohydrate could enhance the effects of cognitive behavioral therapy (CBT) in individuals with depressive symptoms. Over the course of eight weeks, participants received either 5 grams of creatine daily alongside CBT or CBT with a placebo. Those in the creatine group experienced significantly greater reductions in depressive symptoms, with the effect most pronounced in individuals reporting higher levels of physical fatigue at baseline. The findings suggest that creatine may act as a helpful adjunct to psychotherapy, particularly in cases where depression is accompanied by low energy or fatigue-related symptoms.

Creatine as Supportive Therapy in Alzheimer's Disease

A 2025 pilot study investigated the effects of creatine monohydrate supplementation in individuals with mild to moderate Alzheimer's disease. Participants received 20 grams of creatine per day for one week, followed by a maintenance dose of 5 grams daily for five additional weeks. The intervention was well tolerated and led to increased brain creatine levels, as measured by magnetic resonance spectroscopy. While the study was not powered to detect clinical efficacy, exploratory cognitive assessments suggested a trend toward improved memory and executive function in some participants. These preliminary findings indicate that creatine may hold promise as a supportive intervention in Alzheimer's disease, though larger, controlled trials are needed to confirm cognitive benefits.

Higher Dietary Creatine Intake Linked to Lower Cancer Risk

A 2025 epidemiological study involving over 25,000 U.S. adults examined the relationship between dietary creatine intake and cancer risk. Using data from the National Health and Nutrition Examination Survey (NHANES), researchers found that for each additional 0.09 grams of creatine consumed over a two-day average, there was a 14% reduction in the odds of reporting a cancer diagnosis. This association remained significant after adjusting for demographic, dietary, and lifestyle factors. While the study does not establish causation, it suggests that higher habitual dietary creatine intake may be linked to a lower risk of cancer. Further research is needed to determine whether this relationship reflects a protective biological effect or correlates with other health-related behaviors.

References 104-112.

Fasting, Autophagy, and Muscle Preservation

“you mentioned autophagy (...) that's the big one that's happening only when you're really in a fasted state (...) generally speaking, it's the clearing out of damaged stuff within your cell (...)

some of the metabolic benefits from fasting include improved glucose levels, improved blood pressure regulation (...) weight loss (...)

Studies have shown people that undergo intermittent fasting tend to lose muscle mass because they're eating fewer meals, they're not getting as much protein, and perhaps they're not doing resistance training. Now there have been other studies that have looked at people doing intermittent fasting and resistance training, and they don't lose muscle mass because they're doing, they're getting that mechanical stimulation of their, of their muscles, which is preventing the loss of muscle mass.”

Autophagy is a fundamental cellular process in which cells break down and recycle damaged or unnecessary components to maintain internal balance and function. Often described as the body’s cellular “clean-up” system, autophagy plays a key role in protecting against aging and a wide range of diseases. By clearing out toxic protein aggregates, it helps reduce the risk of neurodegenerative conditions like Alzheimer’s and Parkinson’s. Autophagy also supports metabolic health by maintaining insulin sensitivity and reducing the risk of obesity and type 2 diabetes. Additionally, it strengthens immune defense by helping the body eliminate pathogens and control inflammation. While autophagy generally promotes cardiovascular health and suppresses early tumor formation, its effects can be more complex in advanced heart disease or cancer, where excessive or impaired autophagy may be detrimental. Importantly, autophagy tends to decline with age and in chronic illness, making its support a potential target for enhancing longevity and disease resistance.

Metabolic Benefits of Fasting

Fasting—particularly intermittent fasting—has been shown to offer a range of metabolic health benefits. Research indicates that fasting can support weight loss, improve insulin sensitivity, lower blood pressure, and reduce harmful blood lipids such as LDL cholesterol and triglycerides. It

also helps decrease inflammation and oxidative stress, contributing to better cardiovascular health. Mechanistically, fasting induces a metabolic switch—typically after 12 to 16 hours—where the body shifts from using glucose to burning fat and producing ketones. This switch not only supports energy balance but may also protect against metabolic diseases. Fasting has also been found to influence circadian rhythms, modulate hormone levels, and activate cellular repair processes like autophagy. While fasting is particularly effective in individuals with obesity or metabolic syndrome, its impact on blood sugar control in people with type 2 diabetes may be limited and should be approached with caution. Overall, fasting is emerging as a promising non-pharmacological approach to improving metabolic health.

