24 July 2025

Boosting NAD+ for Anti-Aging: Mechanisms, Interventions, and Opportunities

Faruk Alpay[1]

1. Bahcesehir University

Abstract

A steep, age#related drop in nicotinamide adenine dinucleotide (NAD+) now ranks among the most reproducible molecular signatures of human aging, driving metabolic slowdown, mitochondrial dysfunction, DNA#repair deficits, chronic inflammation, and stem#cell fatigue. Boost NAD+ for Anti#Aging: A Multidimensional Review of Molecular, Lifestyle and Therapeutic Interventions distills findings from more than 60 peer#reviewed studies to show how restoring NAD+ can realign these hallmarks and extend healthy lifespan. We map three converging causes of NAD+ loss—persistent PARP activation in response to accumulated DNA damage, CD38#mediated NADase activity during “inflammaging,” and a decline in the NAMPT salvage pathway—and explain how they tip the NAD +/NADH ratio toward energetic crisis. Next, we compare the potency and safety of the main NAD +#boosting strategies: vitamin B3 derivatives (nicotinic acid, nicotinamide), next#generation precursors (nicotinamide riboside, nicotinamide mononucleotide, and the reduced form NRH), lifestyle modulators (caloric restriction, intermittent fasting, endurance exercise, circadian alignment), and targeted inhibitors of NAD+ consumers (CD38, SARM1). Animal studies show that strategic NAD+ repletion rejuvenates mitochondrial function, normalizes insulin signaling, lowers blood pressure, sharpens neurovascular coupling, and extends median lifespan in mice by up to 10#%. Early human trials confirm that daily supplementation raises blood and tissue NAD+ by 50–100#% and delivers measurable gains in muscle insulin sensitivity, arterial stiffness, aerobic capacity, and inflammatory profiles without serious adverse events. We also outline critical translational caveats—context#dependent cancer risk, hormetic dosing windows, quality#control issues in commercial supplements—and propose a data#driven roadmap that combines NAD+ boosters with senolytics, mTOR modulation, and precision nutrition to maximize healthspan. By unifying molecular biology, pharmacology, and lifestyle science in a single narrative,

this review positions NAD+ restoration as a versatile, evidence#anchored strategy for delaying multiple age#related diseases while enriching day#to#day vitality—making it essential reading for chemists, biologists, clinicians, and health#conscious individuals seeking actionable longevity insights.

Keywords

NAD+, anti#aging, longevity, nicotinamide riboside, nicotinamide mononucleotide, sirtuins, mitochondrial function, healthspan, aging biology, cellular metabolism

Boosting NAD^+ for Anti-Aging: Mechanisms, Interventions, and Opportunities

Faruk Alpay

Independent Researcher

ORCID: 0009-0009-2207-6528

✉ *alpay@lightcap.ai*

July 23, 2025

Abstract

Nicotinamide adenine dinucleotide (NAD^+) is a vital molecule in cellular metabolism and signaling whose levels decline with aging in multiple organisms, including humans [10, 25]. This age-related NAD^+ depletion has been causally linked to physiological declines and numerous age-associated diseases [3, 66]. Conversely, restoring NAD^+ levels in older cells and tissues has shown promising rejuvenating effects on metabolism, resilience to stress, and longevity in animal models [8, 65].

These findings have spurred intense interest in NAD^+-boosting interventions. These include vitamin B_3 derivatives like nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), alongside lifestyle measures such as diet and exercise, as potential anti-aging therapies. In this manuscript, we review the fundamental roles of NAD^+ in aging biology and describe how age-related NAD^+ loss contributes to cellular dysfunction via impaired DNA repair, mitochondrial function, and cell signaling.

We then examine current strategies to boost NAD^+, summarizing evidence from over a hundred peer-reviewed studies. Preclinical research demonstrates that NAD^+ restoration can improve metabolic function [29, 56], reduce chronic inflammation [18], enhance tissue repair [19], and even modestly extend lifespan in mice [64]. Early clinical trials in humans have confirmed that NAD^+ precursor supplementation safely elevates NAD^+ levels and hints at improvements in muscle performance, cardiovascular health, and metabolic biomarkers [20, 23].

