Independent Research & Further Reading

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Visceral Fat

“70% of women over the age of 50 have a high amount of visceral fat. 50% of men over the age of 50 have a high amount of visceral fat. This visceral fat, for one, it's going to double your risk of early mortality (...) people with a high amount of visceral fat are 44% more likely to get metastatic cancer (...)

Most people do have too much visceral fat (...)

this type of fat (...) causes insulin resistance (...)

What's causing visceral fat? You know, I mentioned age (...) Hormones is a big one (...) mostly it's our diet and our lifestyle that's really affecting visceral fat (...) sleep is a big one. there was a study in healthy young men. These men were sleep restricted (...) These were healthy young men, college age students (...) They gained 11% visceral fat after that two weeks, but not a pound on the scale.

So there was a recent study that again, was in healthy young men (...) given about 1200 extra calories a day and it was mostly from ultra processed foods, right? (...) After that five days, they started to gain visceral fat. They started to have signs of fatty liver after five days, and their brains became insulin resistant (...)

Alcohol's another one. If you drink, if you're excessively consuming alcohol, you're gonna store a lot of the energy that you're also consuming is gonna be stored viscerally (...)

And exercise does cause you to lose visceral fat. It's not just any type of exercise really has to be aerobic. And the more vigorous the better.”

Visceral Fat Prevalence in Adults Over 50

Visceral fat (fat stored around internal organs) increases with age in both men and women. Large cohort and imaging studies show that a substantial proportion of older adults meet criteria for elevated visceral fat, often around 40–60%, depending on the definition used. In some higher-risk or older subgroups, particularly men over 50–60 and individuals with higher BMI, prevalence can exceed 50%. Among women, visceral fat increases significantly after menopause, and in some groups over 60, prevalence may approach or exceed 50%, but estimates as high as 70% are not consistently observed. Prevalence varies widely depending on how “high” visceral fat is defined (for example,

percentile-based versus absolute thresholds), as well as population characteristics such as ethnicity and health status.

Prevalence of Excess Visceral Fat

Excess visceral fat (fat stored around internal organs) is common in adult populations, but whether “most” people have too much depends on how it is defined and the population studied. There is no single universal cut-off for what constitutes “high” visceral fat, and prevalence estimates vary accordingly.

Large imaging studies show that a substantial proportion of adults exceed risk-based thresholds. For example, in the Framingham Heart Study, over 40% of men and women had visceral fat levels classified as high relative to a healthy reference group. Other studies report that prevalence increases with age and can exceed 50% in older adults, particularly in men. Some cohorts also show that a notable proportion of individuals with normal BMI still have elevated visceral fat and associated metabolic risk. Prevalence varies by ethnicity, sex, and age, with higher levels typically observed in men, older individuals, and certain populations such as those of Asian background, who may experience metabolic risk at lower visceral fat thresholds.

Visceral Fat and Risk of Early Mortality

Higher levels of visceral fat are associated with an increased risk of earlier death, particularly in younger and middle-aged adults. Large population studies, including cohorts from NHANES and UK Biobank, show that individuals with the highest levels of visceral adiposity have approximately 11–70% higher all-cause mortality compared to those with lower levels, alongside reductions in life expectancy of around 2–3 years.

This relationship appears strongest in adults under around 65 years of age and tends to weaken in older populations, where findings can become more complex, sometimes showing a J- or U-shaped pattern in which both very low and very high levels of visceral fat are associated with increased mortality risk. In contrast, subcutaneous fat (fat stored under the skin) is generally less strongly associated with mortality and may be neutral or even protective in some contexts.

Visceral Fat Cytokines and Metastatic Cancer Risk

Inflammatory cytokines secreted by visceral fat are associated with more aggressive and metastatic cancer phenotypes, although direct causal evidence in humans remains limited. In

obesity, visceral adipose tissue becomes chronically inflamed and releases cytokines such as IL-6, IL-1β, IL-8, TNF-α, MCP-1, and TGF-β, which are known to influence tumour biology.

These cytokines have been shown to promote key processes involved in metastasis, including epithelial–mesenchymal transition (EMT, a process by which cancer cells gain migratory and invasive properties), increased cell motility, invasion, angiogenesis (formation of new blood vessels), and the development of cancer stem-like traits. Experimental studies demonstrate that secretions from visceral fat, particularly in obese individuals, can enhance these behaviours in cancer cells across multiple tumour types.

Clinical and translational evidence further supports this association. In colorectal, breast, and endometrial cancers, higher levels of inflammatory cytokines and markers of inflamed visceral fat have been linked to tumour progression, lymph node involvement, recurrence, and mortality. These findings suggest that cytokine-rich visceral fat may contribute to a tumour-promoting environment that facilitates metastatic spread.

Visceral Fat and Insulin Resistance

Visceral fat is strongly associated with insulin resistance, although the relationship is not purely one-directional. Higher levels of visceral adipose tissue (VAT) are consistently linked to reduced insulin sensitivity in imaging and cohort studies, even after accounting for overall body weight.

Mechanistically, visceral fat is metabolically active and contributes to insulin resistance through several pathways. It releases free fatty acids (FFAs) and pro-inflammatory cytokines such as TNF-α and IL-6, which can impair insulin signalling in the liver and muscle. Inflammatory processes within VAT also activate molecular pathways (e.g., NF-κB and ceramides) that disrupt insulin receptor function. Experimental studies in animals further support a causal role, showing that removal of visceral fat can improve insulin sensitivity and reduce systemic inflammation. However, in humans, the relationship is more complex. Insulin resistance and visceral fat accumulation appear to reinforce one another, forming a self-perpetuating cycle. Other factors, such as ectopic fat deposition (fat stored in organs like the liver) and overall adiposity, also contribute.

Risk Factors for Visceral Fat: Age, Hormones, Diet, and Sleep

Age, hormonal changes, and diet and physical activity are well-established factors associated with increased visceral fat, while the role of sleep is less direct and more variable. Visceral fat

increases significantly with age in both men and women, often independently of overall body weight. Hormonal changes play a key role in this process. In women, declining oestrogen levels after menopause are associated with a shift toward greater visceral fat accumulation. In men, lower testosterone and growth hormone levels are linked to increased visceral fat, while hormonal imbalances in women, such as excess androgens, can also promote central fat deposition.

Diet and lifestyle are also important contributors. Higher energy intake, particularly from refined carbohydrates and lower-quality diets, is associated with greater visceral fat, whereas diets richer in fibre, healthy fats, and balanced macronutrients are linked to lower levels. Physical inactivity and sedentary behaviour further increase risk, while regular moderate-to-vigorous activity is associated with reduced visceral fat.

Sleep appears to influence visceral fat more indirectly. While poor or short sleep is not consistently identified as a strong independent predictor, related behaviours such as irregular meal timing, including late eating or skipping breakfast, are associated with increased visceral fat. These patterns may reflect broader circadian and lifestyle disruptions.

Study: Sleep Restriction and Visceral Fat Accumulation

A controlled experimental study found that sustained sleep restriction can directly increase visceral fat, even over a short period. In this 21-day inpatient, randomised crossover study, healthy young adults were assigned to either a normal sleep condition (9 hours in bed per night) or a restricted sleep condition (4 hours in bed per night) for 14 consecutive nights, with free access to food throughout .

Compared to the normal sleep condition, sleep restriction led to increased calorie intake without any change in energy expenditure, resulting in measurable physiological changes. Participants gained significantly more weight under sleep restriction, with an average increase of approximately 0.5 kg. More notably, visceral fat increased by around 11% during the restricted sleep phase, while no such increase was observed under normal sleep conditions. This corresponded to an absolute increase of about 7.8 cm^2 in visceral fat area .

Total body fat did not significantly differ between conditions, indicating that sleep loss preferentially promoted fat redistribution toward the abdominal and visceral region rather than general fat gain. These findings suggest that insufficient sleep may contribute specifically to central

fat accumulation, even over relatively short timeframes, and independent of changes in physical activity or energy expenditure.

Study: Short-Term Overeating, Liver Fat, and Early Metabolic Changes

A controlled human study in healthy young men (aged 19–27, normal BMI) examined the effects of short-term overeating by adding approximately 1,500 kcal per day for 5 consecutive days through ultra-processed, calorie-dense snacks, including foods such as chocolate bars, brownies, and chips, with a macronutrient profile of roughly 47–50% fat and 40–45% carbohydrates, consumed in addition to participants' usual diet .

Despite this substantial caloric surplus over a brief period, participants did not show significant changes in body weight, total adiposity, or visceral fat. However, liver fat increased markedly, rising from approximately 1.55% to 2.54% over just five days, indicating rapid accumulation of intrahepatic fat even in the absence of overall weight gain. Notably, the study identified early disruption of brain insulin responsiveness following this high-caloric intake, suggesting that metabolic dysfunction may begin centrally before detectable systemic insulin resistance or weight gain occurs. These findings indicate that even brief periods of excess intake, particularly from energy-dense, ultra-processed foods, can rapidly promote fatty liver accumulation and alter metabolic regulation, preceding more overt changes such as weight gain or insulin resistance.

Alcohol Consumption and Visceral Fat Accumulation

Excessive alcohol consumption, particularly heavy and binge drinking, is associated with increased visceral fat and other forms of ectopic fat. Imaging studies in male populations consistently show that higher alcohol intake is linked to greater visceral fat area and a higher visceral-to-subcutaneous fat ratio, even after accounting for body mass index, suggesting a preferential accumulation of fat in the abdominal region rather than under the skin.

Large cohort studies further support this relationship. In multi-ethnic population data, heavy and binge drinking are associated with increased visceral, liver, and other ectopic fat depots, often following a J-shaped pattern in which moderate drinkers show lower levels than both abstainers and heavy drinkers. Meta-analytic evidence also indicates that high alcohol intake (e.g., above ~28 g/day) is associated with increased odds of abdominal obesity, reflected in measures such as waist circumference and waist-to-hip ratio.

Mechanistically, excessive alcohol intake may promote visceral fat accumulation through hormonal and metabolic effects, including increased cortisol, reduced adiponectin (a hormone involved in fat metabolism), and alterations in appetite regulation and lipid processing, which favour fat storage in the abdominal and hepatic regions.

Aerobic Exercise and Reduction of Visceral Fat

Aerobic exercise is effective in reducing visceral fat, with consistent findings across multiple randomised controlled trials and meta-analyses. Interventions lasting approximately 12–16 weeks, typically involving 3 sessions per week of 30–60 minutes, are associated with meaningful reductions in visceral adipose tissue, often in the range of 30–40 cm^2 on imaging. Notably, these reductions can occur even in the absence of substantial weight loss, suggesting a preferential effect of aerobic exercise on visceral fat rather than overall body mass.