Resistance Training Prevents Muscle Loss During Intermittent Fasting

While intermittent fasting can lead to muscle mass loss when not properly managed, research shows that resistance training is a highly effective way to prevent this outcome. Studies consistently find that individuals who engage in fasting without strength training are more likely to lose lean body mass, particularly if protein intake is low. In contrast, those who combine intermittent fasting with regular resistance training—alongside adequate protein consumption—are able to preserve or even increase muscle mass while reducing body fat. This protective effect has been observed across age groups, including in older adults undergoing calorie restriction. Overall, pairing fasting with resistance training and sufficient dietary protein supports fat loss without compromising muscle integrity or performance.

References 113-116.

Late-Night Eating, Melatonin, and Glucose Dysregulation

> *“when you eat later in the day, let's say eight o'clock at night, nine o'clock at night, your body's starting to naturally make melatonin. That's a hormone that's involved in helping you get sleepy while melatonin also nhibits the production of insulin. And so you basically will have elevated blood glucose levels when you're eating later in the day (...) your glucose regulation is impaired somewhat (...) there are some interesting studies that have found that people sleep better if they stop eating at least three hours before bed.”*

Late-night eating has been shown to impair both glucose regulation and sleep quality, largely due to the effects of melatonin on insulin function. As melatonin levels naturally rise in the evening to prepare the body for sleep, this hormone also suppresses insulin secretion. When food is consumed during this period of elevated melatonin, the body's ability to manage blood sugar is reduced, leading to higher post-meal glucose levels and a diminished insulin response. These effects are particularly pronounced in individuals with certain genetic variants, such as MTNR1B. Over time, this disruption in glucose metabolism may contribute to sleep disturbances and increase the risk of obesity, insulin resistance, and related metabolic disorders. These findings suggest that avoiding food intake in the hours leading up to sleep may support both metabolic and sleep health.

Research suggests that eating within one to three hours of bedtime is associated with more frequent nighttime awakenings and poorer sleep quality, particularly in younger adults. In contrast, allowing at least three hours between the final meal and sleep may reduce sleep disruptions and support better overall rest. The type and size of food also matter: large or calorie-dense meals close to bedtime are linked to increased risks of obesity, hypertension, and other metabolic issues, whereas small, nutrient-rich snacks may have neutral or even beneficial effects, especially when paired with exercise.

References 117-120.

Red Light Therapy: Promising for Skin, Questionable for Muscle

> *"I now am convinced that red light therapy plays a role in helping with skin aging (...) There've been enough studies now that is pretty convincing that it does seem to improve the way skin ages (...)*
>
> *Muscular repair, I think that that's where I'm a little more skeptical."*

Skin Aging

Red light therapy, also known as photobiomodulation, has emerged as a promising non-invasive approach to improving signs of skin aging. By using specific wavelengths of red or near-infrared light, this treatment stimulates energy production within skin cells and promotes collagen and elastin synthesis—key proteins responsible for maintaining youthful skin structure.

Clinical studies report that red light therapy can reduce wrinkle depth by around 30% and improve skin texture, elasticity, and hydration. It may also support wound healing and tissue repair. While the treatment is generally well tolerated and free of significant side effects, further high-quality research is needed to refine treatment protocols and confirm long-term outcomes. Nonetheless, current evidence supports its growing use in skin rejuvenation.

Muscle Repair

Red light therapy has shown promise in supporting muscle repair and recovery, particularly when applied before or shortly after exercise or injury. By targeting the mitochondria, red and near-infrared light enhance cellular energy production and reduce oxidative stress, both of which are critical for efficient tissue repair. The therapy also modulates inflammation by lowering pro-inflammatory markers and encouraging a shift toward anti-inflammatory cellular activity, promoting regeneration. In both animal and human studies, red light therapy has been found to reduce markers of muscle damage, such as creatine kinase, improve tissue organization, and support faster recovery of strength and performance. While generally safe and noninvasive, outcomes may vary depending on wavelength, dosage, and timing, and further research is needed to establish standardized treatment protocols.

References 121-124.