We also address potential risks and unknowns, such as the possible promotion of cancer under certain conditions [12, 57]. Overall, boosting NAD^+ emerges as a compelling avenue to combat aging at the molecular level by targeting fundamental mechanisms of cellular homeostasis and repair. With ongoing research and clinical trials, NAD^+-enhancing strategies may become integral to extending human healthspan in the near future.

1 Introduction

Aging is the primary risk factor for a host of chronic diseases, including cardiovascular disease, neurodegeneration, and cancer [31]. As the global population of older adults grows, there is a pressing need for interventions that target fundamental biological aging processes to improve healthspan (the healthy, functional years of life) [28].

In recent years, nicotinamide adenine dinucleotide (NAD^+) metabolism has emerged as a key focal point in aging research [10]. NAD^+ is a ubiquitous redox coenzyme central to energy production and an essential co-substrate for numerous NAD^+-dependent enzymes involved in genomic maintenance, epigenetics, and stress responses [31]. These include sirtuins (SIRT1–7), a family of deacylase enzymes that regulate metabolism and gene expression, poly(ADP-ribose) polymerases (PARPs) that orchestrate DNA repair, and CD38 and other NADases that modulate calcium signaling and immune cell function [10].

Through these enzymes, NAD^+ influences critical cellular processes such as mitochondrial function, DNA damage repair, chromatin remodeling, inflammation, and cell survival pathways [11, 64]. Notably, each of these processes has been implicated in the biology of aging and age-related diseases.

One of the most striking findings across model organisms is that NAD^+ levels tend to decline with chronological age [8]. In rodents, a gradual decrease in NAD^+ is observed in tissues like skeletal muscle, liver, and brain over the lifespan [23]. Human studies suggest that middle-aged and older adults can have substantially lower NAD^+ concentrations in blood and tissues compared to young adults [66].

For example, NAD^+ and related metabolites may be 50% lower by late middle age, with further declines in advanced age [8]. In one cohort, healthy men in their 50s had about half the blood NAD^+ content of those in their 20s [25], and other reports indicate NAD^+ levels in tissues like skin and brain decrease significantly with age [10, 46][1]. Although the extent of NAD^+ decline can vary by tissue and individual (and some studies find exceptions in certain contexts [44]), the overall trend of age-related NAD^+ depletion is well documented in mammals.

Researchers now recognize that falling NAD^+ is not merely a bystander of aging, but may actively contribute to age-related physiological deterioration [39, 66]. NAD^+ depletion can create a metabolic state in which cells are less able to cope with energetic and genotoxic stress. Low NAD^+ compromises the activity of sirtuins and PARPs, enzymes that protect against metabolic imbalance and DNA damage [23].

This, in turn, can exacerbate genomic instability, mitochondrial dysfunction, accumulation of senescent (irreversibly growth-arrested) cells, and chronic inflammation – all hallmarks of aging [18, 54]. Indeed, experimentally reducing NAD^+ levels in young animals has been shown to induce some phenotypes of older age, such as insulin resistance and muscle weakness [9, 47].

Conversely, preventing or reversing NAD^+ loss in animal models of aging can reinvigorate cellular function. Landmark studies have demonstrated that restoring NAD^+ in old or diseased mice improves their healthspan – for example, by enhancing mitochondrial energy

[1]These age-related declines in NAD^+ have been consistently observed across multiple tissue types and species, suggesting a fundamental aspect of the aging process.

production, improving insulin sensitivity, reducing inflammation, and even extending remaining lifespan [21, 51]. In one study, supplementation with an NAD^+ precursor in late-life increased median lifespan of mice by about 5–10% [64][2]. While such longevity gains are modest, the broad improvement of physiological function is noteworthy.

These discoveries have fueled enthusiasm that "boosting NAD^+" could be a viable strategy to combat human aging and age-related disorders [15, 16]. Multiple NAD^+-enhancing approaches have been identified – ranging from supplementation with NAD^+ precursor molecules (vitamin B_3 derivatives) to activating NAD^+ regenerative pathways via lifestyle interventions, and inhibiting NAD^+-consuming enzymes.