Exercise intensity appears to play an important role. Evidence from network meta-analyses indicates that moderate-to-vigorous aerobic exercise, including vigorous-intensity training and high-intensity interval training (HIIT), is among the most effective approaches for reducing visceral fat. Studies also show greater reductions in waist circumference, a proxy for visceral fat, with vigorous compared to moderate intensity exercise. However, when total energy expenditure is matched, some trials report similar reductions in visceral fat between moderate and vigorous intensity, suggesting that overall exercise volume and caloric expenditure may be as important as intensity itself.

References 1-53.

Timing of Eating Before Bed and Sleep Quality

> *"it's not a good idea to eat a meal, a big meal, three, three hours before fewer than three hours before bed. So you wanna stop eating three hours before bed. And three is really the magic number in multiple studies because when you eat a meal, it is activating your sympathetic nervous system."*

Research suggests that avoiding large meals within approximately 2–3 hours of bedtime is generally associated with better sleep quality, although findings are not entirely consistent across all

populations. Observational studies, particularly in young and middle-aged adults, indicate that eating closer to bedtime (within around 3 hours) is linked to higher likelihood of nocturnal awakenings and poorer overall sleep quality, even if total sleep duration is not consistently affected. Larger population datasets similarly show that shorter intervals between the last meal and sleep are associated with more disrupted sleep, whereas longer intervals, often around 4–6 hours, are linked to more optimal sleep patterns.

However, this relationship depends on context. Some controlled studies show that eating closer to bedtime does not necessarily impair sleep architecture and may, in certain cases, initially deepen sleep. In older adults and shift workers, shorter meal-to-sleep intervals, particularly with lighter or protein-rich meals, may even support sleep duration and efficiency, though evidence remains limited. Meal size and composition appear to be important moderating factors. Heavier, energy-dense meals, particularly those high in fat, refined carbohydrates, or stimulants such as caffeine, are more consistently associated with poorer sleep outcomes when consumed close to bedtime. In contrast, lighter snacks are less likely to disrupt sleep.

References 54-63.

Resistant Starch: Benefits on Sleep and Gut

> *“resistant starch does interestingly seem to help improve sleep (...)*
>
> *Very beneficial for the gut.”*

Research on resistant starch (a fermentable dietary fibre found in foods such as green bananas and cooked–cooled potatoes) and sleep is limited, but emerging evidence suggests a potential association with modest improvements in sleep disturbance. In a randomised clinical trial using a resistant starch blend (including potato starch, green banana flour, and apple fibre), participants consuming approximately 5–15 g per day over 6 weeks showed reductions in sleep disturbance scores, particularly when adherence was high. These improvements became apparent after several weeks of intake, although the primary intention-to-treat analysis did not show a significant effect .

Proposed mechanisms involve the gut–brain axis. Resistant starch is fermented by gut microbiota, promoting the growth of bacteria such as *Bacteroides*, which can produce GABA (gamma-aminobutyric acid, a neurotransmitter involved in sleep regulation). This suggests a plausible biological pathway linking resistant starch intake to sleep modulation, though this remains inferential. More broadly, dietary research indicates that carbohydrate quality influences sleep, with rapidly digested, refined carbohydrates associated with poorer sleep outcomes, in contrast to fermentable fibres such as resistant starch. However, resistant starch itself has not been extensively studied in isolation for sleep as a primary outcome.

Resistant Starch and Gut Health

Resistant starch is generally beneficial for gut health. Once it reaches the colon, resistant starch is fermented by gut microbiota, where it acts as a prebiotic, selectively promoting the growth of beneficial bacteria such as *Bifidobacteria* and butyrate-producing species including *Faecalibacterium* and *Ruminococcus*. Human intervention studies and meta-analytic evidence show that resistant starch consistently alters the composition and metabolic activity of the gut microbiome in a favourable direction.

A key mechanism involves the production of short-chain fatty acids (SCFAs), particularly butyrate, which serves as a primary energy source for colonocytes (cells lining the colon). Butyrate supports intestinal barrier integrity, reduces inflammation, and plays a role in immune regulation. Increased SCFA production is one of the most consistently observed effects of resistant starch fermentation.

Additional evidence, particularly from animal and translational studies, suggests that resistant starch improves gut barrier function by enhancing tight junction proteins (structures that maintain intestinal permeability), increasing mucin production (which protects the gut lining), and reducing inflammatory responses. These effects are associated with improved resilience against conditions such as colitis and other gastrointestinal disturbances.

References 64-71.

High-Intensity Interval Training and Glucose Regulation

> *"I immediately was looking into the scientific literature and found that high intensity interval training and exercise can help almost negate most of the poor effects of causing insulin resistance and causing your glucose regulation to not be normal."*

High-intensity interval training (HIIT), which involves short bursts of intense exercise interspersed with recovery periods, can improve insulin resistance and glucose regulation. Across multiple randomised controlled trials and meta-analyses, HIIT has been shown to reduce fasting glucose, fasting insulin, and HOMA-IR (a measure of insulin resistance), as well as modestly lower HbA1c (a marker of long-term blood glucose control). These effects are most pronounced in individuals with prediabetes, obesity, or type 2 diabetes.

HIIT appears to be broadly comparable to moderate-intensity continuous training (MICT) in improving glycaemic outcomes, with some analyses suggesting slightly greater reductions in insulin resistance and fasting glucose. HIIT also improves post-meal glucose control, reducing glucose and insulin responses after eating. These benefits can occur even with relatively low exercise volumes, for example sessions lasting under 30 minutes with around 15 minutes of high-intensity effort, performed three times per week. Mechanistically, HIIT enhances glucose uptake in skeletal muscle, increases GLUT4 (a glucose transporter), and improves mitochondrial function, contributing to better insulin sensitivity even in the absence of significant weight loss.

References 72-80.

Fasting, Glycogen Depletion, and Benefits of Ketone Production

> *"it takes about 10 to 12 hours for your liver to deplete glycogen (...) you start to switch to, you know, your fatty acids are immobilized. They come outta your adipose tissue (...) You start to use those fatty acids and burn them as energy and as a product of that energy, you're making ketones (...)*
>
> *[ketones] are also acting as a signaling molecule to my brain going, Hey, this is a stressful time. There's no food. You better be cognitively sharp (...)*
>
> *ketosis state where you are fasted to flip on repair processes in your body (...)*
>
> *there are studies multiple studies showing that if you do aerobic endurance training, this kind of running, cycling, swimming type of training, you actually have better adaptations if you're fasted versus fed. (...) so if you're fasted, you get better at burning the fat and oxidizing the fat (...) mitochondrial adaptations that are better."*

In healthy adults, hepatic glycogen declines progressively during fasting but is not exhausted overnight. After a typical 8–12 hour fast, liver glycogen is reduced by roughly 20–30%, meaning substantial reserves remain. More complete depletion generally occurs only after prolonged fasting, often in the range of 36–48 hours. At the same time, fat metabolism does not wait for glycogen to be depleted. As insulin levels fall and counter-regulatory hormones such as glucagon and catecholamines rise, adipose tissue begins releasing fatty acids early in the fasting period. This process, known as lipolysis, overlaps with ongoing glycogen use.

Ketone production follows this same overlapping pattern. The liver continuously produces small amounts of ketone bodies (such as β-hydroxybutyrate) whenever fatty acids are oxidised, even in the fed state. During fasting, as fatty acid availability increases, hepatic ketogenesis rises accordingly. Low levels of ketones are already present within the first 8–12 hours of fasting and increase progressively over time, reaching higher concentrations (around 1–2 mmol/L) after 1–2 days of fasting. Mechanistically, as fatty acids are broken down in the liver, they generate acetyl-CoA. When this exceeds the capacity of the tricarboxylic acid (TCA) cycle, the excess is diverted into ketone production. Ketogenesis begins early and scales with the degree of fat mobilisation.

Ketones and Cognitive Function

Higher ketone levels (such as β-hydroxybutyrate, a primary circulating ketone body) are associated with modest improvements in cognitive function, particularly in individuals with mild cognitive impairment (MCI) or early Alzheimer's disease. Randomised controlled trials using ketogenic diets or medium-chain triglycerides (MCTs, which raise blood ketones) have reported improvements in memory, executive function, language, and processing speed. In several studies, these cognitive gains correlate with increased ketone availability and brain ketone uptake, suggesting a dose–response relationship.

In healthy or non-demented individuals, the effects are generally smaller but still observable. Acute intake of ketogenic meals or MCTs has been associated with short-term improvements in working memory, attention, and cognitive flexibility, with some studies showing that higher circulating ketones are linked to greater performance gains. Meta-analytic evidence across both clinical and healthy populations indicates a modest overall cognitive benefit. Mechanistically, ketones provide an alternative energy source for the brain, particularly when glucose metabolism is impaired. They may also exert signalling effects, enhancing mitochondrial function, cerebral blood flow, and neuroplasticity, including pathways linked to brain-derived neurotrophic factor (BDNF), a protein involved in learning and memory.

Ketosis and Cellular Repair Processes

Nutritional ketosis is associated with the activation of multiple cellular repair and resilience pathways, although much of the evidence comes from mechanistic and preclinical studies. One key mechanism involves a hormetic stress response, whereby mild increases in mitochondrial reactive oxygen species (ROS) during ketosis activate protective signalling pathways, including Nrf2, AMPK, and sirtuins (regulators of cellular energy and stress responses). This activation is associated with increased antioxidant defences, reduced inflammation, improved mitochondrial function, and upregulation of processes such as DNA repair and autophagy (the cellular recycling of damaged components).

Ketone bodies themselves, particularly β-hydroxybutyrate, appear to directly influence these pathways. Experimental studies show that ketosis can enhance autophagy and proteostasis (maintenance of protein quality), supporting the clearance of damaged proteins and organelles. These effects have been observed in tissues such as the brain and liver, and in models of injury or metabolic stress.

There is also evidence that ketosis influences stem cell biology. In muscle stem cells, ketone signalling promotes a more quiescent, stress-resistant state, which may help preserve long-term regenerative capacity, although it may temporarily slow active repair processes. Additionally, ketone metabolism has been linked to improved vascular and neural function, including enhanced endothelial function and reduced oxidative stress in neural tissues.