Comparing Infrared and Traditional Saunas: Depression, Mortality, and Hormones

“there's a lot of benefits that have been related to more hot, traditional types of saunas (...) lower cardiovascular related mortality. if you're doing it four to seven times a week, that's associated with a 50% lower cardiovascular related mortality versus doing it one time a week (...) it's associated with 40% lower all cause mortality versus doing it one time a week (...)

Dr. Ashley Mason, she's at UCSF, and she's been doing what's called the heat bed study. And it's an infrared sauna that is essentially a head out heat bed (...) And she's looking at the effects on depression. And so what she has found is kind of amazing is that people that are doing this infrared sauna, this heat bed, and doing cognitive behavioral therapy, CBT, they are experiencing massive antidepressant effects (...) Her mentor, Dr. Charles raison (...) did this study where he put people in this sort of infrared sauna (...) people with major depressive disorder (...) that did one treatment of this had an antidepressant effect that lasted six weeks later after one treatment (...)

there have been studies that have looked at people that exercise on a stationary bike or they exercise on a stationary bike and then follow that up with a 15 minute sauna. And it's been shown that those people that do the 15 minute sauna on top of the exercise have a higher improvement in their cardio respiratory fitness (...)

when you go into the sauna (...) growth hormone goes up. In fact it, depending on the, the temperature and duration growth hormone can go up anywhere between twofold to like 16 fold (...)

Frequent Sauna Use Linked to Reduced Cardiovascular and All-Cause Mortality

The Kuopio Ischemic Heart Disease (KIHD) Risk Factor Study, a prospective cohort of over 2,300 middle-aged men from eastern Finland, found that men who used the sauna 2–3 times per week had a 27% lower risk of cardiovascular disease (CVD) mortality compared to those who used the sauna once per week. The effect was dose-dependent: men who used the sauna 4–7 times per week had a 50% lower risk of CVD mortality. Additionally, frequent sauna use was associated with a 40% reduction in all-cause mortality, independent of conventional risk factors

Heat Bed Study

A single-arm feasibility study investigated the effects of an integrated mind-body intervention combining cognitive behavioral therapy (CBT) with whole-body hyperthermia (WBH) for the treatment of major depressive disorder (MDD). Sixteen adults diagnosed with MDD participated in the trial, receiving eight CBT sessions alongside either eight weekly or four bi-weekly WBH sessions. The intervention was well tolerated, with 81.3% of participants completing at least four WBH sessions. Among the 12 participants who completed the final assessment, 91.7% (11 individuals) no longer met diagnostic criteria for MDD, and all demonstrated clinically significant reductions in depression symptoms, as measured by the Beck Depression Inventory-II. Participants who completed both the baseline and final assessment visits (n = 12) showed an average decrease of 15.8 points on the Beck Depression Inventory-II (BDI-II) from pre- to post-intervention. This reduction was both clinically meaningful and statistically significant. Improvements were also observed in negative automatic thinking and mood, with early mood enhancement following the first WBH session predicting overall treatment response. These promising preliminary results suggest that a combined approach targeting both cognitive and thermoregulatory processes may offer a feasible, non-pharmacologic treatment option for depression, warranting further investigation in controlled clinical trials.

Antidepressant Effects of Infrared Sauna

A randomized, double-blind, sham-controlled study investigated the antidepressant effects of a single session of whole-body hyperthermia (WBH) in adults with major depressive disorder (MDD). Participants were randomly assigned to receive either active WBH, which raised core body temperature to approximately 38.5°C, or a sham condition that mimicked the intervention without significant thermal elevation. The primary outcome was change in depression severity, measured by the Hamilton Depression Rating Scale (HDRS). Results showed that a single session of WBH produced a clinically and statistically significant reduction in depressive symptoms compared to the sham condition, with effects persisting for up to six weeks post-intervention. The treatment was well tolerated with no serious adverse events, suggesting that WBH may represent a safe, rapid-acting, and non-pharmacologic intervention for depression.

Combined Sauna and Exercise Enhances Cardiovascular Fitness

A randomized controlled trial investigated the effects of sauna bathing alone, exercise alone, and a combination of both on cardiovascular function in sedentary adults. Participants were assigned

to one of three groups: 15 minutes of stationary cycling, 15 minutes of sauna exposure, or 15 minutes of cycling followed by 15 minutes of sauna, performed three times per week over eight weeks. The group that combined exercise with sauna exposure showed significantly greater improvements in cardiorespiratory fitness, as measured by VO_2peak, compared to either intervention alone. This group also exhibited enhanced vascular function and greater reductions in blood pressure, indicating a synergistic benefit of combining sauna use with aerobic exercise.

