Evaluating NAD and NAD precursors for health and longevity

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Peter Attia December 11, 2024

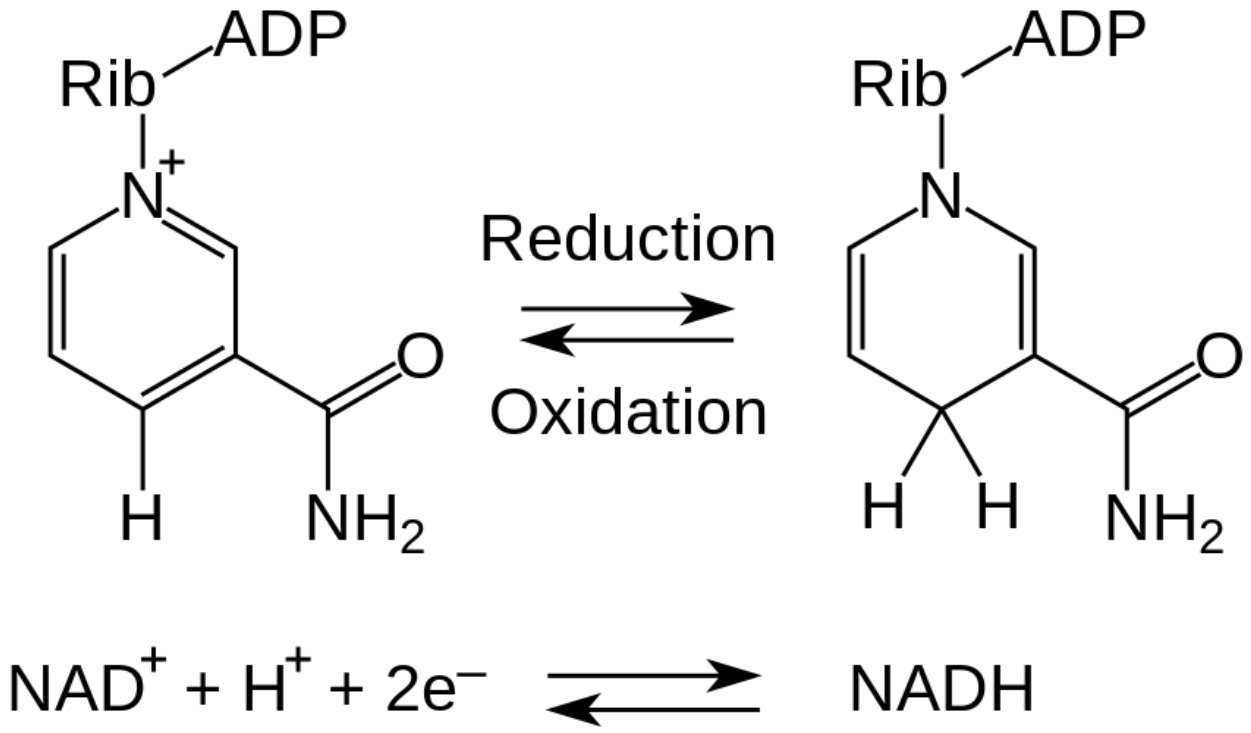

Figure 1: Chemical structures and interconversion between NAD+ (left) and NADH (right) – the oxidized and reduced forms of NAD, respectively.

When it comes to potential "longevity drugs," separating legitimate promise from unfounded claims can be a challenging and frustrating task, and the greater the hype, the more difficult it can be to filter out the noise in search of a signal. For one particular therapy, hype (and commercial popularity) has surged over the last several years: nicotinamide adenine dinucleotide, or NAD. Indeed, we would be hard-pressed to overestimate the importance of this molecule for many cellular processes necessary for survival, and declining levels of NAD have been implicated in age-related diseases and cellular senescence. Thus, NAD-boosting therapies – i.e., NAD itself or NAD precursors, mainly NR (nicotinamide riboside) and NMN (nicotinamide mononucleotide) – have garnered attention for numerous purported benefits, including lifespan extension, improvements in metabolic health, exercise performance enhancement, and others.

But do we have evidence that *supplementing* NAD levels with exogenous NAD or NAD precursors can improve health and longevity? Why did NAD become such a focal point in the conversation about lifespan extension in the first place? Which, if any, of the alleged benefits of supplementing with exogenous NAD are supported by existing evidence? And are some NAD-

boosting treatments more effective than others? In this article, we turn our attention to these questions and more as we attempt to disentangle fact from fiction and advertising claims from scientific evidence with respect to the therapeutic value of NAD and NAD precursors.

Why should we care about NAD?

NAD is a molecule that is present in all cells, where it serves as a critical coenzyme in hundreds of metabolic reactions and other processes. “NAD” refers collectively to the two forms of this molecule: NAD+ and NADH, reflecting NAD’s role in facilitating the transfer of electrons between molecules – a function necessary for catabolism, anabolism, and cellular responses to oxidative stress. NAD+ (the “oxidized” form) can act as an electron *acceptor* from other molecules, while NADH (the “reduced” form) can act as an electron *donor* (**Figure 1**). (For more information on NAD in electron transfer reactions and the importance of these reactions for metabolism, please refer to my podcast interview with Dr. Josh Rabinowitz.) Beyond its role in metabolism and oxidative stress, NAD is also required for several reactions involved in DNA repair and regulation of gene expression. Let it suffice to say that as far as biological molecules are concerned, NAD is kind of a big deal.