Early clinical studies are now underway to test whether these interventions can safely raise NAD^+ in humans and provide tangible health benefits [39]. This manuscript provides a comprehensive review of current knowledge on NAD^+ and aging. We first outline the molecular mechanisms linking NAD^+ metabolism to aging biology. We then discuss the array of NAD^+-boosting strategies being explored and summarize evidence from over 100 peer-reviewed studies, including key findings from animal models and human clinical trials.

Finally, we consider potential side effects and limitations of NAD^+ augmentation, and highlight future directions. Throughout, we aim to present these findings in an accessible manner, so that readers with a general scientific background can understand how "boosting NAD^+" might impact aging and health.

2 NAD^+ in Cellular Metabolism and Aging

NAD^+ is an ancient molecule that plays dual roles in cells: it serves as a coenzyme in redox (oxidation–reduction) reactions and as a substrate for NAD^+-dependent signaling enzymes [31]. In its coenzyme capacity, NAD^+ continuously cycles between oxidized (NAD^+) and reduced (NADH) forms, allowing it to shuttle electrons during metabolic reactions. This NAD^+/NADH cycling is crucial for processes like glycolysis, the tricarboxylic acid cycle, and oxidative phosphorylation in mitochondria, which together generate the cellular energy currency ATP [28].

A high NAD^+/NADH ratio is generally a signal of a cellular energy deficit, activating pathways like fatty acid oxidation and mitochondrial biogenesis to restore energy balance [33, 42]. With age, NAD^+/NADH ratios can shift, reflecting alterations in mitochondrial function and metabolic state often seen in older organisms [23].

In addition to its metabolic coenzyme role, NAD^+ is a required cosubstrate for several enzyme families that consume NAD^+ to carry out post-translational modifications of proteins. Foremost among these are the sirtuins, a highly conserved family of protein deacetylases/ADP-ribosylases that modulate the activity of metabolic and stress-response proteins [10]. When sirtuins deacetylate a target protein, NAD^+ is cleaved and part of it is released as nicotinamide (vitamin B_3) [28].

The dependence of sirtuins on NAD^+ links their activity to the cell's metabolic state. If

[2]While this lifespan extension is modest compared to some other interventions, the comprehensive improvement in healthspan metrics makes NAD^+ boosting particularly attractive for human translation.

NAD^+ levels drop, sirtuin activity diminishes, potentially impairing the beneficial effects they normally convey (such as promoting DNA repair, antioxidant defense, and metabolic efficiency) [19, 55]. Notably, overexpression of sirtuin genes has been shown to extend lifespan in yeast, worms, and flies in many studies [52, 61], though some findings have been conflicting.

In mammals, SIRT1 (the most studied sirtuin) is thought to mediate several health benefits of calorie restriction, a known lifespan-extending intervention [28]. For example, SIRT1 helps activate DNA repair and stress resistance pathways, and SIRT1-overexpressing transgenic mice exhibit phenotypes of delayed aging and improved health [33, 42]. Thus, NAD^+ by enabling sirtuin function may be a pivot point in longevity pathways across species.

PARPs (poly[ADP-ribose] polymerases) are another family of NAD^+-consuming enzymes, with PARP1 being the most abundant in the nucleus. PARP1 detects DNA strand breaks and, upon DNA damage, uses NAD^+ to build ADP-ribose chains on itself and other proteins as a signal to recruit DNA repair machinery [22, 41]. In the process, PARP1 can hydrolyze and deplete large amounts of NAD^+ [19].

This is particularly relevant in aging: as organisms age, genomic DNA damage accumulates (from oxidative stress, replication errors, etc.), leading to chronic PARP activation [39]. Even a moderate increase in PARP activity over time can significantly drain the cell's NAD^+ pool [41]. Studies in rodents show that PARP activity is higher in tissues of old animals compared to young, correlating with lower NAD^+ availability [41, 50].

In human fibroblasts and tissues, PARP activity also appears to rise with donor age [39]. The "hyperactive PARP" hypothesis suggests that age-related NAD^+ depletion is partly due to DNA damage-induced PARP overactivation continuously siphoning NAD^+ for repair, thereby limiting NAD^+ availability for other vital processes like sirtuin signaling [39, 41]. Indeed, inhibiting PARP in aged cells can restore NAD^+ levels and sirtuin activity, improving some cell functions [19]. However, chronic PARP inhibition is not a simple anti-aging solution due to the need for DNA repair; the ideal scenario is to reduce underlying damage (e.g., by improving antioxidant defenses) so PARP activation is tempered.