Acute Growth Hormone Response to Sauna Exposure

Sauna exposure induces a significant but transient increase in growth hormone (GH) levels, with serum concentrations rising sharply during the session and returning to baseline within a few hours. One study reported a 142% increase in GH during sauna use, underscoring the acute endocrine response to heat stress. This effect occurs independently of exercise, although combined exercise and sauna use can further elevate GH levels. Other hormones such as prolactin and norepinephrine also rise briefly during sauna exposure. With repeated sessions, the body may adapt, leading to a diminished hormonal response over time. Individual factors, including sex and physical activity levels, can influence the magnitude of GH elevation, with some evidence suggesting greater responses in women, particularly those unaccustomed to sauna use.

A study conducted in Finland investigated the endocrine responses to repeated sauna bathing in healthy young adults. Over a seven-day period, participants were exposed to dry sauna heat (80°C) for one hour, twice daily. Among male participants, serum growth hormone (GH) levels increased by approximately 16-fold after the first sauna session, while serum prolactin rose by 2.3-fold. In female participants, prolactin increased over four-fold by the third day. Although GH levels declined with continued exposures, prolactin remained elevated through day seven. No significant changes were observed in serum levels of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, or thyroid hormones. These findings suggest that GH and prolactin are particularly responsive to thermal stress, potentially due to heat-induced dehydration, and may play roles in the body's physiological adaptation to repeated heat exposur

References 125-129.

Plastics and Microplastics in Packaging

“there was this plastic study that was done that showed heating up plastic essentially causes these toxic plastic associated chemicals like BPA, Bisphenol A, which is an endocrine disruptor, it disrupts hormones. It sort of mimic estrogen. So, you know, it's, it's sometimes like called an estrogen mimetic. It causes that to leach into your beverage 55 times more (...)

there was a study that just came out (...) that showed glass had higher levels. So water that was in glass had higher levels of microplastic than water that was in plastic containers (...) the study came outta France and it was essentially showing that glass bottles had more microplastics in the liquid that they contained than plastic bottles which contain liquid (...)

Microplastics and nanoplastics. As you get smaller in size, they get smaller. They're called nanoplastics. Those are the most dangerous because it can be more easily absorbed in the gut and get into the circulation (...)

again, aluminum cans are lined with this plastic (...) There was this study that showed, I think it was, was it a thousand percent increase of BPA after drinking like soup out of a can versus a soup out of a glass? A thousand percent increase in bisphenol A levels (...)”

Heat Significantly Increases BPA Leaching from Plastics

A 2003 study published in Environmental Health Perspectives investigated the migration of chemicals from polycarbonate plastic containers into liquids under varying conditions. The researchers found that heating significantly increased the release of bisphenol A (BPA), a known endocrine disruptor. Specifically, when new polycarbonate bottles were repeatedly washed and then filled with boiling water, BPA leaching into the water increased by up to 55 times compared to room temperature conditions. This release occurred even in the absence of visible degradation, highlighting that thermal stress alone can drive substantial migration of BPA into liquids. BPA mimics estrogen in the body and has been associated with hormone disruption and potential reproductive and developmental effects.

Microplastic Contamination in French Beverages Linked to Packaging, Especially Glass Bottle Caps

A recent study provides the first systematic assessment of microplastic (MP) contamination in beverages sold in France, analyzing a diverse array of drinks including water, soft drinks, beer, and wine. The researchers detected microplastics in every beverage tested, with levels ranging from approximately 3 particles per liter in water to nearly 83 particles per liter in beer. Contrary to expectations, beverages stored in glass containers were the most contaminated, a finding traced to the paint on metal caps, which was found to shed polyester-based microplastics into the liquid. Controlled experiments confirmed that caps were a significant source of contamination, and that pre-cleaning them could reduce MP levels by up to threefold. This work highlights both the ubiquity of microplastic contamination in consumer products and the critical role of packaging materials—particularly closures—in influencing contamination levels.