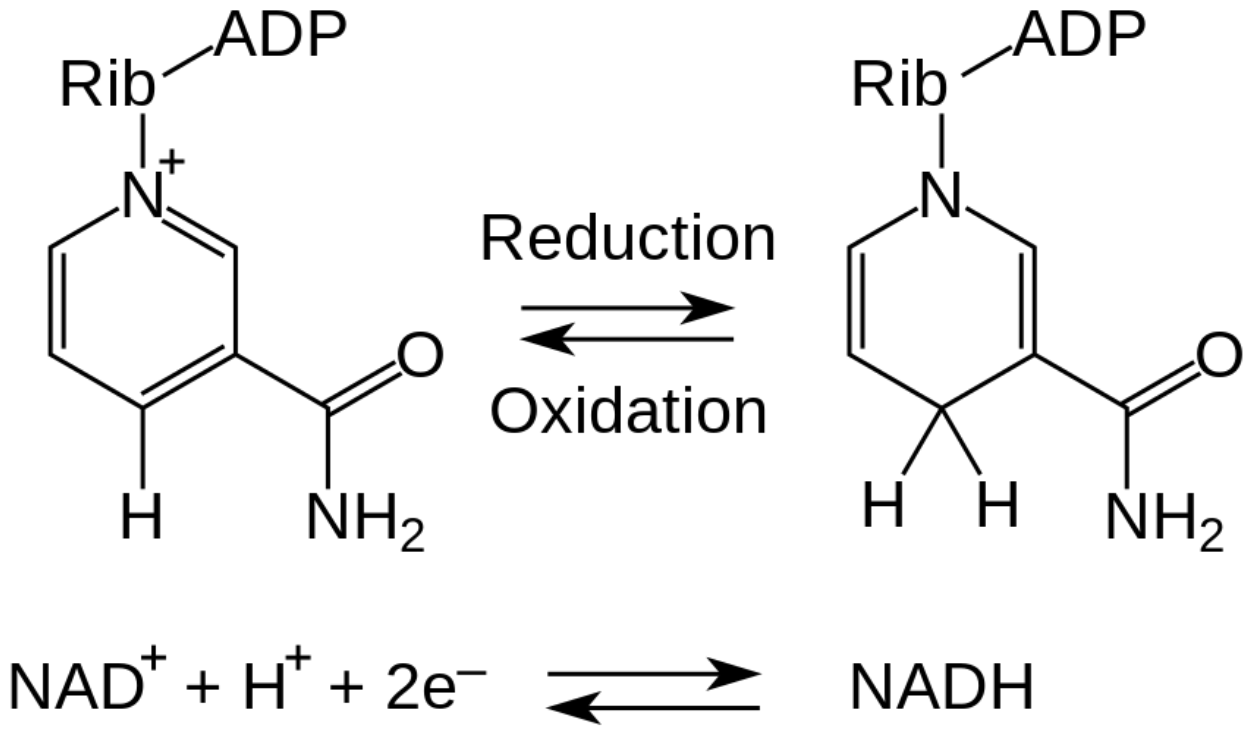

Figure 1: Chemical structures and interconversion between NAD+ (left) and NADH (right) – the oxidized and reduced forms of NAD, respectively.

Despite its importance for cell survival and function, NAD (and its precursors) did not attract attention as a potential player in aging until the late 1990s and early 2000s, as excitement grew around a class of highly-conserved enzymes known as sirtuins. Investigators at the time discovered that sirtuins, which require NAD to function, appeared to play a role in extending lifespan – but how?

The rise and fall of the sirtuin hypothesis

The sirtuin family of enzymes (there are seven sirtuin enzymes in mammals; SIRT1-7) functions in modifying other proteins, which can serve various purposes in the cell, including in the regulation of gene expression. But around the turn of the millennium, interest in sirtuins surged after researchers found that overexpression of a sirtuin gene (SIR2) in yeast extended the yeast lifespan.[1] Others subsequently reported that overexpression of sirtuins in nematode worms and fruit flies also extended lifespan in those organisms, fueling the sirtuin hype by demonstrating that results in yeast also appear to extend to multicellular organisms.

So what does all of this have to do with NAD? As mentioned above, sirtuins use NAD to carry out their protein modification reactions. Unlike reactions in which NAD serves as a coenzyme (interconverting between NAD+ and NADH), sirtuin reactions are among the few NAD-requiring processes that *completely consume* NAD, breaking it down into ADP ribose and nicotinamide.[2] Thus, sirtuin activity is dependent upon intracellular NAD levels, and increasing NAD can trigger sirtuin activation.[3] This finding was particularly intriguing because it linked longevity and gene expression (i.e., sirtuins) to metabolic processes (i.e., NAD), leading to the hypothesis that sirtuin activity might mediate the well-documented lifespan-extending effects of calorie restriction. The excitement intensified when researchers observed that NAD levels tend to decline with age across various tissues, leading to the seemingly logical conclusion that boosting NAD levels might help combat aging.

The narrative is compelling: if sirtuins promote longevity, and sirtuins need NAD to function, and NAD levels decline with age, then perhaps maintaining or increasing NAD levels could promote longevity. But how well has this logic held up in light of research over the past 25 years?

Lifespan effects of sirtuin overexpression in yeast have been fairly robust and reproducible, though they may be dependent on yeast strain and have been shown definitively to be independent of lifespan effects of calorie restriction.[4] However, interventions that extend yeast lifespan are only interesting if they tell us something about lifespan in *humans* (or at the very least, other multicellular organisms, and ideally mammals), and unfortunately, it is now clear that that is not the case with sirtuins. Researchers have not been able to reproduce results showing lifespan extension from sirtuin activation in worms and flies, and the original data demonstrating such an effect have since been determined to result from inadequate controls rather than any true impact on longevity.[5] Perhaps most tellingly, several studies in mice have shown that manipulation of various sirtuins has no effect on lifespan.[6–8]

Thus, the hypothesis that sirtuins broadly promote longer lifespan has been largely discredited. However, this doesn't mean that *NAD* can't influence aging through other, non-sirtuin mechanisms. NAD is involved in countless cellular functions, so there are many potential ways that an age-related decline in NAD might impact aging and health beyond its role in sirtuin activation.

Alternative links between NAD, health, and aging

While the sirtuin story hasn't held up, NAD has held interest as a potential geroprotective or health-promoting molecule because of its involvement in other critical cellular processes. Alternatives to the sirtuin hypothesis have focused on NAD's role in DNA repair, mitochondrial function, oxidative stress, and various other processes associated with cellular aging.

Involvement in DNA repair is a particularly attractive route by which NAD might impact health and longevity. NAD is a substrate for a class of enzymes called PARPs (poly(ADP-ribose) polymerases), some of which play key roles in DNA repair. Like sirtuins, PARPs *consume* NAD rather than merely interconverting it between NAD+ and NADH, and when DNA damage occurs, the action of PARPs for repair can result in tremendous NAD depletion.[9] Since DNA damage increases with age, the demand for DNA repair (and thus NAD) presumably increases as well. This creates an interesting hypothesis: perhaps age-related NAD decline compromises DNA repair capacity, leading to increased genomic instability and accelerated aging.