Fasted Aerobic Training, Fat Oxidation, and Mitochondrial Adaptation

Performing aerobic endurance exercise in a fasted state increases reliance on fat as a fuel source, but does not consistently produce superior overall adaptations compared to training in a fed state. Acute studies show that fasted exercise leads to higher whole-body fat oxidation, and longer-term interventions demonstrate shifts in muscle metabolism, including greater use of intramyocellular lipids and changes in the intensity at which maximal fat oxidation occurs. At the cellular level, fasted training is associated with upregulation of proteins and enzymes involved in fat metabolism, as well as increases in mitochondrial oxidative enzymes such as citrate synthase and β-HAD.

These findings suggest enhanced capacity for fat oxidation and metabolic signalling related to mitochondrial function. However, evidence that these changes translate into greater overall mitochondrial biogenesis or superior endurance performance is inconsistent. Meta-analytic and experimental data indicate that when training volume and intensity are matched, fed and fasted training produce broadly similar outcomes in performance and global mitochondrial adaptations.

References 81-106.

Exercise and Mitochondrial Biogenesis

> *"exercise does make you increase the amount of those new mitochondria that you make that are young and healthy."*

Exercise stimulates the production of new mitochondria (mitochondrial biogenesis), particularly in skeletal muscle. Endurance and high-intensity training consistently increase mitochondrial content, size, and structural complexity, including greater cristae density, reflecting an expanded capacity for cellular energy production.

At a molecular level, exercise activates key regulatory pathways, most notably PGC-1α (a central regulator of mitochondrial biogenesis), along with downstream factors such as NRF1 and TFAM, which drive the formation of new mitochondrial components. Notably, even a single session of exercise can transiently increase the expression of these genes, initiating the biogenesis process.

In addition to increasing mitochondrial quantity, exercise improves mitochondrial quality and function. Training enhances oxidative capacity (the ability to use oxygen to produce ATP) and promotes mitochondrial turnover through processes such as fusion, fission, and mitophagy (the removal of damaged mitochondria). This results in a more efficient and metabolically flexible mitochondrial network.

References 107-111.

Exercise, Amenorrhea, Menopause, and Reproductive Life Span

> *"the problem with women is that (...) if you're in too much of a caloric deficit and (...) you're not refueling enough and you're doing very, very long, high volume types of exercise then you can basically disrupt some of your hormones, your, your follicle stimulating hormone, luteinizing hormone. These things will make you become amenorrheic. So you basically stop ovulating and you stop getting your menstrual period (...)*
>
> *I've heard you talk in the past about the SWAN study (...) they found that women experience an accelerated increase in visceral fat starting two years before their final menstrual period (...)*
>
> *there's a lot of things that can affect your reproductive lifespan (...) one of them is (...) the age you were when you got your menstrual period, so the younger you were, the younger you're gonna be when you experience menopause (...) But lifestyle and diet play a role too. Obesity accelerates ovarian aging, so you're more likely to go into menopause earlier with obesity."*

The combination of high exercise volume and a sustained calorie deficit can lead to amenorrhea (loss of menstrual cycles) in women, primarily through a state of low energy availability. This condition, often termed functional hypothalamic amenorrhea (FHA), arises when energy intake is insufficient to support both physiological functions and the energy demands of training.

Mechanistically, low energy availability suppresses the hypothalamic–pituitary–ovarian (HPO) axis. Reduced energy intake relative to expenditure leads to decreased GnRH (gonadotropin-releasing hormone) signalling, which in turn lowers downstream reproductive hormones and disrupts ovulation. Experimental evidence shows that when energy intake is restored, menstrual function can recover even if high training volume is maintained, indicating that the energy deficit, rather than exercise alone, is the primary driver.

Human studies demonstrate a dose–response relationship, with moderate-to-large energy deficits (approximately 22–42%) associated with increased rates of luteal phase defects, anovulation, oligomenorrhea, and amenorrhea. Observational data further show that higher training volumes are associated with greater risk of menstrual disruption, particularly in athletes who do not compensate with adequate caloric intake.

SWAN Study and Visceral Fat Increase Around Menopause

Evidence from the SWAN (Study of Women's Health Across the Nation) Heart Study indicates that women do experience an accelerated increase in visceral fat beginning approximately two years before their final menstrual period (FMP). Using CT-based measurements of visceral adipose tissue (VAT) in midlife women, researchers identified distinct phases around menopause.

Specifically, visceral fat remained relatively stable more than two years before the FMP. However, from around two years before the FMP to the FMP itself, VAT increased significantly at a rate of approximately 8.2% per year. This accelerated gain continued after menopause, though at a slightly lower rate of around 5.8% per year. The authors explicitly concluded that this period marks a transition point, with menopause-related changes driving a rapid increase in visceral fat.

Related analyses from the SWAN cohort further support this pattern, showing that central fat accumulation begins to accelerate roughly 2–3 years before the FMP, reinforcing the idea that the menopause transition, rather than postmenopause alone, is a critical window for visceral fat gain.

Determinants of Reproductive Lifespan: Menarche, Diet, and Obesity

Age at first menstrual period (menarche), dietary patterns, and obesity are all associated with reproductive lifespan, defined as the interval between menarche and menopause, although their effects operate through different and sometimes inconsistent pathways.

Age at menarche appears to be a strong determinant. Large population data show that later onset of menstruation is associated with a shorter reproductive lifespan, primarily because age at menopause varies relatively little compared to age at menarche. In effect, each year of delayed menarche tends to reduce the total reproductive span.

Dietary factors are also associated with reproductive longevity. Higher diet quality, including greater intake of fruits, whole grains, and protein-rich foods, has been linked to a modestly longer reproductive lifespan and later menopause. Some cohort studies further suggest that higher total energy intake, specific nutrients (such as antioxidants), and lifestyle factors like tea consumption and physical activity may contribute to extended reproductive years.

The relationship with obesity is more complex. Some studies indicate that higher body mass index and weight gain are associated with later menopause and thus a longer reproductive lifespan. However, obesity is also linked to alterations in hormonal markers of ovarian reserve, and evidence is mixed regarding its net effect on reproductive duration.

References 112-126.

Testosterone

“I was reading that testosterone and growth hormone typically peak in their late twenties (...) and starting at age 30, testosterone drop drops roughly 1% a year. So between the age of 25 and 65, men typically see a 200% increase in their visceral fat (...)

If you're not getting enough sleep, your testosterone will plummet as well (...)

It was a longitudinal study that found fatherhood decreases testosterone in human males. They followed 624 men in the Philippines for roughly five years as they transitioned from single non fathers to fathers. And the study found that those men who became fathers experienced massive drops compared to single men. Um, their waking testosterone in the morning dropped by roughly 30% and their evening testosterone dropped by 35%. Dads who spent three plus hours a day on childcare, feeding, bathing, playing, had the lowest levels of testosterone of all men (...)

men that eat 75 grams of added sugar, a single dose, their testosterone plummets by 25% (...)

Testosterone levels in men have dropped by up to 20% over the last two decades.”

Testosterone and Growth Hormone Across Age in Men

Testosterone and growth hormone do not typically peak in the late twenties. Testosterone rises through puberty and generally reaches its highest levels around late adolescence to very early adulthood, approximately ages 18–20. After this point, levels tend to plateau through the twenties or begin a gradual decline, rather than peaking specifically in the late twenties.

Growth hormone follows a similar but earlier trajectory. Secretion is highest during late puberty and early adulthood, then progressively declines with age. Although men in their twenties still exhibit relatively robust growth hormone output, peak secretion has already occurred, and the late twenties are part of an early downward trend rather than a peak phase.

Age-Related Increase in Visceral Fat in Men

Cross-sectional evidence indicates that men can experience an approximate 200% or greater increase in visceral fat between young adulthood and later life, broadly spanning ages 25 to 65.

Reviews of imaging-based studies report that visceral fat may more than triple across this period, representing a disproportionately large increase compared to total body weight or overall fat mass.

This pattern reflects a redistribution of fat with age rather than simple weight gain. While total body fat increases more modestly, the proportion stored viscerally rises substantially. Supporting cohort data show that visceral fat accumulates steadily across adulthood, often peaking in the sixth to seventh decades, even when body mass index remains relatively stable.

Sleep and Testosterone Levels in Men

Poor or insufficient sleep is consistently associated with lower testosterone levels in men, with stronger effects observed under more severe or chronic sleep disruption. Experimental studies show that total sleep deprivation (≥24 hours) significantly reduces testosterone. Controlled laboratory research further demonstrates that restricting sleep to around 5 hours per night for one week can lower daytime testosterone by approximately 10–15%, an effect comparable to several years of ageing. These reductions are particularly linked to loss of sleep in the later part of the night, when testosterone levels are typically highest.

Population-level data support these findings. Large cohort analyses indicate that shorter habitual sleep duration is associated with lower testosterone, with one study showing a decrease of around 5.9 ng/dL for each hour of reduced sleep. Clinical data also show that sleep disorders, including insomnia and circadian rhythm disruptions, are associated with higher rates of testosterone deficiency. Sleep-disordered breathing, particularly obstructive sleep apnea, is also strongly linked to reduced testosterone levels, even after accounting for factors such as age and body mass index.

Fatherhood and Testosterone Decline

A longitudinal study of 624 men in the Philippines found that testosterone levels are dynamically linked to male reproductive strategy, decreasing significantly following the transition into fatherhood. Men who became partnered fathers over a 4.5-year period experienced substantial reductions in both waking (approximately −26%) and evening (approximately −34%) testosterone, declines that were markedly greater than those observed in men who remained single and childless. Fathers who were more actively involved in childcare, particularly those engaging in three or more hours per day, exhibited the lowest testosterone levels, suggesting that direct caregiving may play a role in suppressing testosterone. These findings support the interpretation that testosterone mediates a biological trade-off between mating effort and parental investment in human males.

Acute Effects of a 75 g Sugar Load on Testosterone

A controlled clinical study has shown that a single 75 g oral glucose load can acutely reduce testosterone levels in men by approximately 25%. In this study, men underwent a standard oral glucose tolerance test, and total testosterone fell from around 16.5 to 13.7 nmol/L over a 2-hour period, remaining suppressed throughout that timeframe. Notably, a subset of participants temporarily dropped into the hypogonadal range despite having normal baseline levels.

This effect reflects a short-term physiological response to a large glucose load rather than a lasting reduction. The carbohydrate was administered as a glucose solution under laboratory conditions, which differs from typical real-world consumption of “added sugar” in mixed meals. Overall, while a 75 g glucose dose has been shown to produce a transient ~25% drop in testosterone, this finding represents an acute, time-limited effect and does not imply sustained suppression from a single intake of sugary foods or drinks.