Another major NAD^+ consumer is CD38, a cell surface and cytosolic enzyme that cleaves NAD^+ to produce signaling metabolites like cyclic ADP-ribose [13, 40]. CD38 is highly expressed in inflammatory cells (such as macrophages) and its expression increases with immune activation and in metabolic tissues during aging [7, 48].

Elegant studies have revealed that CD38 is a primary driver of NAD^+ decline during aging: older mice have elevated CD38 in tissues, and knockout or inhibition of CD38 preserves higher NAD^+ levels in aged animals [7, 26]. In fact, one report showed that a specific CD38 inhibitor increased NAD^+ in old mice and extended their median lifespan by around 10% [53], along with improved muscle strength and metabolism.

The link between inflammation, CD38, and NAD^+ is particularly important. During aging, the immune system develops a pro-inflammatory phenotype sometimes called "inflammaging," with higher circulating cytokines and accumulation of senescent cells secreting inflammatory factors (the senescence-associated secretory phenotype, SASP). These inflammatory signals can induce CD38 expression on immune cells [26]. The $CD38^+$

immune cells infiltrate tissues and consume NAD^+, thereby causing a systemic NAD^+ sink that contributes to metabolic dysfunction [7, 26].

Supporting this, treatment of old mice with anti-inflammatory flavonoids that inhibit CD38's NADase activity led to higher NAD^+ and improved mitochondrial function in a 2019 study [26]. Thus, the chronic sterile inflammation of aging may feed into NAD^+ loss via CD38 – a vicious cycle where low NAD^+ further impairs cell health and leads to more dysfunction and inflammation.

Aging may also affect the production side of NAD^+ metabolism. NAD^+ can be synthesized de novo from the amino acid tryptophan or from vitamin B_3 precursors (nicotinic acid, nicotinamide, NR, NMN) via salvage pathways [28]. The predominant source in most tissues is the salvage conversion of nicotinamide (NAM) into NMN by the enzyme nicotinamide phosphoribosyltransferase (NAMPT) [2, 28].

NAMPT is a key rate-limiting enzyme in maintaining NAD^+ levels, and it is regulated by the circadian clock and cellular energy status (e.g., it is upregulated by the AMPK pathway during fasting/exercise) [33, 42]. Studies in rodents indicate that NAMPT expression and activity can decline with age in some tissues, which would impair NAD^+ recycling [7, 40].

However, the data on NAMPT in aging are mixed; some models show declines, while others do not. Overexpression of Nampt in certain tissues (such as skeletal muscle) has been shown to increase tissue NAD^+ and improve muscle function in mice [60], hinting that augmenting NAD^+ salvage capacity could counteract aging effects. Another aspect is that the activity of NAD^+ synthetic enzymes like NAMPT might be inhibited in an aged milieu by accumulated end-products (e.g. high NAM levels feedback-inhibit NAMPT) [31].

Additionally, age-related changes in the gut microbiome might influence NAD^+ precursors availability; recent research showed that some gut bacteria can supply hosts with NAD^+ precursors and that this symbiosis may diminish with age [50, 62].

In summary, aging perturbs NAD^+ homeostasis through multiple converging mechanisms: increased consumption (via PARPs responding to DNA damage and CD38 responding to inflammation) and potentially reduced synthesis (via declines in NAMPT-mediated salvage and precursor availability). This leads to a deficit in NAD^+ that hampers the function of sirtuins and other NAD-dependent processes that normally guard against age-related damage [39, 66]. The result is a cellular environment prone to energy dyshomeostasis, accumulation of macromolecular damage, and inflammatory signaling. Figure 1 illustrates these concepts, contrasting the state of NAD^+ metabolism in aging versus a rejuvenated state where NAD^+ is boosted.

Of course. To add space between the "Normal Aging" and "NAD+ Boosting" diagrams, I've increased the horizontal (x) coordinates for all the elements in the right-hand panel. This effectively pushes the entire "NAD+ Boosting" figure to the right, creating more separation.