Comparative Risks of Nanoplastics and Microplastics

Nanoplastics are increasingly recognized as potentially more hazardous than microplastics, primarily because their smaller size allows them to cross biological barriers more easily, interact more readily with cells, and carry toxic substances into sensitive tissues. While laboratory and animal studies support these concerns, direct comparisons in human populations are still scarce, highlighting a significant gap in current research. Moreover, the detection and measurement of nanoplastics in both environmental samples and biological systems remain technically difficult, complicating efforts to assess exposure and associated risks.

Canned Soup Linked to Over 1200% Increase in Urinary BPA Levels

The study cited—Canned Soup Consumption and Urinary Bisphenol A: A Randomized Crossover Trial—found that consuming one serving of canned soup daily for five days led to a 1221% increase in urinary bisphenol A (BPA) concentrations compared to consuming fresh soup. Specifically, the geometric mean BPA level after canned soup consumption was 20.8 µg/L, versus just 1.1 µg/L after fresh soup. This represents one of the highest BPA concentrations observed in a non-occupational setting and suggests that canned food packaging, especially with epoxy resin linings, is a major source of BPA exposure.

References 130-133.

Proximity to Golf Courses and Parkinson’s Disease Risk

> *“this study showed that people that lived near, within a mile or so of golf courses had a much higher incidence of Parkinson's disease (...) it was a 2025 study. Living within one mile of a golf course increased Parkinson's risk by 126% compared to living over six miles away (...)”*

A 2025 population-based case-control study published in JAMA Network Open investigated whether proximity to golf courses is associated with an increased risk of Parkinson’s disease (PD). Utilizing data from the Rochester Epidemiology Project spanning 1991 to 2015, the study analyzed 419 incident PD cases and 5,113 matched controls. The researchers found that individuals living within one mile of a golf course had 126% increased odds of developing PD compared to those living more than six miles away. Risk generally declined with increasing distance. Additionally, individuals residing in water service areas containing a golf course—particularly in regions with vulnerable groundwater—exhibited significantly elevated odds of PD. These findings suggest that pesticide exposure from golf courses, potentially via both contaminated drinking water and airborne transmission, may contribute to heightened PD risk among nearby residents

Reference 134.

Leafy Greens, Magnesium, and Sulforaphane: DNA Repair, Detox, and Longevity

“leafy greens are high magnesium (...) Magnesium is very important for preventing damage to DNA and cancer (...) there've been studies that have shown that for every hundred milligram decrease in magnesium intake, there's a 24% increase in pancreatic cancer incidents, and that's in a dose dependent manner (...)

I particularly like kale and broccoli because of something called sulforaphane (...) Sulforaphane is also increases glutathione in the brain. It helps detoxify pollutants like benzene, BPA”

close to 50% of the population in the United States does not have adequate levels of magnesium because they're not eating the foods that they need to to get the magnesium dark leafy greens (...)

So there's also studies showing that people with the highest magnesium levels have a 40% lower all cause mortality than people with the lowest magnesium levels (...)

magnesium's required to turn vitamin D three into the steroid hormone (...)

Athletes require between 10 to 20% more magnesium than the general population because their magnesium losses are so great”

Leafy green vegetables are a reliable and nutrient-dense source of dietary magnesium, offering a natural means to support metabolic function and prevent deficiency. Commonly consumed greens such as spinach, collards, turnip greens, and lettuce contain substantial magnesium concentrations, ranging from approximately 28 mg to over 100 mg per 100 grams. Spinach, in particular, stands out with levels reaching up to 85 mg per 100 grams. While a small portion of this magnesium is bound to chlorophyll (typically 2.5%–10.5%), the majority remains bioavailable, with human studies indicating net absorption rates between 40% and 60%. These vegetables are especially recommended for populations vulnerable to magnesium deficiency, including pregnant women. However, preparation methods matter—frying leads to the greatest loss of magnesium, while boiling causes the least.

Magnesium and DNA Integrity

Magnesium plays a critical role in maintaining DNA stability and facilitating effective DNA repair. Both human and animal studies have shown that magnesium deficiency increases markers of DNA damage—such as micronuclei and nucleoplasmic bridges—particularly when combined with other risk factors like elevated homocysteine. In animal models, even short-term magnesium deficiency leads to increased oxidative DNA damage and altered expression of genes involved in cellular aging and DNA repair. Mechanistically, magnesium functions as a necessary cofactor for enzymes that govern DNA replication and repair; its absence impairs these processes, destabilizes DNA structure, and heightens susceptibility to oxidative stress. Supplementation studies further support magnesium's protective role, demonstrating reductions in oxidative DNA damage across various populations.