NAD is also crucial for mitochondrial function, serving as a key coenzyme in ATP production and helping to maintain proper redox status (i.e., avoiding oxidative stress, to which mitochondria are especially susceptible) in these cellular powerhouses. Since mitochondrial dysfunction is a hallmark of aging, this represents another potential mechanism through which NAD might influence the aging process.

Indeed, maintaining mitochondrial health is also a potential alternative mechanism by which *sirtuins* promote longevity, as the role of NAD in counteracting oxidative damage and promoting the generation of new mitochondria appears to involve various sirtuin enzymes. For instance, *in vitro* administration of NAD+ has been shown to increase cellular antioxidant capacity in a manner that requires NAD+-induced activation of SIRT2.[10] Further, sufficient NAD+ levels are required to activate SIRT1 and SIRT3, which in turn trigger downstream signaling processes involved in mitochondrial biogenesis and mitochondrial energy production.[11]

How does NAD change with age?

Before we evaluate the efficacy of NAD supplementation on improving health or slowing aging, we must first take a closer look at how NAD levels change as we age. After all, hypotheses regarding the utility of NAD supplementation rely heavily on the observation that levels decline over time.

While it seems clear the NAD levels do indeed fall with age, different tissues appear to experience different degrees of decline. According to a 2022 review, the drop is likely most dramatic in skin tissue, as NAD+ levels among young adults were shown to be approximately 68% lower, on average, than levels in newborns, while levels in middle-aged adults were an additional 60% lower than in young adults (no further decline was observed between middle age and older age groups).[12] By contrast, multiple studies have reported a difference in NAD+ levels in the brain of just 10-20% between young adults and old age (70+).[13,14] Comparable

drops in NAD+ (~10-20%) have also been reported in whole blood between young adulthood and old age, though some evidence has indicated that this decline is absent among women.[12,15]

The cause of the decrease in NAD+ with age is not clear, however. Ultimately, it comes down to the balance between NAD+ consumption and NAD+ biosynthesis – an increase in the former, a decrease in the latter, or a combination of both might lead to depleted NAD+ levels, but even at this basic level, we don't yet know how aging affects this balance (or whether different mechanisms are at play in different tissues). As we've noted above, one possible cause of increased NAD+ consumption might be an increase in DNA damage, triggering PARP activity for DNA repair and consuming NAD+ in the process. Additionally, aging-associated increases in cellular senescence (i.e., a state in which old or stressed cells have ceased dividing; see here for more detail) could drive increased expression of CD38 – a protein that consumes NAD+ and is present on many of the immune cells that respond to senescent cells. On the other side of the equation, a drop in NAD+ might result from a decrease in NAD+ production, such as might arise from diminished activity of enzymes involved in pathways for NAD biosynthesis or recycling.[16]

Intriguingly, some evidence indicates that the apparent "decline" in NAD with age might not be a decline at all, but rather a general shift in the balance between NAD+ and NADH – at least in certain tissues. Not all studies that have examined NAD levels have employed methods that are capable of distinguishing between the molecule's two redox states, yet in a handful of investigations that have utilized more discerning spectroscopic techniques, reductions in NAD+ with age were accompanied by *elevations* in NADH. Such a shift toward the reduced form has been observed in kidney, liver, heart, and lung tissue in rats,[17] as well as in at least one study of human neural tissue (**Figure 2**).[14]

The possibility that NAD decline instead represents a change in redox state does not imply that it has no impact on cellular health and metabolism (though it does suggest that effects on aging are mediated by NAD's functions as a coenzyme, not its role in sirtuin activity). A net decrease in intracellular NAD+/NADH ratio corresponds to a drop in NAD redox potential – meaning that the NAD+/NADH system has lower antioxidant capacity and has become less effective in its critical role of combating oxidative stress. As we described above, this deficiency can promote mitochondrial dysfunction and genomic instability, two hallmarks of cellular aging. Importantly, the shift in the NAD+/NADH ratio could mean that simple supplementation to increase overall NAD levels might not address the underlying problems resulting from a decline in NAD+ with age.