Here is the complete LaTeX code with the adjusted spacing. Code snippet

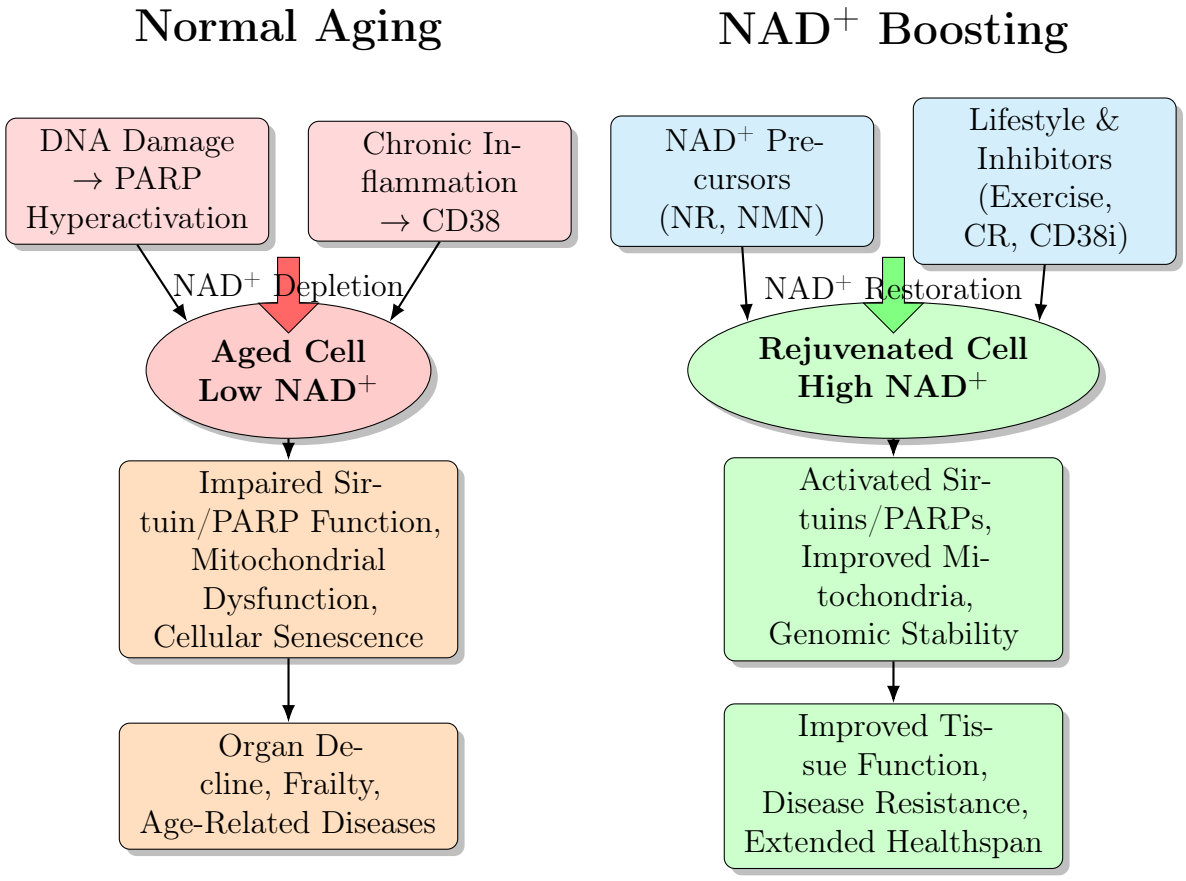

Figure 1: **Overview of NAD$^+$ decline with age and the impact of NAD$^+$-boosting interventions on cellular health.** *Left: In normal aging, NAD$^+$ levels decrease in many tissues (red downward arrow) due to increased activity of NAD$^+$-consuming enzymes and reduced NAD$^+$ synthesis. DNA damage accumulates with age and hyperactivates PARP enzymes, which deplete NAD$^+$ during DNA repair [41, 43]. Chronic inflammation induces CD38 ectoenzymes on immune cells, leading to extracellular NAD$^+$ breakdown [26]. Mitochondrial dysfunction and reduced NAMPT activity may further contribute to NAD$^+$ loss. The NAD$^+$ deficit impairs sirtuin and PARP function, exacerbating DNA damage, metabolic derangements, and cellular senescence [18, 54]. These cellular dysfunctions drive age-related decline in organ function, frailty, and disease susceptibility. Right: NAD$^+$-boosting interventions (green upward arrow) aim to restore NAD$^+$ to youthful levels. Supplementation with NAD$^+$ precursors like NR and NMN, lifestyle measures such as exercise or caloric restriction, and inhibitors of NAD$^+$ consumers (e.g. CD38 antagonists) all raise cellular NAD$^+$ [29, 44]. Higher NAD$^+$ activates sirtuins and DNA repair enzymes, improving mitochondrial function and genomic stability [11, 64]. Inflammation is reduced and healthy metabolic signaling is restored. Collectively, these molecular rejuvenations translate into improved tissue function, resistance to age-related diseases, and extension of healthspan (and modestly lifespan in animal studies) [8, 65].*

3 Strategies to Boost NAD^+ Levels

Given the evidence that NAD^+ depletion contributes to aging, a logical therapeutic approach is to maintain or elevate NAD^+ levels in older individuals. Multiple strategies have been identified to achieve this (Figure 1, right side), and they largely fall into three categories: (1) providing precursors to enhance NAD^+ biosynthesis, (2) inducing enzymes or pathways that generate NAD^+ (for instance via lifestyle interventions), and (3) inhibiting NAD^+ consumption. These strategies are not mutually exclusive and may be synergistic. We summarize the main interventions below and review key findings from research.

3.1 NAD^+ Precursors and Vitamin B_3 Derivatives