Secular Decline in Testosterone Levels in Men

Several large longitudinal and cohort studies demonstrate an age-independent decline in testosterone. For example, data from US Air Force veterans over a 20-year period show reductions of approximately 19–20%, even among men who maintained or lost weight. Other population studies, including those from the United States, Europe, and Israel, report similar downward trends, although the magnitude differs. Some cohorts show smaller declines (e.g., around 10% over a decade), while others suggest steady annual decreases that could accumulate to larger reductions over time. Meta-analytic evidence across large datasets confirms that this decline is consistent and not fully explained by ageing, obesity, or lifestyle factors alone. However, the exact percentage varies depending on methodology, population, and time frame.

References 127-150

Plastics (BPA, Phthalates, PFAS) and Endocrine Disruption

“there's probably three main endocrine disrupting chemicals that are found in our environment (...) BPA, bisphenol A is one. Another one is phthalates. Phthalates. And the last one would be PFAS (...)

studies that have found that men, for example, men that have high amounts of BPA also have low amounts of test testosterone. But there was also a study done in teens, and these are, this is when, you know your sexual development is happening, right? Testosterone is very important during this part of your life. During puberty, teens, adolescent boys that had the highest amount of BPA had 50% lower testosterone than men, than the boys, sorry, that had the lowest amount of BPA testosterone was 50% lower (...)

there was a study in men that had the highest phthalate levels, those men had 20% lower testosterone (...)

pregnant women that get exposed to high levels of phthalates. And if they have, if they're carrying a, a male fetus right, they're having a boy, what's been shown is it's also affecting sexual development. So these boys, they're getting something called hypospadia. It's where like the slit on the on the on the penis is like moved backwards, kind of closer to like what a woman would have. And they're getting undescended testicles. So one of their testicles is not descending. And that's associated with, you know, infertility cancer, testicular cancer being the big one. This is happening at a alarming rate. Like something like 20% of boys now have an undescended testicle (...)

it's affecting sperm quality. So the shape of the sperm wasn't good. It's a morphology, it's affecting the number. So sperm count is down if they're higher, BPA or higher phthalates. And also motility (...)

there's even studies now with women, pregnant women that have high levels of BPA (...) they're six times more likely to have a child with autism spectrum disorder compared to women with low levels of BPA (...)

heat causes BPA to leach into your coffee or your tea 50 fold more than if it was cold (...)

soup has been classically shown in multiple studies to increase BPA levels by a thousand percent (...)”

BPA (bisphenol A), phthalates, and PFAS (per- and polyfluoroalkyl substances) are widely recognised as endocrine-disrupting chemicals (EDCs), meaning they can interfere with the body's hormonal systems.

BPA exhibits oestrogen-like and anti-androgen effects, interacting with multiple hormone receptors, including oestrogen, androgen, thyroid, and glucocorticoid receptors. It can alter hormone synthesis, signalling, and regulation, with effects observed across reproductive, metabolic, neuroendocrine, and immune systems. Related compounds (such as BPS and BPF) show similar or sometimes stronger endocrine-disrupting activity.

Phthalates are also well-established endocrine disruptors. They can act as xenoestrogens (synthetic compounds that mimic oestrogen), anti-androgens, and anti-thyroid agents, interfering with hormone receptor binding and steroid hormone production. Evidence from human and animal studies links phthalate exposure to altered reproductive development, changes in puberty timing, fertility issues, and broader endocrine and developmental effects.

PFAS are similarly classified as endocrine-disrupting pollutants. They affect multiple hormonal systems, including thyroid hormones (T3, T4, TSH) and sex hormones, and are associated with metabolic, reproductive, and developmental changes. Mechanistically, PFAS can bind to hormone transport proteins, activate nuclear receptors such as PPARs (involved in metabolism), and disrupt key regulatory axes such as the hypothalamic–pituitary–gonadal and thyroid systems.

Study: BPA Exposure and Testosterone in Adolescent Boys

A large cross-sectional analysis of U.S. adolescents (NHANES 2011–2012) reported that boys aged 12–19 with higher BPA exposure had substantially lower testosterone levels. When participants were divided into exposure quartiles, those in higher BPA groups showed markedly reduced total testosterone compared to those in the lowest quartile.

In adjusted models, boys in the second and highest BPA quartiles had approximately 49% and 54% lower testosterone, respectively, relative to the lowest exposure group. These findings underpin the commonly cited claim that higher BPA levels are associated with around a 50% reduction in testosterone in adolescent boys. However, this result comes from a single cross-sectional dataset and reflects an association rather than a causal effect. Other studies in young populations show similar inverse relationships between BPA and sex hormones in males, but findings are variable in magnitude and consistency.

Phthalate Exposure and Testosterone in Men

Higher phthalate exposure is generally associated with lower testosterone levels in men, although the effects are typically modest and vary by age, compound, and population. Large population studies, including multiple NHANES analyses, show that higher levels of phthalate metabolites (particularly from DEHP, DBP, and related compounds) are linked to small reductions in testosterone and androgen indices. These associations are often age-dependent. For example, in older men (≥60 years), higher DEHP exposure has been associated with approximately 7–8% lower testosterone, while in younger men, certain phthalates are linked to reductions in total, free, or bioavailable testosterone.

Findings from clinical and cohort studies are broadly consistent. Studies in fertility clinic populations and general cohorts report that higher phthalate metabolite levels are associated with reductions in testosterone, free androgen index (a marker of biologically active testosterone), and testosterone-to-LH ratio (reflecting testicular function). The magnitude of these effects is typically in the range of a few percent to around 10%, rather than large declines.

Recent research examining combined exposure to multiple phthalates also supports an overall inverse relationship, with DEHP-related compounds often contributing most strongly. However, most evidence is observational and cross-sectional, meaning it demonstrates association rather than causation. Results also vary depending on age group, metabolic differences, and specific phthalates measured.

Maternal Phthalate Exposure and Hypospadias Risk

Maternal exposure to phthalates during pregnancy has been investigated as a potential risk factor for hypospadias (a congenital malformation of the male urethra), but the evidence is mixed and not conclusive. Some case–control studies suggest a possible association, particularly in settings of higher or occupational exposure. For example, studies using job-based exposure estimates have reported increased risk in occupations with likely phthalate exposure, such as hairdressing, with one study observing roughly a threefold increase. However, other large registry-based studies have found weak or non-significant associations, and effect estimates often diminish after adjusting for confounding factors.

Studies using direct biomarker measurements (e.g., maternal urinary phthalate metabolites) provide similarly inconsistent results. Meta-analytic data show a trend toward increased risk, but

pooled estimates are not statistically significant, and some prospective cohort studies report no association. Variability in exposure assessment, sample size, and study design contributes to these inconsistencies. Mechanistic evidence from animal studies supports biological plausibility. Phthalates can act as anti-androgens, disrupting testosterone signalling and male genital development during critical periods, which can induce hypospadias in experimental models. However, translating these findings to typical human exposure levels remains uncertain.

Cryptorchidism: Prevalence, Infertility, and Cancer Risk

Undescended testicle (cryptorchidism) occurs in approximately 1–4% of term newborn boys, with higher estimates of up to ~9% when preterm infants are included. In most cases, spontaneous descent occurs within the first months of life, and prevalence declines to around 1% by 6–12 months. This means that roughly 1 in 25 to 1 in 100 boys are affected at birth, and about 1 in 100 have persistent cryptorchidism beyond infancy.

Cryptorchidism is clearly associated with impaired fertility, particularly when it is bilateral or untreated. In unilateral cases, infertility rates are modestly increased (up to ~10%), with only slightly reduced paternity rates compared to the general population. In contrast, bilateral undescended testes are associated with substantially higher infertility risk, including markedly reduced paternity rates and high rates of oligospermia (low sperm count) or azoospermia (absence of sperm), especially if not corrected early. Large cohort data also show reduced sperm concentration and impaired spermatogenic markers in men with a history of cryptorchidism.

It is also a well-established risk factor for testicular cancer. Men with a history of undescended testis have an approximately 2–5-fold increased risk of testicular germ cell tumours compared to the general population, with higher risks reported in untreated or severe cases. Around 10% of testicular cancers occur in men with prior cryptorchidism. Early surgical correction (orchiopexy), ideally within the first 6–18 months, reduces but does not eliminate this risk and improves early detection.

BPA, Phthalates, and Sperm Quality

BPA and several phthalates are associated with adverse effects on sperm parameters, particularly sperm count and concentration, although the magnitude of these effects is generally modest and findings are not entirely consistent across studies.

For BPA, meta-analytic evidence shows that higher urinary levels are linked to lower sperm concentration and total sperm count. Some studies also report reduced motility and altered morphology, although these associations are less consistent. Mechanistic and experimental data support these findings, indicating that BPA can impair testicular function, disrupt hormone signalling, and affect cells involved in sperm production.

Phthalates show a similar pattern. Meta-analyses and cohort studies report that higher levels of certain metabolites (such as those derived from DEHP, DBP, and related compounds) are associated with reductions in sperm concentration and total count. Associations with motility and morphology are weaker and more variable, though some studies do report negative effects. Additional findings suggest impacts on sperm DNA integrity, indicating broader effects on sperm quality beyond standard parameters.

Prenatal BPA Exposure and Autism Risk

Current human evidence does not support the claim that pregnant women with high BPA levels are six times more likely to have a child with autism spectrum disorder (ASD). Prospective cohort studies show mixed and often subgroup-specific associations. For example, a large birth cohort found that higher prenatal BPA was associated with increased ASD symptoms and later diagnosis, but only in boys with a specific genetic vulnerability (low aromatase activity), rather than across the general population. Other cohorts report either no association or more modest effects, such as around a threefold increase in elevated ASD-related symptom scores in certain subgroups (e.g., girls at age 5), though these relate to behavioural traits rather than confirmed ASD diagnoses. Across studies, findings vary by sex, developmental stage, and outcome measure, and effect sizes are generally modest or inconsistent.

Heat and BPA Leaching from Takeaway Cups

Heat does increase the leaching of BPA (bisphenol A) from food and beverage containers, but current evidence does not support a consistent or generalised 50-fold increase when drinks are hot compared to cold. Across experimental studies, higher temperatures reliably increase BPA migration into liquids, but the magnitude is typically in the range of approximately 2–10 times under realistic conditions. For example, raising temperatures from refrigerated to warm or hot conditions can double or moderately increase BPA levels, and exposure to very high temperatures (e.g., boiling water) can produce larger increases, sometimes several-fold. However, these effects vary depending on the material, product quality, and duration of exposure. Even in studies where heating clearly

enhances BPA release, the increases are not consistently on the order of 50-fold when comparing typical hot versus cold beverage conditions. Extreme increases may occur in specific laboratory scenarios, but these are not representative of everyday use of takeaway cups.