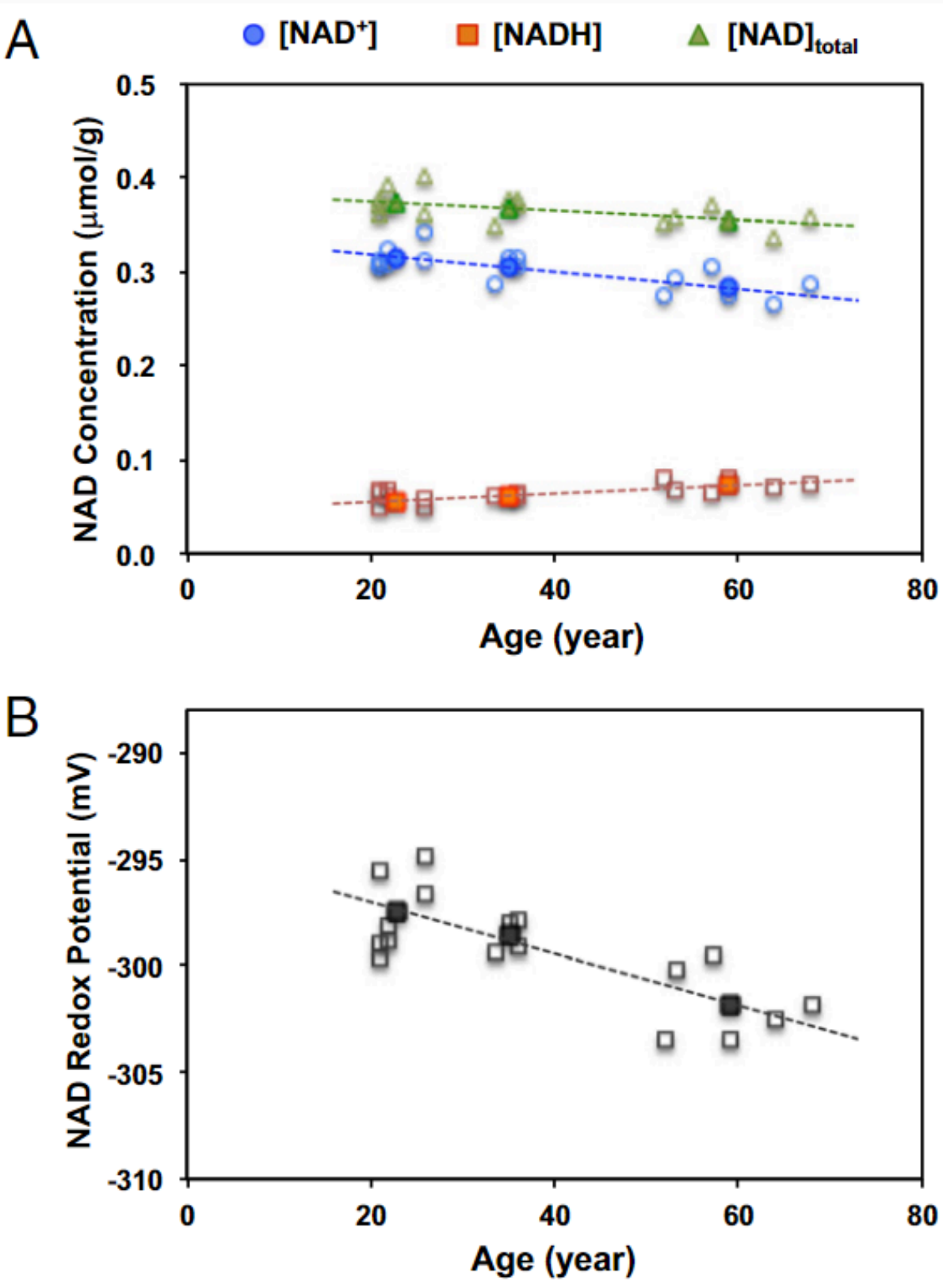

Figure 2: Relationship between age and A) intracellular NAD+, NADH, and total NAD. B) NAD redox potential observed in healthy human brains. Open symbols denote data from individual subjects, while filled symbols denote average data from three age groups of younger (21–26 years; n=7), middle (33–36 years; n=4), and older (59–68 years; n=6) subjects. From Zhu *et al.*, 2015.[14]

Can NAD supplementation enhance health and longevity?

We've seen that NAD is vital for cell survival and healthy functioning and that levels of NAD+ appear to decline with age. So it seems logical that supplementation with NAD might be beneficial in counteracting cellular dysfunction (and as a result, many aging hallmarks) by maintaining NAD+ at more youthful levels.

Alas, few problems in biology are that simple. (For instance, oxygen is also vital for cells, and oxygen saturation also declines with age, yet hooking everyone up to oxygen machines won't fix aging, as it doesn't solve the underlying problems that *lead* to the decline.) The link between NAD supplementation and health effects is similarly complex. Beyond the question of whether NAD levels are truly decreasing or are instead merely changing redox state, two issues challenge the potential utility of NAD supplementation. The first has to do with the natural regulation of NAD levels in cells, while the second has to do with bioavailability.

We know that NAD serves vital purposes in the cell, and this means that cells can't tolerate imbalances and must be capable of buffering NAD levels very well to avoid catastrophic problems associated with either high or low NAD+. Generally, NAD+ levels fluctuate in the range of 200–500 μM, though they vary by cell type and environmental conditions. When NAD+ levels fall too low, glycolysis is inhibited, resulting in cell death. On the other hand, excessively *high* levels of intracellular NAD+ result in an increase in intracellular nicotinamide (NAM), which in turn inhibits the activity of PARPs (as these enzymes produce NAM as a product of NAD+ consumption). Inactivation of PARPs and the consequent impairment of DNA repair mechanisms can cause genomic instability, which in turn leads to cell death. So the question is, if NAD levels really decline during aging, do they decline enough to move cells out of that buffered range, to a point where it would cause problems? It's possible, but the truth is that we don't currently know.

A more definite problem with NAD supplementation for longevity concerns its bioavailability. When taken orally, NAD is broken down in the gastrointestinal tract rather than being absorbed intact. Administering NAD intravenously bypasses the gut and liver and avoids degradation in those organs, but even then, there's no clear mechanism for NAD to enter cells from the bloodstream. Thus, even if we accept that increasing or maintaining NAD levels might be beneficial for aging, its poor bioavailability poses a challenge for doing so. In more recent years, researchers have attempted to circumvent this obstacle by supplementing instead with NAD *precursors* – molecules that cells can use as raw materials for the synthesis of NAD.

What are NAD precursors?

Mammals primarily use internal recycling systems (known as "salvage routes") to maintain tissue NAD+ levels, but a small amount of NAD precursors (20 mg of niacin or niacin equivalents for humans) is required through diet. Thus, it is clear that NAD precursors must be absorbable to some degree and capable of contributing to the body's overall NAD pool through conversion to NAD.

Tryptophan, nicotinic acid (NA, aka niacin), nicotinamide (NAM), nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) are precursors that can be used for producing NAD+ (**Figure 3**). Each of these precursors has different properties in terms of absorption and cellular uptake, but even here, the story is complicated. For example, NMN appears to be converted to NR in the gut before absorption, and while NR can be absorbed, a significant portion is degraded to NAM in the gut.