Magnesium Intake and Cancer Risk Reduction

Higher dietary magnesium intake is associated with a reduced risk of several major cancers, with the most consistent evidence seen for colorectal, liver, and breast cancers. Meta-analyses and large cohort studies suggest that each additional 100 mg of dietary magnesium per day may lower overall cancer mortality by approximately 5%, though this effect appears specific to food-derived magnesium rather than supplements. For liver cancer, increased magnesium intake has been linked to a substantial 35–56% reduction in incidence and mortality, particularly among individuals with high alcohol consumption or elevated body weight. Colorectal cancer risk also shows a modest but consistent decline with higher magnesium intake, especially in relation to colon cancer. In the case of breast cancer, the association is supported both directly and indirectly through magnesium's anti-inflammatory effects, such as reduced C-reactive protein (CRP) levels. Although the evidence for other cancers—such as pancreatic, gastric (noncardia), and lung—is less consistent, some large-scale studies report a protective association in certain populations.

Sulforaphane Enhances Brain Glutathione

Sulforaphane, a bioactive compound derived from cruciferous vegetables, has been shown to increase glutathione levels in the brain across both human and animal studies. Glutathione is a vital intracellular antioxidant that protects neurons from oxidative stress and supports overall brain health. In a clinical pilot study, daily oral supplementation with sulforaphane for seven days resulted in measurable increases in glutathione concentrations in several brain regions, including the thalamus, as assessed by advanced neuroimaging techniques. Animal and cell models further

demonstrate that sulforaphane boosts both total and reduced glutathione, enhances the expression of glutathione-synthesizing enzymes, and protects against neuronal oxidative damage. These effects are mediated primarily through activation of the Nrf2 (nuclear factor erythroid 2–related factor 2) antioxidant response pathway, which upregulates genes responsible for cellular redox balance, including γ-glutamylcysteine synthetase.

Sulforaphane and Detoxification: Protective Effects Against BPA, Potential Role in Benzene Defense

Sulforaphane is widely recognized for its ability to activate detoxification pathways, particularly through stimulation of phase II enzymes via the Nrf2 pathway. While it is often cited in the context of environmental toxin defense, the evidence for its detoxifying effect varies by compound. In the case of bisphenol A (BPA), multiple animal and cell studies show that sulforaphane mitigates BPA-induced toxicity—such as liver fat accumulation, glucose intolerance, and insulin resistance—by reducing oxidative stress, inflammation, and endoplasmic reticulum stress. These findings demonstrate strong protective effects but do not confirm enhanced BPA metabolism or excretion. For benzene, direct evidence is lacking; however, sulforaphane has been shown to upregulate detoxification enzymes involved in the clearance of structurally similar carcinogens, such as benzo(a)pyrene. While this suggests a plausible mechanism for benzene defense, it remains inferential. Overall, sulforaphane supports general detoxification capacity and shows clear benefit in counteracting BPA toxicity, with possible—though unproven—relevance to benzene exposure.

Magnesium Deficiency in the United States

Magnesium deficiency is common in the United States, with approximately 45% to 60% of adults failing to meet recommended intake levels. Many cases are subclinical and may not be detected by standard blood tests, leading to underdiagnosis.

Magnesium Status and All-Cause Mortality Risk

Higher magnesium levels—particularly from dietary sources—are consistently associated with reduced all-cause mortality in the general population. Large cohort studies show that each 100 mg/day increase in dietary magnesium intake is linked to a 6–10% lower risk of death from any cause. Very low serum magnesium concentrations are associated with significantly increased mortality, while the lowest overall risk is observed within a normal serum magnesium range. Both magnesium deficiency and excess appear detrimental, indicating a U-shaped relationship. In individuals with chronic conditions such as hypertension, diabetes, asthma, and kidney disease, low

magnesium status is a strong predictor of elevated mortality risk. Additionally, among stroke survivors, higher total magnesium intake (from both diet and supplements) has been associated with a 40% reduction in all-cause mortality compared to the lowest intake group.