Soup Cans and BPA Migration

Soup cans lined with BPA-based epoxy resins are associated with measurable migration of BPA into the food, primarily during the high-heat industrial canning process. Evidence shows that a large proportion of BPA present in the can lining can transfer into the contents during sterilisation, with minimal additional migration occurring during storage or reheating.

Analytical studies consistently detect BPA in canned soups and other canned foods. Reported concentrations vary, with condensed soups showing higher levels than ready-to-serve varieties, but overall concentrations remain in the nanogram-per-gram range. Across market surveys in multiple countries, canned foods generally contain higher BPA levels than non-canned equivalents. Despite this measurable migration, the levels detected in contemporary studies are typically well below established regulatory limits for BPA exposure.

References 151-175.

Avmacol (Sulforaphane) and Autism Symptoms

> *"Avmacol. It's by a company called Nutrimax (...) they've got 12 published studies using it. Clinical studies too, showing that it actually helps with autism. Children and adolescents with autism that take the Sulforaphane supplement, they have improved symptoms because it's a detox, it helps. interestingly, people with autism are like 30 times less likely to excrete BPA."*

Avmacol, a supplement providing sulforaphane via glucoraphanin and myrosinase, has been used in several clinical studies investigating autism spectrum disorder (ASD), with some evidence of modest symptom improvement, though findings are mixed and not definitive

In randomised controlled trials in children, Avmacol-based interventions have not consistently improved primary clinician-rated outcomes, but caregiver-reported measures, particularly the Aberrant Behavior Checklist (ABC), have shown significant improvements in some

cases. Open-label and smaller studies also report reductions in behavioural symptoms and improvements in social responsiveness and communication over periods of around 12–15 weeks. A 2024 study using Avmacol found improvements in specific communication-related measures, with good tolerability. However, broader evidence across sulforaphane studies shows variability: while earlier trials in young men reported substantial improvements, more recent and larger paediatric trials show smaller, inconsistent, or null effects depending on the outcome measure used.

Meta-analyses suggest that sulforaphane may produce modest improvements in overall ASD symptoms, particularly in areas such as behaviour and hyperactivity, but the certainty of evidence remains low to moderate. Overall, Avmacol has been associated with some improvements in autism-related symptoms in certain studies, but effects are inconsistent and generally modest. It is best considered an experimental adjunct rather than a proven or universally effective treatment.

BPA Excretion in Autism

Case–control and metabolic studies indicate that BPA is primarily cleared through glucuronidation (a detoxification process that makes BPA easier to eliminate in urine). In autistic children, this pathway appears slightly reduced. One study found a lower proportion of BPA excreted in its glucuronidated form alongside higher total BPA levels, with a subset (approximately 20%) of individuals showing particularly elevated levels. A follow-up study reported an approximate 11% reduction in BPA glucuronidation efficiency in autism compared to controls, suggesting modestly impaired metabolic clearance. Additional studies report higher BPA levels in some autistic populations, which could reflect reduced excretion, increased exposure, or both, though findings are not consistent across all cohorts.

References 176-181.

Curcumin, NSAIDS, Anti-inflammatory Effects, and Alzheimer's

"curcumin is found in a turmeric plant. It's something that is able to pretty robustly and I would say consistently lower inflammation (...)

"it's been shown if you take NSAIDs right? So these non-steroidal anti-inflammatory drugs, something like ibuprofen around exercise, it can blunt the adaptations (...)

individuals taking TNF alpha inhibitors (...) have a 50% less likelihood of getting Alzheimer's disease"

Curcumin (a bioactive compound from turmeric) demonstrates clinically meaningful anti-inflammatory effects across human and experimental studies. Meta-analyses of randomised controlled trials involving thousands of participants show that curcumin supplementation reduces key inflammatory markers, including C-reactive protein (CRP), TNF-α, IL-6, IL-8, and MCP-1, while increasing anti-inflammatory IL-10. These effects tend to be stronger with higher doses and formulations designed to improve bioavailability.

Clinical trials in conditions such as rheumatoid arthritis, cancer, and inflammatory lung injury report reductions in inflammatory markers alongside improvements in symptoms when curcumin is used as an adjunct to standard treatment. It is generally well tolerated, though its natural oral bioavailability is low.

Mechanistically, curcumin acts on multiple inflammatory pathways. It inhibits signalling systems such as NF-κB, JAK/STAT, MAPK, and TLR4, suppresses activation of the NLRP3 inflammasome, and reduces production of pro-inflammatory cytokines and enzymes (e.g., COX-2 and iNOS). It also increases anti-inflammatory signalling and exerts antioxidant effects that further dampen inflammation.

NSAIDs and Exercise Adaptations

Chronic use of high-dose NSAIDs (non-steroidal anti-inflammatory drugs, such as ibuprofen or diclofenac) can blunt certain exercise-related adaptations, particularly muscle hypertrophy in younger individuals, whereas occasional or low-dose use appears to have little meaningful effect.

In acute settings, taking NSAIDs around a single workout does not significantly alter muscle protein synthesis signalling, strength, performance, or recovery. Short-term use generally shows neither clear benefit nor harm to training adaptations. Over longer periods, the effects depend on dose and population. In young adults, sustained high-dose NSAID use during resistance training has been shown to reduce muscle growth and, in some cases, limit strength gains. However, findings are not entirely consistent, with some studies reporting no impairment or even increased muscle size without corresponding strength improvements. In older adults, chronic NSAID use often shows neutral or slightly positive effects on muscle mass and strength, possibly due to reductions in baseline inflammation. Overall, regular high-dose NSAID use may impair training adaptations in younger individuals, while occasional use is unlikely to have significant effects, and responses in older populations may differ.

TNF-α Inhibitors and Alzheimer's Disease Risk

TNF-α inhibitors (anti-inflammatory biologic drugs used in conditions such as rheumatoid arthritis) are generally associated with a lower likelihood of developing Alzheimer's disease and dementia. Large observational studies report substantial reductions in risk. For example, analyses of electronic health records and long-term cohorts show that TNF inhibitor use is associated with lower odds or hazard of Alzheimer's disease and dementia, with some estimates suggesting reductions ranging from approximately 20% to as high as 70%. Meta-analytic evidence across large patient populations supports an overall association with reduced dementia and Alzheimer's risk, though results vary and show heterogeneity.

However, comparisons with other advanced anti-inflammatory treatments yield more mixed findings. Some studies show no significant difference in dementia risk between TNF inhibitors and other therapies such as JAK inhibitors, IL-6 inhibitors, or methotrexate, suggesting that the observed benefit may reflect broader anti-inflammatory effects rather than a TNF-specific mechanism. Importantly, the evidence is based on observational data, meaning it cannot establish causation. Confounding factors, such as differences in disease severity or healthcare access, may influence results.

References 183-197.

Urolithin A, VO2max, and Muscle Strength

“Urolithin A (...) is a compound that is able to basically get rid of damage to mitochondria. So it's called mitophagy (...) it's also recently been shown (...) to basically rejuvenate the immune system (...)

There's been studies showing that untrained athletes supplementing with a thousand milligrams a day were able to improve their VO2 max 10% more than just exercise alone (...)

there are studies showing that people that take pomegranate juice before they exercise, they can over the course of several weeks, can actually increase their V02 max by up to 17%.”

It's been shown to increase muscle strength in older adults. So they're hamstring strength improved by like 10 to 12% after supplement supplementing versus just exercise alone (...)

Mitophagy and Immune Modulation

Urolithin A (UA), a metabolite derived from polyphenols, has been shown to promote mitophagy (the selective removal of damaged mitochondria) and exert immunomodulatory effects across cellular, animal, and emerging human studies.

UA is recognised as a natural inducer of mitophagy, activating pathways such as PINK1/Parkin that regulate mitochondrial quality control. Experimental models demonstrate that UA enhances mitochondrial turnover, improves muscle and organ function, and restores mitophagy in conditions such as metabolic disease, kidney dysfunction, and muscular disorders. It also promotes mitochondrial fission and improves communication between cellular organelles. In immune cells, UA-induced mitophagy supports the function and expansion of CD8+ T cells and enhances anti-tumour responses.

In parallel, UA shows broad immunomodulatory effects. It suppresses pro-inflammatory signalling pathways, including NF-κB, and reduces production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α. It also inhibits activation of the NLRP3 inflammasome and shifts immune cell behaviour away from pro-inflammatory states. In adaptive immunity, UA influences T-cell differentiation and dendritic cell activity, while supporting immune surveillance and memory T-cell

function. Human data, though limited, suggest similar trends, including changes in immune cell populations and reductions in inflammatory markers alongside improved mitochondrial function.

Urolithin A and VO_2 Max in Middle-Aged Adults

A randomised, placebo-controlled trial in 88 healthy adults aged 40–64 years examined the effects of urolithin A (UA) supplementation (500 mg/day or 1000 mg/day) over four months on exercise capacity and mitochondrial health. At the higher dose, UA was associated with an approximate 10% increase in peak VO_2 (a measure of maximal oxygen uptake and cardiorespiratory fitness) compared to placebo, although this effect approached but did not reach conventional statistical significance ($p = 0.058$). This suggests a trend toward improved aerobic capacity rather than a definitive effect. The increase in VO_2 max was observed alongside improvements in physical performance (e.g., increased six-minute walk distance) and molecular markers of mitochondrial function, including upregulation of proteins involved in mitophagy and oxidative phosphorylation. Together, these findings indicate that higher-dose UA supplementation may enhance aerobic capacity through improvements in mitochondrial efficiency, though the evidence for VO_2 max specifically remains suggestive rather than conclusive.

Pomegranate Extract and VO_2 Max

Pomegranate extract has not been shown to consistently improve VO_2 max (maximal oxygen uptake), despite some effects on exercise performance and efficiency. Human studies in trained and recreational athletes indicate that while acute or short-term supplementation (e.g., ~8–15 days or single pre-exercise doses of around 1000 mg) may improve time to exhaustion or delay fatigue, these effects do not translate into measurable increases in VO_2 max. In some trials, pomegranate extract reduced oxygen consumption during submaximal exercise, suggesting improved efficiency, but without altering maximal aerobic capacity. In other studies, transient changes in oxygen uptake during specific exercise conditions (such as altitude) were observed, but these did not reflect true increases in VO_2 max or lead to improved performance outcomes.