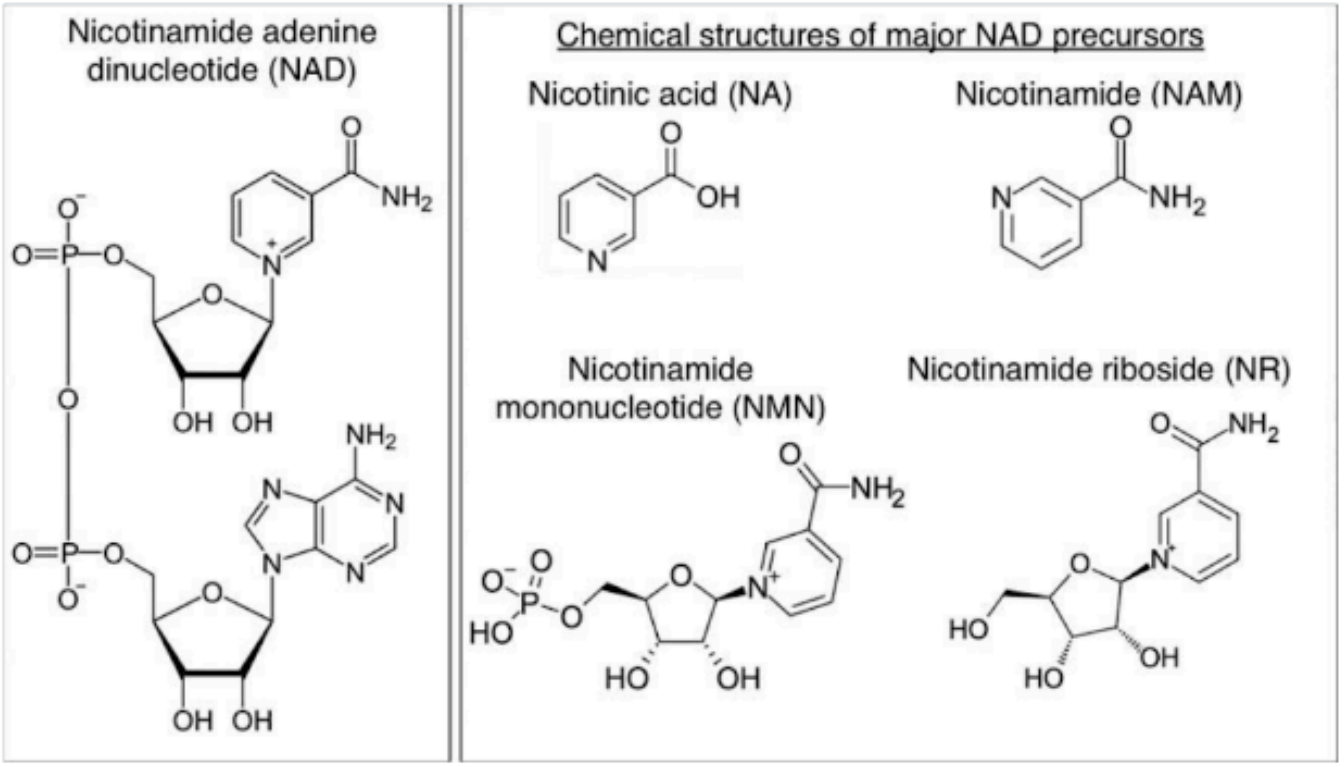

Figure 3: Structure of NAD+ and its major precursors: NA, NAM, NMN, and NR. From Williams et al. 2017.[18]

Still, because we can't directly absorb NAD from the GI tract or transport it into cells, supplementation with NAD precursors is currently considered to be the most promising means of raising intracellular NAD levels. We know, for example, that NR can enter cells directly through a class of transporters known as ENTs (equilibrative nucleoside transporters).[19] While some have speculated that NMN may also have a transporter to facilitate direct entry into cells, a more prevailing view is that NMN is first converted to NR and is therefore taken up by cells via ENTs. Tryptophan and NA are likely taken up by cells via other solute transporters (SLCs), while NAM can diffuse across plasma/mitochondrial membranes without need of any active transport.

Do NAD precursors raise intracellular NAD+ levels?

Entry of NAD precursors into cells ought to stimulate the biosynthesis pathways by which cells produce or recycle NAD+, leading to increases in overall intracellular NAD+ levels (**Figure 4**). Different precursors are used as substrates for different pathways – for instance, intracellular NR can be converted to NMN, which can subsequently be converted to NAD+ in a process known as the "salvage pathway." (Of note, NMN appears to be the key precursor for *mitochondrial* NAD+ pools. Other NAD precursors raise mitochondrial NAD+ through conversion to NMN.[20]) NA and tryptophan can likewise be converted to NAD+ through a series

of steps in the Preiss-Handler pathway and *de novo* synthesis pathways, respectively.[21] Thus, any NAD precursor capable of entering cells should theoretically be effective in boosting intracellular NAD+.