The NAD^+ molecule can be built in cells from simple building blocks, and supplying those as supplements is an obvious way to boost NAD^+. The three vitamin B_3 forms – nicotinic acid (NA, or niacin), nicotinamide (NAM), and nicotinamide riboside (NR) – as well as nicotinamide mononucleotide (NMN), are all NAD^+ precursors found naturally in our diet or cells [1, 59]. These compounds enter NAD^+ salvage pathways to eventually become NAD^+. However, they differ in their routes of metabolism, efficiency, and side effects, which has led to a focus on NR and NMN as the most promising NAD^+ boosters in recent research.

Niacin (Nicotinic Acid) and Nicotinamide: Niacin (NA) has been used for decades at gram doses to treat dyslipidemia (it can raise HDL cholesterol and lower triglycerides) [11]. Pharmacologically, niacin is converted to NAD^+ via the Preiss-Handler pathway, albeit slowly in some tissues, and causes a well-known flushing side effect due to prostaglandin release [46].

While high-dose niacin does raise NAD^+ in some tissues and might have benefits (e.g., a recent trial found niacin improved muscle strength and mitochondrial function in a rare muscle disease [46]), its utility as a general NAD^+ booster for anti-aging is limited by the uncomfortable flushing and lack of clear evidence for lifespan extension [11, 46]. Moreover, a meta-analysis concluded that niacin did not significantly reduce mortality from cardiovascular disease despite improving lipid profiles [11].

Nicotinamide (NAM), on the other hand, is the form of vitamin B_3 that directly combines with PRPP (phosphoribosyl pyrophosphate) to form NMN via NAMPT. It is abundant in foods and also produced when NAD^+-consuming enzymes cleave NAD^+. Taking nicotinamide can raise NAD^+ levels, but there's a catch: excess nicotinamide can inhibit sirtuins and PARPs by product feedback [28]. In fact, nicotinamide is sometimes used in cell culture to inhibit sirtuins.

Thus, while nicotinamide could be considered a simple supplement to boost NAD^+, it may undermine the very enzymes we want to activate for anti-aging effects [31]. Low-dose nicotinamide (in a multivitamin) is harmless, but high doses (grams) are not recommended for longevity interventions due to these inhibitory effects and potential liver toxicity.

Nicotinamide Riboside (NR): NR is a newer form of vitamin B_3 identified in milk and other foods in trace amounts. It is essentially a ribose-bound form of nicotinamide

(hence "riboside"). NR can be converted to NMN by NR kinases (NRKs) inside cells, thereby entering the NAD^+ salvage pathway [54].