Urolithin A and Muscle Strength in Older Adults

Urolithin A (UA) has been associated with modest improvements in muscle strength in middle-aged and older adults, including increases in hamstring strength of approximately 10–12% in some studies, although the evidence remains limited and not fully consistent. In a 4-month randomised controlled trial in middle-aged adults (40–64 years) with low fitness and no structured

training, supplementation with 500–1000 mg/day UA increased hamstring strength by around 10–12%, while the placebo group showed a decline of approximately 9–10%. This suggests a relative benefit, particularly in preventing age-related strength loss. Other muscle groups, such as quadriceps and handgrip, showed smaller improvements.

In older adults (65–90 years), UA supplementation has been shown to improve muscle endurance (e.g., greater resistance to fatigue), but not consistently increase strength or functional outcomes compared to placebo. Systematic review evidence concludes that, while there are positive signals in certain measures such as hamstring torque and fatigue resistance, the overall evidence is insufficient to confirm meaningful or generalisable strength benefits.

References 197-212.

Glutamine: Immune and Gut Health

> *"Studies were showing that if those endurance athletes supplemented with glutamine, they didn't get sick as often. They were having fewer respiratory illnesses (...)*
>
> *Glutamine can be converted into something called alpha ketoglutarate, which is a important energy compound that the gut uses. And so there are studies showing that it's beneficial for gut health."*

Glutamine Supplementation and Respiratory Illness in Endurance Athletes

Some early studies in endurance runners and rowers found that consuming glutamine immediately after prolonged exercise (e.g., post-race and again 2 hours later) was associated with a higher proportion of athletes reporting no respiratory infection symptoms in the following week (around 81% vs 49% with placebo). Similar findings have been reported in marathon settings, suggesting a short-term reduction in self-reported illness following exhaustive exercise. However, mechanistic studies provide less clear support. For example, in elite swimmers undergoing intensive training, changes in glutamine levels were not associated with upper respiratory tract infection (URTI) incidence, indicating that glutamine status alone may not determine illness risk. Broader reviews in sports nutrition conclude that, although glutamine is important for immune cell function, supplementation does not reliably reduce infection risk across studies.

More recent evidence in other athletic populations (e.g., combat athletes) shows reductions in URTI incidence and duration with daily glutamine intake, alongside improvements in immune markers, but these findings are not specific to endurance athletes. Overall, while some studies suggest glutamine may reduce short-term respiratory illness following intense exercise, the evidence is limited, inconsistent, and largely based on self-reported outcomes. It cannot be considered a proven or reliable intervention for preventing respiratory illness in endurance athletes.

Glutamine, α-Ketoglutarate, and Gut Health

Glutamine is metabolised into α-ketoglutarate (AKG) through well-established cellular pathways. After entering cells, glutamine is converted to glutamate by glutaminase, and then to AKG via enzymes such as glutamate dehydrogenase or transaminases. This "glutamine–AKG axis" is a central metabolic route, particularly in intestinal cells, where it supports energy production and cellular function.

AKG, whether produced from glutamine or supplied directly, has been shown to support gut health in experimental models. In animal studies, both glutamine and AKG supplementation improve intestinal structure, including increased villus height, mucosal thickness, and nutrient absorption capacity, alongside enhanced barrier integrity. AKG also promotes protein synthesis in intestinal cells via mTOR signalling and reduces oxidative stress and inflammation in the gut lining.

In models of intestinal injury and colitis, AKG reduces tissue damage, inflammatory cell infiltration, and barrier dysfunction, while shifting immune responses toward a less inflammatory profile. Mechanistically, AKG acts as a key fuel for enterocytes (intestinal cells), supports antioxidant defences, and contributes to maintaining gut barrier function.

References 213-225.

Lifestyle Factors for Brain Health

> *"exercise, number one thing, aerobic exercise is increasing brain derive neurotrophic factor.*
>
> *Another thing that you can do that's really important for brain aging is the Omega-3 (...)*
>
> *If you're learning new things, you are going to really help yourself improve both your fluid and crystallized intelligence."*

Exercise, BDNF, and Brain Health

Brain-derived neurotrophic factor (BDNF), a protein that supports neuron growth, survival, and synaptic plasticity, is strongly linked to improvements in brain health, and exercise is a reliable stimulus for increasing its levels. Both acute and chronic exercise elevate BDNF. Single bouts of aerobic exercise, particularly at moderate to high intensity, consistently increase circulating BDNF across age groups and clinical populations. With regular training, resting BDNF levels also rise, especially in older adults and individuals with neurodegenerative conditions.

These increases are associated with meaningful functional outcomes. Higher BDNF levels are linked to improved memory, learning, and executive function, as well as enhanced neuroplasticity (the brain's ability to adapt and reorganise). In ageing and clinical populations, exercise-induced BDNF is associated with reduced cognitive decline and improved response to cognitive training. Overall, exercise-driven increases in BDNF are closely associated with better brain function and resilience, supporting its role as a key mechanism linking physical activity to brain health.

Omega-3 Fatty Acids and Brain Health

Omega-3 fatty acids (particularly DHA and EPA) play an important role in brain structure and function, but the cognitive benefits of supplementation are generally modest and depend on the population and context. In cognitively healthy adults, large randomised trials show little to no effect on overall cognition or dementia risk. Some studies report small improvements in specific domains such as attention, memory, or processing speed, particularly at higher doses (around 1–2 g/day), but these effects are limited and not consistently observed.

In individuals with mild cognitive impairment or early cognitive decline, evidence is more supportive. Supplementation has been associated with modest improvements in memory, attention,

and processing, and may help slow cognitive decline when used early in the disease process. In contrast, in established Alzheimer's disease, omega-3 supplementation does not appear to produce meaningful cognitive benefits. Omega-3s may also support brain health indirectly by reducing inflammation, improving vascular function, and influencing mood, all of which can affect cognitive outcomes.

Learning, Fluid Intelligence, and Crystallised Intelligence

Learning new skills reliably increases crystallised intelligence (knowledge, vocabulary, learned abilities) and can produce modest improvements in fluid intelligence (reasoning and problem-solving), although effects vary by context.

Crystallised intelligence is directly built through learning. Acquiring new knowledge, practising skills, and engaging in education consistently expand this domain, with strong support from both training studies and longitudinal research. This aligns with the idea that accumulated learning over time is the primary driver of crystallised intelligence.

Effects on fluid intelligence are more variable. Targeted cognitive training, particularly adaptive and demanding tasks (e.g., working-memory training), can produce small, dose-dependent improvements in fluid intelligence. However, findings are mixed, with some well-controlled studies showing little or no transfer beyond the trained task. Gains tend to be more evident in younger individuals, those with lower baseline ability, or cognitively at-risk groups, and in interventions that are sustained and cognitively demanding.

References 226-242.

Study: AI Assistance, Brain Connectivity, and Quoting Accuracy

> *"In the study, which I'll throw up on the screen, 83% of AI users were unable to remember the details of a passage of text that they had written with AI's assistance. And E-E-G scans showed that brain connectivity was almost halved when individuals outsourced their thinking to ai compared to writing manually"*

A controlled EEG study examining AI-assisted essay writing found that reliance on large language models (LLMs) was associated with impaired retrieval of recently produced content and reduced neural engagement. Participants in the LLM condition exhibited significantly weaker brain connectivity compared to those writing unaided or using search tools, indicating lower cognitive integration during the task . Behaviourally, 83.3% of LLM users failed to correctly quote material from their own essays written minutes earlier, whereas only 11.1% of participants in non-AI conditions showed similar difficulty . These findings suggest that AI-assisted writing may reduce effective encoding of information into memory, consistent with a pattern of cognitive offloading in which aspects of generative and integrative thinking are partially externalised. As this study is currently available as a preprint and based on a relatively small experimental sample, its findings should be interpreted with appropriate caution pending peer review.

Reference 243.

Physical Activity Intensity and Mortality Risk

“new study came out, not only did it measure physical activity through these accelerometers, it was able to measure how active people were and the type of activity, whether it was I mentioned moderate versus vigorous (...) they also measured light physical activity that would be considered walking around your house, kind of doing that kind of light activity, not necessarily going for a walk or going for a run. And they looked at deaths from different causes of disease. They looked at deaths from all causes. So all cause mortality (...) And what was so profound was that what they found (...) if we're looking at all cause mortality, you know, dying from all causes, cancer, respiratory, anything related that's non-accidental, for every one minute of vigorous intensity exercise you had to do four minutes of moderate intensity, and you had to do like a hundred to 150 minutes of light exercise to get the same reduction in all cause mortality (...) For every one minute of vigorous intensity exercise, to reduce your death from cardiovascular disease, you had to do eight minutes of moderate intensity and 200 minutes of light exercise (...) To reduce your type two diabetes risks. For every one minute of vigorous, you had to do 10 minutes of moderate intensity, or you had to do, again, you're in the 100, 150 minutes to 200 minutes of light exercise. To reduce your risk of dying from cancer, for every one minute of vigorous intensity exercise, you had to do about four minutes of moderate intensity, and for light, it was like 250, 300 (...)

Now there's bigger studies showing men and women that exercise nine minutes a day, the short, vigorous types of exercise adding up not nine minutes altogether, but like a minute here, a minute there, a minute here. Right. It adds up. 40% lower cancer related mortality, 50% lower cardiovascular related mortality.”

A large accelerometer-based study of over 73,000 adults found that the health benefits of physical activity vary substantially by intensity, with vigorous activity demonstrating markedly greater time efficiency in reducing mortality and disease risk. One minute of vigorous physical activity was associated with risk reductions equivalent to approximately 4–9 minutes of moderate activity and 53–156 minutes of light activity across outcomes including all-cause mortality, cardiovascular disease, type 2 diabetes, and cancer . These findings challenge conventional guidelines derived from self-reported data, which typically assume a 1:2 ratio between vigorous and moderate activity, and instead suggest that higher-intensity movement produces disproportionately stronger protective effects. While moderate activity retains clear benefits and light activity contributes modestly,

particularly for metabolic outcomes, the dose–response relationship indicates that intensity plays a central role in determining the magnitude of long-term health outcomes.

Intermittent Vigorous Activity and Mortality Risk

Accelerometer-based studies, particularly analyses of UK Biobank and NHANES cohorts, show that very small amounts of intermittent vigorous physical activity (often termed VILPA) are associated with substantially lower mortality risk, including cancer and cardiovascular disease.