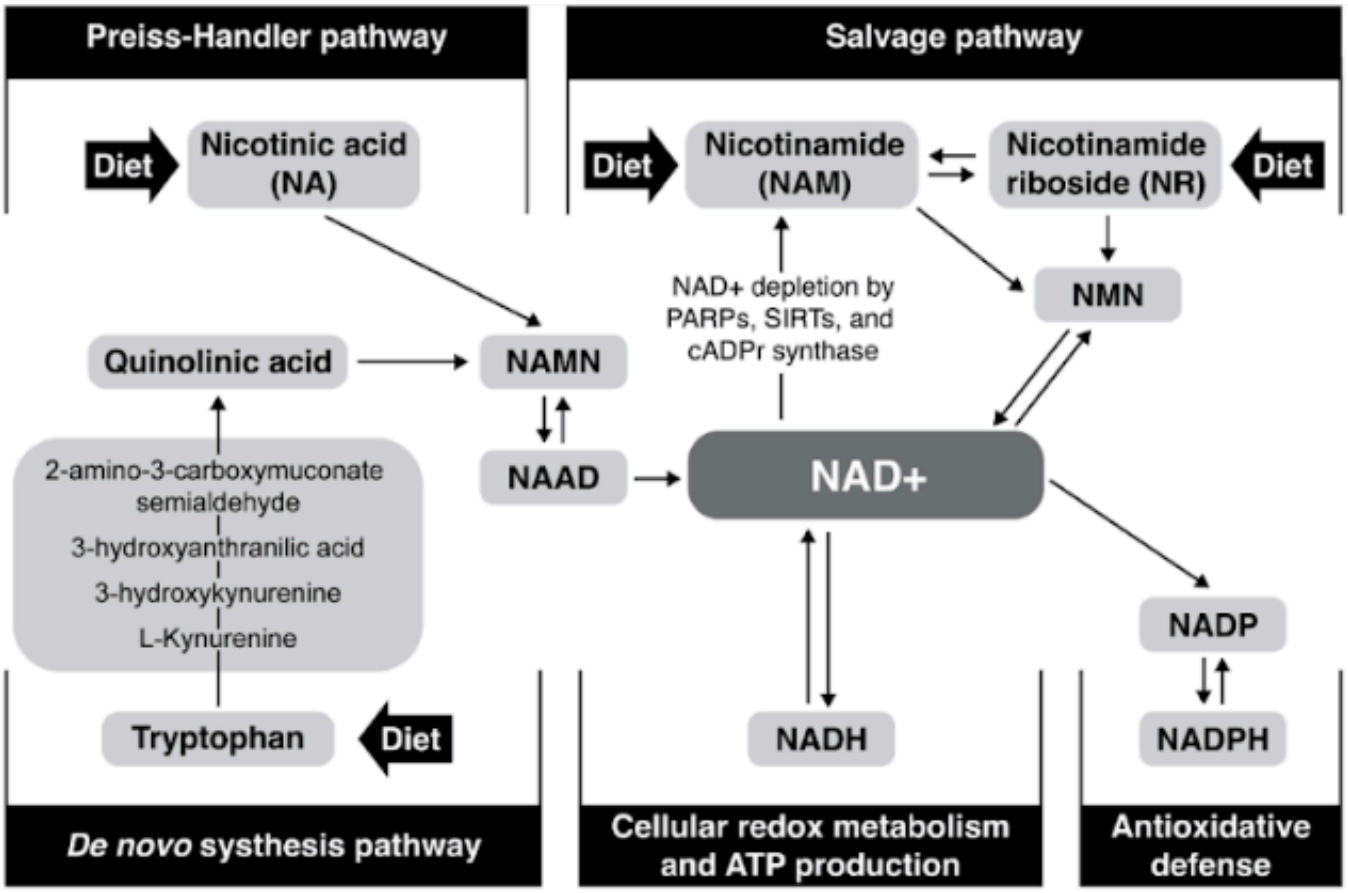

Figure 4: Major NAD+ biosynthetic and redox pathways. From Poljšak *et al.*, 2022.[21]

Yet as we've seen so many times already with NAD, the truth has proven less straightforward than theory, as different tissues display differences in rates of NAD precursor uptake and NAD biosynthesis, as well as in which biosynthetic pathway predominates.

According to a 2019 study by Liu *et al.*, the small intestine and spleen are the sites of greatest NAD flux, whereas most health claims about NAD-boosting supplements revolve around their benefits for muscle, fat, and brain – tissues with some of the *lowest* rates of NAD turnover. (NAD+ flux in the small intestine is more than 50-fold greater than that of muscle or fat and more than 10-fold greater than that of the brain.) Further, while the liver and, to a lesser extent, the kidneys account for virtually all activity through the de novo synthesis pathway, most other tissues rely primarily on the salvage pathway, typically utilizing NAM produced from the liver.[21,22]But although these findings raise questions about existing theories regarding NR and NMN supplementation, they don't necessarily mean that NAD precursors do *not* have meaningful effects on intracellular NAD in tissues such as muscle and the brain.

Ultimately, theories and mechanistic insights can only take us so far. What counts is whether real, *in vivo* data actually *show* an increase in intracellular NAD with NAD precursor supplementation (and, as we'll discuss shortly, whether this translates to health improvements). Initially, most reports involving increases in intracellular NAD with NR or NMN treatment were based on *in vitro* experiments, which have been shown to be poor models for NAD metabolism

at the whole-body level.[22] But more recently, *in vivo* data in rodents have given us cause for greater optimism regarding the ability of NAD precursors to increase NAD within certain tissues of interest. Multiple studies in mice have demonstrated that supplementation with NR over the course of 4-10 weeks significantly raises NAD+ levels in skeletal muscle relative to placebo.[23,24] A mouse study using NMN, by contrast, found little increase in NAD+ in skeletal muscle following a single oral NMN administration, though other tissues – including white adipose tissue, the pancreas, and the liver – did demonstrate significant NAD+ enhancement.[25] Both NR[26] and NMN[27] have also been seen to raise NAD+ in mouse brains. Importantly, these studies typically involved doses that, after accounting for body size and allometric scaling (i.e., the fact that larger body sizes are associated with slower metabolism[28]), would be well above those used in humans, but they nevertheless serve as a basic proof of principle that NAD precursors are capable of raising intracellular NAD+ levels in tissues that are relevant to purported benefits to metabolism, cognition, and overall health.

Do NR or NMN increase lifespan?

Of course, the ability of NAD precursors to raise intracellular NAD is just a prerequisite for the real question: is supplementation with these precursors effective in combatting aging and extending lifespan? As is the case for most alleged "longevity drugs," no human trials have investigated lifespan effects of NAD precursors, as such studies would be prohibitively long and costly. Thus, the most direct tests of the geroprotective efficacy of these molecules have been performed in rodents.

The most rigorous assessment comes from the Interventions Testing Program (ITP), which conducts thorough lifespan studies in outbred mice. The investigators treated 136 female and 156 male mice across three testing sites with NR mixed with their normal diet starting at 8 months of age (roughly equivalent to humans in their early 30s) and continuing throughout the rest of their lives. Comparing these animals to 607 controls (50% female) on standard diet, NR supplementation showed no effect on median or maximum lifespan in either males or females. While some NAD advocates have pointed out that data from one of the three testing sites demonstrated a very slight increase in female lifespan with NR, this finding should not be taken as supportive evidence, as it was balanced out by another site that observed a slight *decrease* in lifespan in NR-treated females, as well as a third site that found decreased lifespan in males.[29]

As for NMN, the ITP has not performed its rigorous assessments of potential lifespan effects with this NAD precursor. However, earlier this year, a research group led by Dr. David Sinclair – one of the most vocal supporters of NAD and the sirtuin hypothesis – published results of their own investigation of NMN supplementation. The researchers reported that female mice treated with approximately 550 mg/kg/day of oral NMN (starting at 13 months, or mid- to late-40s for a human) exhibited an increase in median lifespan of 8.5% relative to controls, as well as an increase in maximum lifespan of 7.9%.[30] Yet these results – which have not been subject to peer-review – require careful interpretation: the lifespan of NMN-treated females didn't differ from either control or NMN-treated males, suggesting the apparent "extension" might actually reflect unusually *short* lifespan in female controls rather than a true benefit of NMN.