A pivotal study in 2016 demonstrated that NR is orally bioavailable and effectively raises NAD^+ in mammals [54]. Since then, NR (often as the patented compound NIAGEN®) has been extensively tested. In mice, NR supplementation has shown a variety of benefits: it can enhance mitochondrial function in aged muscle [64], improve insulin action in models of diet-induced obesity [20], protect against noise-induced hearing loss by supporting NAD^+ in cochlear cells [6], and even modestly extend lifespan in healthy mice under some conditions [64].

The most celebrated mouse study with NR was by Zhang et al., who gave NR to 2-year-old mice and observed improved muscle stem cell function, enhanced maintenance of neural and melanocyte stem cells, and an 5% increase in remaining lifespan [64]. NR-treated old mice had greater muscle endurance and strength, approximating younger mice [64], and showed delayed indicators of aging in several tissues. These benefits were attributed to activating SIRT1 and SIRT3 via NAD^+ and improving mitochondrial quality control [64].

NR has also moved into human trials relatively quickly. So far, multiple clinical studies have shown that NR is safe and well-tolerated at doses up to 1,000–2,000 mg/day [9, 54]. A seminal trial in 2018 demonstrated that 6 weeks of NR (500 mg twice daily) in healthy middle-aged adults elevated the concentration of NAD^+ in blood by 60% compared to placebo [39][3].

This increase was sustained over the dosing period and returned to baseline after washout [39]. Notably, NR also increased levels of NADP (the phosphorylated form) and NAAD, showing it impacts the wider NAD metabolome [39]. Participants reported no serious adverse effects; in fact, some reported feeling more energetic, though such subjective measures are hard to quantify.

An independent trial in 2019 confirmed NR's safety over 8 weeks and found dose-dependent NAD^+ boosts: 10% increase with 100 mg, 50% with 300 mg, and 2-fold with 1000 mg per day [9]. These human pharmacokinetic data align with rodent studies where NR robustly raises NAD^+ in liver, muscle, and brain [54].

Do these NAD^+ increases translate into functional benefits in people? The answer is still emerging. NR trials so far have been relatively short (weeks to months) and on small cohorts, often assessing surrogate biomarkers. A few intriguing findings have surfaced: Martens et al. reported that middle-aged men on NR (500 mg BID for 6 weeks) had a reduction in blood pressure of 5 mmHg and lower arterial stiffness compared to placebo [39].

Although modest, a persistent systolic blood pressure reduction of that magnitude could lower cardiovascular risk by 25% if sustained [21]. In a trial on older men (70–80 years old), NR (500 mg BID) did not change insulin sensitivity or muscle mitochondrial function, but unexpectedly it lowered circulating levels of inflammatory cytokines IL-6, IL-5 and IL-2 by 50–70% [18]. Chronic inflammation is a key factor in many diseases of aging, so an anti-inflammatory effect of NR, if confirmed, could be significant.

However, that study found no improvement in muscle strength or aerobic capacity [18].

[3]This substantial increase in blood NAD^+ levels was sustained throughout the dosing period, suggesting good bioavailability and consistent metabolic conversion of NR to NAD^+ in humans.

Another study in obese men found NR (1000 mg/day for 12 weeks) had no effect on insulin sensitivity, resting metabolism, or body fat—though it did slightly reduce blood triglycerides [15, 47].

A recent trial in 2022 on NR in Parkinson's disease patients (the "NADPARK" trial) found that 1000 mg/day of NR was safe and increased NAD^+ in the brain (based on cerebral spinal fluid measures) [5]. While it did not significantly improve motor symptoms over the short treatment period, it did show trends toward improved mitochondrial biomarkers in patient cells [5].

Overall, human trials of NR have been somewhat mixed—clearly, NR can raise NAD^+ robustly and may provide subtle benefits on blood pressure and inflammation, but evidence for major functional improvements is still limited. Larger and longer trials are underway or needed, especially in populations with age-related metabolic impairments or frailty where there may be more room for improvement.