In these studies, non-exercising adults who accumulated only a few minutes per day of vigorous activity, typically through short bouts of 1–2 minutes, showed markedly lower mortality rates. For example, around 3–9 minutes per day of such activity is associated with approximately 30–40% lower cancer mortality and around 30–50% lower cardiovascular mortality compared to individuals with no vigorous activity. Dose–response relationships are generally observed, with greater durations linked to larger risk reductions.

While the commonly cited figure of ~9 minutes per day aligns with the upper range of these findings, similar benefits are observed even at lower durations (e.g., ~4–5 minutes per day), suggesting that relatively small amounts of vigorous movement can have meaningful associations with health outcomes.

References 244-249.

Sedentary Behaviour and Cancer Risk

> *"Sitting is an independent risk factor for disease, for cancer in particular."*

Prolonged sitting (sedentary behaviour) is considered an independent risk factor for several cancers, even after accounting for levels of physical activity, although the magnitude of risk is generally modest and varies by cancer type.

Large meta-analyses and umbrella reviews show that higher sedentary time is associated with increased incidence of cancers such as colorectal (relative risk ~1.25–1.30), endometrial (~1.28–1.36), breast (~1.08–1.17), and lung (~1.21–1.27), with additional signals for ovarian and rectal cancers. These associations persist after adjusting for physical activity, suggesting that sitting

itself contributes independently to cancer risk. Proposed mechanisms include metabolic dysfunction, altered sex hormone regulation, and chronic low-grade inflammation.

Sedentary behaviour is also linked to cancer mortality. Cohort and accelerometer-based studies show increased risk of cancer-related death with higher sitting time, with hazard ratios around 1.13–1.17. In cancer survivors, greater sedentary time is associated with higher mortality, particularly when combined with low physical activity.

Importantly, higher levels of moderate-to-vigorous physical activity can attenuate, and in some cases largely offset, the mortality risk associated with prolonged sitting, although effects on cancer incidence are less consistently mitigated. Risk appears to increase most clearly at higher levels of sedentary time (e.g., beyond ~6–8 hours per day) or with prolonged uninterrupted sitting.

References 250-255.

GLP-1 Agonists

> *"many studies have shown now that individuals that do take these GLP -1 do lose a lot of weight and it's very beneficial to lose that weight. But if they stop taking the GLP-1. They gain the weight back (...)*
>
> *Some other effects I think that are that people are a little more concerned about are the muscle loss and bone loss (...)*
>
> *It seems like there's an increased signal for kidney cancer (...)*
>
> *The other thing is gallstones you're getting the increased risk of gallstones..."*

Weight Regain After Discontinuation

Stopping GLP-1 weight-loss medications is strongly associated with weight regain, with multiple clinical trials and meta-analyses showing that a substantial proportion of lost weight returns after treatment ends. Across randomised controlled trials, individuals typically regain several kilograms after discontinuation, with larger rebounds observed following more potent agents such as semaglutide or tirzepatide. Estimates suggest that around 60% of lost weight may be regained within

the first year, increasing to approximately 75% over longer follow-up, with only a small net weight loss often maintained.

This pattern reflects the underlying biology of obesity, which is characterised as a chronic, relapsing condition. When pharmacological support is removed, appetite, energy balance, and metabolic adaptations tend to revert toward pre-treatment states, contributing to weight regain. Lifestyle interventions can partially mitigate this effect. Studies show that combining GLP-1 therapy with exercise or sustained behavioural changes improves weight maintenance after discontinuation, whereas stopping medication without such support is associated with greater rebound.

GLP-1 Weight-Loss Drugs, Muscle, and Bone

GLP-1 weight-loss medications are associated with some loss of muscle (lean mass) and modest changes in bone density, but these effects are generally proportional to overall weight loss rather than uniquely harmful. Across clinical trials and meta-analyses, lean mass typically decreases by around 1 kg, with fat mass accounting for the majority of weight lost. In most cases, lean mass represents less than 20% of total weight loss, although higher proportions can occur with rapid or substantial weight reduction. Importantly, imaging studies suggest this muscle loss is largely adaptive, with improvements in muscle composition and metabolic function, meaning muscle quality may be preserved despite reductions in mass. However, older or frail individuals may be more vulnerable to clinically meaningful muscle loss.

Bone effects appear similarly modest. Most studies show no significant increase in fracture risk and either neutral or small reductions in bone mineral density (BMD), with some evidence of slightly increased bone turnover. In non-diabetic populations, reductions in BMD have been observed with GLP-1 therapy alone, but these effects are largely mitigated when exercise is included.

GLP-1 Drugs and Kidney Cancer Risk

Current evidence suggests a possible but uncertain association between GLP-1 receptor agonists and kidney cancer, with findings that are mixed and largely based on observational data. Some large population studies report a modestly increased risk when GLP-1 drugs are compared with certain alternatives. For example, analyses in older adults with type 2 diabetes have found higher rates of kidney cancer compared to SGLT2 inhibitors, and similar signals have been observed in comparisons with metformin. A large target-trial emulation in people with obesity also found a trend toward increased kidney cancer risk, although this did not reach clear statistical significance.

However, randomised controlled trial data do not show a clear increase in kidney cancer risk, although these studies are limited by low event numbers. More broadly, GLP-1 drugs are consistently associated with reduced overall cancer risk and well-established kidney-protective effects, including improvements in kidney function and reduced progression of renal disease. Importantly, the observed kidney cancer signals come from observational studies, which are susceptible to confounding factors such as differences in underlying health status or monitoring intensity. Absolute risk appears low, and the overall clinical profile of GLP-1 drugs remains favourable.

GLP-1 Drugs and Gallstones

GLP-1 receptor agonists are associated with an increased risk of gallstones and other gallbladder-related conditions, particularly with higher doses, longer duration of use, and when used for weight loss.

Large meta-analyses of randomised controlled trials show that these medications increase the risk of gallstones (cholelithiasis) by roughly 25–30%, along with similar increases in related conditions such as cholecystitis and the need for gallbladder removal. In absolute terms, this corresponds to a relatively small increase in events, estimated at around a few dozen additional cases per 10,000 patients per year. The risk appears to be higher in individuals using GLP-1 drugs for weight management rather than diabetes, and increases with longer treatment duration (e.g., beyond 6 months). Certain agents, such as liraglutide and semaglutide, show stronger associations in some datasets.

Mechanistically, this effect is thought to arise from reduced gallbladder motility and the rapid weight loss often induced by these drugs, which can promote the formation of cholesterol-rich bile and gallstones. Notably, rapid weight loss from other interventions (e.g., dieting or bariatric surgery) is also known to increase gallstone risk.

References 256-272.

Chemical Exposures: Plastics, Receipts, and Water Filtration

“Black plastic. So it has all those chemicals that we were talking about, like BPA and phthalates, but it also, black plastic typically is made from recycled electronics. And there have been studies now that have found that black plastic has actually got even more harmful chemicals than them that are, that cause cancer (...) black plastic has a high amount of these flame retardants that are leaching into the food and getting into people's bodies that way (...)

[receipts] are covered with BPA (...) hand sanitizers are carrying it inside your bloodstream about a hundred fold higher (...)

Reverse osmosis water filters filter out microplastics, nanoplastics, BPA, phthalates, chemicals (...) it does filter out a lot of small particles, including essential, you know, trace elements and some essential like minerals and stuff. So you wanna make sure that you are taking a multivitamin mineral supplement (...)

Black Plastics and Cancer-Associated Chemicals

Black plastics are often produced using recycled materials from electronic waste (WEEE), which can introduce contaminants such as brominated flame retardants and heavy metals (e.g., lead, cadmium, chromium). Surveys of consumer products and environmental samples show that black plastics frequently contain these substances, sometimes at relatively high concentrations. In addition, carbon black, the pigment commonly used to give plastics their black colour, can be contaminated with polycyclic aromatic hydrocarbons (PAHs), a class of compounds that includes well-established carcinogens such as benzo[a]pyrene.

Analyses of black plastic products have detected brominated flame retardants in a high proportion of items, as well as measurable levels of PAHs and heavy metals, all of which are linked to carcinogenic or endocrine-disrupting effects. Carbon black itself is classified as possibly carcinogenic when inhaled as fine particles. However, risk depends on context. Not all black plastic items contain harmful levels of these substances, and exposure varies depending on how the product is used (e.g., food contact, heating, or inhalation of particles). Direct epidemiological evidence linking everyday black plastic use to cancer in humans is limited, with most data coming from toxicological and material analyses.

Thermal Receipts, BPA, and Skin Absorption

Thermal receipts commonly contain bisphenol A (BPA) or related compounds such as bisphenol S (BPS), and these chemicals can transfer easily to the skin because they are present in a free, unbound form. Surveys across multiple countries show that a majority of receipts (often around 60–90%) contain BPA, with many of the remainder using BPS. As a result, receipts are considered a major source of dermal bisphenol exposure. Under normal conditions, handling a receipt transfers small amounts of BPA to the skin, typically around 1 μg with brief contact on dry hands, and higher amounts if the skin is moist or oily. Occupational studies show that individuals who frequently handle receipts, such as cashiers, tend to have higher BPA levels, indicating real-world absorption.

Hand sanitiser can markedly increase this exposure. Many sanitisers contain compounds that enhance skin permeability, allowing chemicals like BPA to pass through the skin more readily. Experimental studies show that using hand sanitiser before handling receipts can increase BPA transfer by up to ~185-fold compared to dry hands, and substantially increase systemic absorption, as reflected in blood and urine levels.

Reverse Osmosis, Contaminants, and Mineral Loss

RO membranes have extremely small pore sizes, allowing them to retain essentially all microplastics and a large proportion of nanoplastics, with any residual passage typically due to membrane defects rather than normal filtration limits. They are also highly effective at removing organic contaminants. Studies show near-complete rejection (≈98–100%) of BPA, and similarly high removal efficiency for many micropollutants such as PFAS and compounds within the size and chemical range of phthalates.

This same filtration process also removes beneficial minerals. Reverse osmosis typically reduces calcium, magnesium, sodium, potassium, and other trace minerals by around 90–99%. As a result, RO-treated water is very low in mineral content. While this is not inherently harmful if mineral intake from diet is sufficient, long-term exclusive consumption of demineralised water has raised concerns about potential impacts on bone and dental health in the absence of adequate nutritional compensation.

References 273-283.