What about other possible health benefits?

Even in the absence of compelling data on longevity enhancement, the fact that NAD is involved in so many vital cellular functions has led some to hypothesize that NAD+ depletion may contribute to the pathogenesis of various age-related ailments. Thus, NAD precursors have also been studied for their efficacy in treating and preventing the “four horsemen” – metabolic syndrome, neurodegenerative disease, cancer, and cardiovascular disease. Further, given the importance of NAD for mitochondrial function and cellular energy production, investigators have also explored the possible utility of NAD precursors in *enhancing* physical performance, apart from the context of disease. Below, we evaluate the current state of research on each of these potential benefits, for which investigations to date have largely focused on NR in particular.

Metabolic disease

As described earlier, cellular metabolism relies critically on NAD. Yet despite the strong mechanistic links between NAD and metabolism, clinical trials have consistently failed to demonstrate meaningful benefits in the context of metabolic disease.

One of the largest of such studies involved 40 obese, non-diabetic men randomized to either NR supplementation (2000 mg/day) or placebo for a period of 12 weeks. Results demonstrated that NR had no significant effect on body composition, energy expenditure, insulin sensitivity, cholesterol metrics, or liver function, though the NR group exhibited a small, non-significant trend toward greater reduction in liver lipid content.[31] Indeed, the only significant change relative to the placebo group was a modest *increase* in plasma triglycerides among participants on NR – hardly a desired outcome, though post-treatment values remained within normal ranges. A subsequent analysis of data from this trial focused on other aspects of metabolic health – namely, pancreatic function and glucose-stimulated incretin hormone (GLP-1and GIP) release – but likewise found no effect with NR supplementation,[32] as did a follow-up analysis concerned with metrics of mitochondrial function in skeletal muscle.[33]

Neurodegenerative disease

NAD+ depletion is associated with neurodegenerative diseases, including Alzheimer’s disease and Parkinson’s disease. A fair amount of mechanistic evidence might suggest that reversing this depletion would improve cognitive trajectories, and studies in rodents have generated promising results, though human studies have been less consistent.

Both NR and NMN have been investigated for their efficacy in improving cognitive trajectories in various contexts. This body of work has demonstrated, for instance, that treatment with these NAD precursors reduces neuroinflammation and oxidative stress and improves memory and cognitive performance (e.g., through maze tests) in rodent models of Alzheimer’s disease.[34,35] Similarly promising findings have been reported for vascular dementia, age-related cognitive decline, and Parkinson’s disease, though it’s worth noting that many of these studies involved direct injection of NAD precursors (particularly with NMN) rather than administration through an oral route.[36,37]

Despite compelling preclinical data, direct evaluations of NAD precursor administration in humans have been very limited, and results have been more equivocal. In a recent trial, 20 subjects with mild cognitive impairment were treated with NR (1 g/day) or placebo over 10 weeks, and while NR treatment resulted in a 2.6-fold increase in blood NAD+ in the NR group, no changes were observed in any cognitive metrics.[38] Likewise, a 24-week trial involving treatment with nicotinamide (NA) or placebo among 31 patients with mild to moderate Alzheimer's disease failed to show any difference in cognitive function between groups.[39]

Somewhat more optimistic findings have arisen from trials investigating the use of NR for the treatment of Parkinson's disease. In one such trial, 27 participants newly diagnosed with Parkinson's disease were randomized to receive either NR (1 g/day) or placebo for 30 days, and the authors reported that NR treatment enhanced NAD+ levels in the brain (though the increases varied widely across participants) and the increases in cerebral NAD+ correlated with improvements in Parkinson's symptoms (as defined by the Movement Disorder Society's Unified Parkinson;s Disease Rating Scale, or MDS-UPDRS). However, the change was only statistically significant relative to the placebo group when analysis was restricted to the nine (out of 13) NR participants who exhibited at least a 10% increase in cerebral NAD+ with treatment, and even in this subset, the improvement was very small (a mean decrease in MDS-UPDRS score of 2.33±2.35 on a scale ranging from 0-260).[40] Still, the results were corroborated by a 2023 trial involving higher doses of NR (1.5 g twice daily) for four weeks. At this dose, MDS-UPDRS scores improved significantly in the NR group relative to placebo (NR mean change: –10.7±9.94; placebo mean change: 0±9.59; P=0.024), and the magnitude of the change demonstrates clear clinical significance. Sub-analyses indicated that the positive impact on MDS-UPDRS scores was driven primarily by improvements in the domain of motor symptoms.[41]

As we see from these examples, human trials have thus far been very limited in length and in number of participants. Results with respect to Parkinson's disease are encouraging, but at the moment, we have no clear indication that supplementation with NAD precursors can delay cognitive decline in a more general sense. However, several clinical trials are ongoing that may shed additional light on this question in the near future.

Cancer

The relationship between NAD and cancer is complex. While NAD depletion might contribute to cancer formation by limiting energy production, DNA repair, and genomic stability, supplementation could theoretically fuel existing cancers, as NAD is crucial for cell division. Thus, it is unsurprising that results on the effects of NAD precursors on cancer risk and cancer treatment have been inconclusive and likely depend on the particular experimental design details and on the cancer models used.

Limited evidence from animal studies hints that NAD precursors may help prevent early-stage malignancies. For instance, using a transgenic mouse model characterized by increased DNA damage and increased frequency of hepatocellular carcinomas, researchers have shown that the heightened cancer risk in these animals can be mitigated by supplementation with NR. However, it must be noted that the genetic manipulation used in this animal model *directly*

affected NAD metabolism, and tumor initiation was *caused* by DNA damage from low NAD+ levels (and thus impaired DNA repair).[42] While NAD+ repletion with NR supplementation would be expected to counteract the abnormality in this case, not all cancers feature this particular mechanism of initiation, which perhaps explains why other studies investigating NAD precursors and cancer prevention have yielded mixed results.[43–45]

Still, although data on NAD precursors and cancer prevention may be unconvincing at best, these molecules do appear to be effective in limiting the negative effects of cancer *treatment*. Chemotherapy induces substantial collateral damage to normal tissue, and multiple studies in mice and cell lines have demonstrated that treatment with NR or NMN significantly reduces chemotherapy-associated DNA damage and neurotoxicity.[46–48] However, these benefits may be offset by the possibility that NAD precursors may also accelerate cancer progression, as we'll discuss in more detail later in this piece.