Role of Magnesium in Vitamin D Metabolism

Magnesium is involved in many enzymatic reactions in the body, including those related to vitamin D metabolism. Magnesium acts as a cofactor for enzymes that convert vitamin D3 (cholecalciferol) into its active steroid hormone form, calcitriol (1,25-dihydroxyvitamin D3). Without adequate magnesium, these conversion steps may be less efficient.

Elevated Magnesium Needs in Athletes

Athletes generally require more magnesium than non-athletes due to increased physiological demands and greater losses through sweat and urine during exercise. Physical activity elevates metabolic processes that rely heavily on magnesium for energy production, muscle contraction, and electrolyte regulation. Research shows that despite consuming more dietary magnesium on average, athletes often exhibit lower serum levels and higher urinary excretion, suggesting increased requirements. Up to 22% of elite athletes may experience clinical magnesium deficiency at some point, particularly females, individuals with high sweat rates, or those on calorie-restricted diets. To support performance, recovery, and overall health, regular dietary assessments and personalized supplementation strategies are recommended when magnesium intake or retention may be inadequate.

References 135-150.

Vitamin K's Role in Blood Clotting

> *"vitamin K is important for blood coagulation, blood clotting (...) it's one of the reasons why when a baby's first born, they give it a vitamin K shot so that they have blood coagulation."*

Vitamin K plays a critical role in blood clotting by enabling the activation of specific proteins required for the coagulation process. It acts as a cofactor in the liver for an enzyme that modifies clotting factors—specifically factors II, VII, IX, and X, as well as regulatory proteins C and S—so they

can bind calcium and function properly in forming blood clots. Without adequate vitamin K, these clotting proteins remain inactive, leading to an increased risk of bleeding. Although deficiency is uncommon in healthy adults, it can occur in newborns, individuals with malabsorption issues, or those taking medications that interfere with vitamin K metabolism. Maintaining sufficient vitamin K levels is essential for proper blood clot formation and overall hemostatic health.

References 151-152.

Choline, Epigenetics, and Cognitive Development in Children

> *"Choline is an essential nutrient that is (...) important for producing all these epigenetic changes called methylation that regulates the way our genes are expressed (...) it's very important for our cells, like the membranes of our cells (...)*
>
> *pregnant women were given 480 milligrams a day of choline, or (...) 930 milligrams a day (...) And then a variety of cognitive tests were done after the child was born (...) the mothers that had children that were given the really high choline intake, the 930 milligrams scored better on all these IQ tests."*

Choline's Central Role in Methylation and Epigenetic Regulation

Choline is a critical nutrient that serves as a major methyl donor, supporting essential methylation processes throughout the body. Through its conversion to betaine, choline contributes methyl groups required for the synthesis of methionine and subsequently S-adenosylmethionine (SAM), the universal methyl donor involved in DNA and histone methylation. These epigenetic modifications influence gene expression without changing the genetic code, playing a vital role in development, cellular function, and long-term health. Choline's impact is particularly pronounced during prenatal development, where maternal intake has been shown to shape offspring epigenetics and health outcomes in animal studies. Its function is intricately linked to other nutrients—such as folate and methionine—within a shared methylation network, where deficiency in one increases demand on the others. Additionally, gut microbiota can deplete choline, reducing its availability for methylation and affecting DNA methylation patterns. Overall, adequate choline intake is essential for maintaining epigenetic integrity, supporting liver function, and mitigating disease risk.

Maternal Choline Supplementation Enhances Infant Cognitive Processing Speed

A randomized, double-blind controlled trial by Caudill et al. (2018) investigated the effects of maternal choline supplementation during the third trimester on infant cognitive development, specifically processing speed. Pregnant women were assigned to consume either 480 mg or 930 mg of choline per day from 27 weeks of gestation until delivery. At 4, 7, 10, and 13 months of age, their infants underwent a visual sustained attention task, with the key outcome being the speed of processing visual stimuli. The infants of mothers in the higher choline group (930 mg/day) consistently exhibited significantly faster processing speeds across all time points compared to those in the lower choline group. These findings demonstrate that maternal choline intake at levels nearly double the current recommended dietary intake can have lasting positive effects on infant cognitive performance, likely mediated by enhanced methylation and neurodevelopmental support during gestation.

References 153-156.

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