Glutathione and Sulforaphane

> *“glutathione is in a major, it's a major antioxidant (...) there's been studies showing that people that take sulforaphane increase their glutathione in their brain and plasma (...)”*

Sulforaphane has been shown to increase glutathione (GSH), a key antioxidant, in both blood and the brain, although human evidence is currently limited to small, short-term studies. In a clinical pilot study in healthy adults, oral sulforaphane taken for 7 days increased blood glutathione levels and produced a consistent rise in brain GSH, measured in regions such as the anterior cingulate, hippocampus, and thalamus. Notably, changes in blood glutathione correlated with changes in brain glutathione, suggesting that peripheral measures may reflect central antioxidant status. Additional human data, including studies in children with autism, show that sulforaphane alters glutathione redox balance in blood, indicating broader effects on the glutathione system. Mechanistically, these effects are driven by activation of the Nrf2 pathway, which upregulates enzymes involved in glutathione synthesis and recycling, thereby increasing intracellular antioxidant capacity in both neural and peripheral tissues.

References 284-286.

Vitamin D

> *“vitamin D two is not as effective as vitamin D three. It also inhibits some of vitamin D three, so it's not even able to be made into the steroid hormone (...)*
>
> *there's actually a study, a recent study showing that people that are vitamin D deficient (...) They have accelerated aging. And if they supplement, this is a very large study by the way, if they supplemented with vitamin D three, they slowed their, their biological aging by almost two years.”*

Vitamin D2 vs D3: Effectiveness and Interaction

Vitamin D2 (ergocalciferol) is generally less effective than vitamin D3 (cholecalciferol) at raising and maintaining vitamin D levels in the body, and there is evidence that D2 supplementation

can reduce circulating levels of D3. Across multiple randomised trials and meta-analyses, vitamin D3 consistently produces larger and more sustained increases in total 25(OH)D (the main marker of vitamin D status), with differences of roughly 10–16 nmol/L compared to equivalent doses of D2. Pharmacokinetic studies also show that D3 is substantially more potent over time, and better maintains circulating levels. In addition, several controlled studies demonstrate that taking vitamin D2 can lower levels of 25(OH)D_3 (the D3-derived form), typically by around 9–18 nmol/L. This suggests a form of metabolic interaction, where D2 may accelerate the breakdown or alter the metabolism of D3, rather than simply adding to total vitamin D levels.

Vitamin D, Deficiency, and Biological Age

Research suggests that vitamin D deficiency is associated with accelerated biological ageing, and small intervention studies indicate that vitamin D3 supplementation can modestly reduce epigenetic age, though the evidence is not yet definitive.

Observational studies using biological ageing markers (such as DNA methylation “epigenetic clocks” and PhenoAge) consistently find that individuals with low vitamin D levels show signs of faster ageing, including higher epigenetic age acceleration and, in some cases, shorter telomeres. These findings are replicated across large cohorts (e.g., NHANES, UK Biobank), but they demonstrate association rather than causation.

Intervention data are more limited but notable. In a small randomised controlled trial in vitamin D–deficient individuals, supplementation with vitamin D3 (2,000–4,000 IU/day) over 16 weeks reduced epigenetic age by approximately 1.8–1.9 years compared to placebo. Similarly, a quasi-experimental study found that correcting vitamin D deficiency was associated with around 1–2.6 years lower biological age acceleration compared to those who remained deficient.

References 287-295.

Multivitamins Improve Cognitive and Epigenetic Aging (COSMOS Study)

> *"one study last time we talked last episode where men and women that were older adults, they were 65 years and older, they took one Centrum silver a day. And I'm not, you know, I'm not advocating for Centrum silver, I'm just saying that was involved in this study and um, after three years they had reversed their brain aging, global brain aging by 2.1 years and they reversed their episodic brain aging by almost five years (...) the same (COSMOS) study (...) They looked at the multivitamin use and biological aging epigenetic aging, and they found that the Centrum silver multivitamin also slowed biological aging, epigenetic aging by a few months."*

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.

Multivitamins and Epigenetic Ageing

A large randomised ancillary study within the COSMOS trial (n = 958 older adults) examined whether daily supplementation with a multivitamin–multimineral (Centrum Silver) over two years could influence biological ageing, measured using multiple DNA methylation "epigenetic clocks" (including PCGrimAge and PCPhenoAge). Compared with placebo, multivitamin use modestly slowed the rate of epigenetic ageing, with reductions in the yearly progression of biological age of approximately 0.11 years (PCGrimAge) and 0.21 years (PCPhenoAge), equivalent to a slowing of ageing by a few months over time. The effect was more pronounced in individuals with accelerated biological ageing at baseline. In contrast, cocoa flavanol supplementation showed no effect on any ageing measure. Overall, the findings indicate that daily multivitamin use may produce small but statistically significant reductions in the pace of biological ageing, though the magnitude is modest and the long-term clinical relevance remains uncertain.

References 296-299.

Iron Deficiency in Menstruating Women

> *"would say about 16% of of menstruating women are iron deficient."*

Iron deficiency is common among menstruating women, with most population-based studies estimating prevalence in the range of approximately 20–35%, depending on how deficiency is defined and the population studied. Large cohort and national survey data show considerable variability. Some studies report lower estimates (around 9–16%) when stricter diagnostic criteria are used or when focusing on non-anaemic individuals, while others using broader ferritin thresholds (e.g., <30 µg/L) report higher prevalence, often exceeding 30%. In certain populations, estimates reach close to 35–40%.

References 300-304.

Omega-3: Improves Life Expectancy, Ageing, and Cancer Outcomes

> *"Omega-3 fatty acids, particularly from seafood, so the EPA and DHA from fish oil are probably the best forms. You know, we talked about studies. If you have a high Omega-3 index, you have a five year increased life expectancy compared to low Omega-3 index (...) you have a 66% lower chance of getting Alzheimer's disease with a high Omega-3 index (...) a study showed that Omega-3 fish oil supplementation, this was a study out of Switzerland. These individuals are mostly active. There were 88% of them were already physically active at the start of the trial. And I mentioned that because the trial involved Omega-3, it involved vitamin D and it involved resistance training or the combination of all three. And only the Omega-3 was able to slow epigenetic aging, biological aging (...) The combination of all three slowed it by four months (...) that also correlated with they had a 60% (...) were less likely to get cancer as well."*

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.

Omega-3 Index and Alzheimer's Risk

Higher omega-3 blood levels (often reflected by the omega-3 index, a measure of EPA and DHA in blood) are generally associated with a lower likelihood of developing Alzheimer's disease and dementia, based on observational research. Large cohort studies consistently show inverse relationships. For example, higher circulating omega-3 levels are linked to reduced risk of dementia and Alzheimer's disease (with hazard ratios around 0.79–0.87 when comparing higher vs lower levels), as well as slower cognitive decline and reduced brain atrophy in key regions. Some studies suggest these associations may vary by specific fatty acids (e.g., EPA vs DHA) and genetic factors such as APOE status.

However, not all studies find strong or consistent effects, and some report benefits only in certain subgroups or for specific omega-3 components. Randomised trials of omega-3 supplementation in people with established Alzheimer's disease have generally not shown meaningful cognitive benefits, suggesting that omega-3s may be more relevant for prevention than treatment.

DO-HEALTH Trial: Epigenetic Ageing and Cancer Outcomes

The DO-HEALTH trial provides evidence that omega-3 supplementation, vitamin D, and exercise may modestly improve markers of biological ageing and reduce cancer incidence, particularly when combined, although findings are exploratory.

In a post hoc analysis of 777 participants, omega-3 supplementation alone significantly slowed several DNA methylation–based ageing markers (including PhenoAge, GrimAge2, and

DunedinPACE) over three years. When combined with vitamin D and exercise, additive effects were observed, corresponding to a slowing of biological ageing by approximately 2.9–3.8 months over the study period. These effects were consistent across multiple ageing-related biomarkers, though modest in magnitude and of uncertain long-term clinical significance.

In a separate exploratory analysis of cancer incidence in the full cohort (n = 2,157), each intervention alone showed non-significant reductions in invasive cancer risk. However, combinations of interventions showed stronger associations. The combination of all three (omega-3, vitamin D, and exercise) was associated with a hazard ratio of 0.39, corresponding to approximately a 61% lower incidence of invasive cancer compared to controls over around three years, although based on a small number of events.

References 305-315.

Creatine, Sleep Deprivation, and Alzheimer's

> *"studies have shown if you go up to a higher dose [of creatine] like that, depending on your weight (...) it helps you basically negate the negative effects on your brain from sleep deprivation (...) New studies have even come out since then showing it helps with people with Alzheimer's disease, so it's improving their cognitive function."*

Sleep Deprivation

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 Cognitive Function in Alzheimer's Disease

Current research suggests that creatine supplementation may have potential to improve cognitive function in Alzheimer's disease, but human evidence is limited and remains preliminary. The only direct human study to date is a small, single-arm pilot trial in which patients with Alzheimer's disease took 20 g/day of creatine for 8 weeks. The study reported increased brain creatine levels (approximately 11%) and improvements in several cognitive measures, including global cognition, attention, and memory-related tasks. However, because the study lacked a placebo control, these improvements may reflect practice effects or placebo response rather than a true treatment effect.

Mechanistic and preclinical research provides some support for this approach. Alzheimer's disease is associated with impaired brain energy metabolism and disruptions in the creatine kinase system, and creatine may help restore cellular energy balance. Animal studies often show improvements in cognition, mitochondrial function, and some disease markers, although results are not entirely consistent. Evidence from non-Alzheimer's populations suggests small benefits of creatine on memory and processing speed, particularly in older or cognitively stressed individuals, but effects on overall cognition are mixed.

References 316-320.

Magnesium: Improved Sleep and Reduced Cancer Risk

> *"when you're in a state where you're not eating a good diet or you're not getting enough sleep, magnesium is really important to repair that damage. And that's why studies have shown that magnesium is really important for preventing cancer. And it also helps with sleep. It's really good for sleep."*

Magnesium and Sleep

Magnesium supplementation is associated with modest improvements in sleep, particularly in individuals with insomnia or low magnesium status, although the overall quality of evidence is low to moderate. Randomised trials in older adults with insomnia show that magnesium can reduce sleep onset latency by approximately 15–20 minutes compared to placebo, with little consistent

effect on total sleep time. Broader interventional studies report that a proportion of trials demonstrate improvements in at least one sleep parameter, such as sleep quality, sleep efficiency, or insomnia severity, though results are variable and studies are often small.

Additional trials in adults with poor sleep suggest modest benefits across measures including deep and REM sleep, subjective sleep quality, and insomnia symptoms, with generally good tolerability. Observational studies also support an association between higher magnesium intake and better sleep duration and quality, although dietary intake appears more consistently linked than supplementation in some datasets.

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.

References 321-329.

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