Cardiovascular disease

The role of NAD in energy generation and response to oxidative stress – both of which have implications for cardiometabolic health – has led some to believe that NAD precursors may be protective against cardiovascular disease (CVD). Indeed, the heart has some of the highest levels of NAD in the body,[49], and *in vitro* experiments have indicated that treating cardiac muscle precursor cells improves their survival following hypoxic stress.[50] Yet few investigations have directly evaluated the utility of NAD precursors for treating or preventing CVD, with one exception – niacin.

Research as early as the 1950s has demonstrated the efficacy of niacin in lowering plasma triglycerides and concentrations of apoB-containing lipoproteins[51] – the lipoproteins that drive atherogenesis. A number of small-scale clinical trials have since revealed niacin to be effective in slowing progression of CVD and in reducing risk of cardiovascular events,[52–55] but as Dr. Benoît Arsenault and Dr. Dan Rader have explained on *The Drive*, subsequent larger trials have shown benefits to be quite small by comparison to more standard treatments (e.g., statins), whereas side effects (primarily flushing) can be substantial and impact nearly everyone on the drug.[56,57] Thus, despite initial promise, niacin is seldom used for CVD prevention or treatment in the present day.

As for the more common NAD-boosting supplements, NR and NMN, we have few insights from existing data. The couple of clinical trials for which results have been published have focused primarily on outcomes related to arterial stiffness, and reported benefits have been unconvincing. For instance, in a crossover trial (6 weeks on placebo, 6 weeks on NR) comprising 24 healthy participants, researchers observed a trend toward lower aortic stiffness with NR treatment, though the result did not achieve statistical significance.[58] Similar results have been reported from a 12-week parallel-group trial with NMN, in which the NMN group (n=17) showed a non-significant trend toward reduced arterial stiffness relative to placebo.[59] However, no trials thus far have investigated cardiovascular events or reported significant cardiovascular benefits, so at present, we have no reason to put faith in these molecules for cardiovascular health.

Exercise performance

As we've seen, NAD is vital for cellular energy production and mitochondrial function, which in turn are required for movement. Thus, increasing intracellular NAD+ might theoretically enhance physical performance, and a handful of clinical trials have investigated NAD precursors for this purpose. The results of such studies, however, have shown minimal (if any) effect.

In the context of *acute* supplementation, a crossover study in 12 young men (mean age 22.9 years) and 12 older men (mean age 71.5 years) indicated that supplementation with 500 mg of NR two hours before performance assessments did not affect VO_2 max in either age group relative to placebo, though it modestly improved resistance to fatigue among the older participants.[60] Among the studies investigating the effects of *repeated* NAD precursor supplementation, the most positive results come from a six-week trial in amateur runners, which showed that treatment with moderate (600 mg/day) or high (1200 mg/day) doses of NMN increased oxygen uptake (VO_2) at the first ventilatory threshold (the first major uptick in breathing rate as exercise intensity increases) and in power output at the first ventilatory threshold, but no significant changes were observed in VO_2 max, peak power output, max heart rate, or other metrics.[61] A six-week crossover study in older adults (65±7 years) supplemented 1000 mg NR or placebo similarly showed no effect on VO_2 max, nor on treadmill time to exhaustion, leg muscle fatiguability, grip strength, or metrics of mobility and dexterity.[58]

Are there any risks to NAD precursors?

While NAD precursors appear generally safe in short-term studies, two potential risks deserve attention.

Flushing is generally the most common negative side effect associated with NAD, though this effect is typically associated primarily with niacin and intravenous NAD infusions and not with NR or NMN.[62,63] Ironically, while flushing is often significant enough to cause discontinuation of *niacin* treatment, some patients seem to *value* this effect as evidence that treatments are "working" in the context of pricey i.v. NAD sessions. In actuality, the flushing associated with i.v. NAD and niacin results from the increased production of prostaglandins by immune cells in the skin (which causes vasodilation and redness or warmth of the skin, often accompanied by itching),[64] and the effect has no apparent relationship to potential health or longevity benefits of NAD.

Another important downside of NAD precursors is that they may accelerate the growth of existing cancers. In a past newsletter, we highlighted results of a study demonstrating that among mice injected with breast cancer cells, those treated with NR exhibited faster tumor development and more brain metastases than control animals[65] – results which align with an earlier pilot study by Dr. Iñigo San Millán, discussed in Episode #201 of *The Drive*. The findings make sense when we consider that NAD is indispensable for glycolysis, a process upon which tumors rely heavily to fuel their rapid growth, and indeed, interventions designed to *reduce* NAD biosynthesis have shown promise as anti-cancer treatments in preclinical research.[66,67]

However, we must emphasize that all of these data only indicate that NAD precursors may fuel cancer *progression*; they do not imply that NAD precursors cause cancer to develop in the first place.

Bottom line

Despite enormous interest and investment, the evidence supporting NAD precursors as anti-aging therapeutics remains surprisingly thin. While these compounds clearly play important roles in cellular function, their potential as interventions to extend healthy lifespan faces several key challenges, including the fact that even at the most basic mechanistic level, the relationship between NAD precursors, intracellular NAD, and the biology of cellular aging remains poorly understood.

Even so, this doesn't mean that we can write off NAD-based therapies as completely worthless. Though we have no compelling evidence to support the anti-aging claims often made about these supplements, some preclinical evidence (and even a few isolated clinical trials) have left us with intriguing clues about disease-specific benefits, particularly with respect to the treatment of Parkinson's disease. More extensive and rigorous study may *eventually* establish these molecules as having reliable clinical utility, either alone or in combination with other interventions, but at present, support for even the most promising applications is still very preliminary.

Thus, while it certainly never hurts to keep an eye on emerging research on alleged "longevity drugs" such as NAD and NAD precursors, I wouldn't pin my hopes on these molecules as a means to a longer, healthier life. In the time we spend waiting for more compelling data (which may never come), we'd be better served sticking to the tried-and-true tactics of exercise, nutrition, quality sleep, and emotional well-being.

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