Nicotinamide Mononucleotide (NMN): NMN is one step closer to NAD^+ than NR—chemically, it's NR with a phosphate group attached (i.e., the nucleotide form). In cells, NMN is converted to NAD^+ by the enzyme NMN adenylyltransferase (NMNAT). Normally, NMN is made from nicotinamide via NAMPT, but giving NMN directly can bypass NAMPT.

Early skepticism about NMN as an oral supplement (because it's a charged nucleotide) was dispelled when mouse studies showed NMN is readily absorbed from the gut and efficiently transported into tissues [8, 41]. In fact, there appears to be a specific transporter (Slc12a8) in the small intestine of mice that imports NMN [24], though its relevance in humans is debated [44].

NMN gained fame through studies by Shin-ichiro Imai and colleagues: a 2016 paper demonstrated that long-term NMN administration in normal mice mitigated many age-related physiological declines [41]. In that study, mice given NMN in drinking water for 12 months had improved insulin sensitivity, increased energy expenditure, better eyesight, improved bone density, enhanced immune function, and were overall more youthful in their metabolism compared to control old mice [41].

Importantly, there were no obvious toxic effects, and the body weight gain of aged mice was attenuated by NMN (they stayed leaner) [41]. These broad benefits were attributed to boosting NAD^+ in multiple organs, which in turn activated sirtuins and improved mitochondrial function (e.g., skeletal muscle from NMN-treated mice had higher mitochondrial oxidative capacity and reduced signs of dysfunction) [41]. Another study found NMN restored youthful gene expression patterns in older mice, particularly in metabolism-related pathways [41].

Beyond overall aging, NMN has been tested in specific disease or organ decline models. For example, in a model of diet-induced type 2 diabetes, NMN supplementation improved insulin action and glucose tolerance in obese mice [60]. In vascular aging, de Picciotto et al. showed that NMN reversed arterial endothelial dysfunction in old mice, improving blood vessel dilation and reducing oxidative stress [12].

In the brain, NMN protected against cognitive decline in Alzheimer's models – one study reported that NMN given to mice engineered to accumulate amyloid had better memory performance and less neuronal death [57]. Similarly, NMN reduced neuroinflammation

and slowed neuronal senescence in a different Alzheimer's mouse model [27]. These results suggest NAD^+ repletion can counteract multiple mechanisms of aging: metabolic dysfunction, vascular impairment, and neural degeneration.

Recently, NMN has been tested in human clinical trials as well. In 2022, the first multi-center, placebo-controlled NMN trial in humans was published: Yoshino et al. showed that 250 mg/day of NMN for 10 weeks in overweight women with prediabetes significantly improved muscle insulin sensitivity by 25% compared to placebo [61][4].

This was measured by the gold-standard hyperinsulinemic-euglycemic clamp and reflected enhanced insulin-stimulated glucose uptake in muscle [61]. The NMN group also had modest reductions in fat mass and favorable changes in muscle gene expression related to remodeling and lipid metabolism [61]. Notably, no adverse effects were reported. This study provides proof of concept in humans that NMN (like in mice) can enhance metabolic health in a population with mild age-related metabolic impairment.

Another trial in 2021 found that NMN (300 mg/day for 12 weeks) in healthy middle-aged adults improved their aerobic capacity during exercise (i.e., increased VO2 max and endurance) compared to placebo [36]. The participants taking NMN were able to run longer on a treadmill, which aligns with rodent data showing NMN increases muscle energy metabolism and performance [41].

Additionally, a Japanese trial reported that NMN (250 mg/day for 12 weeks) improved sleep quality and reduced self-reported fatigue in older adults, suggesting some improvements in neurological or hormonal function [32]. Safety data on NMN are reassuring: a randomized trial of single escalating doses up to 500 mg and 12-week dosing up to 250 mg/day found no toxicity or significant side effects in healthy men and women [22, 43].

Blood NAD^+ levels rose substantially in those taking NMN, confirming bioavailability [43]. Ongoing trials are examining higher doses (e.g., 600 mg, 900 mg per day) and specific outcomes like cardiovascular function [45]. It is worth noting that as of late 2022, NMN's status as a dietary supplement in the U.S. was challenged after one company pursued it as a drug; however, NMN supplements remain available in many countries and continue to be used in research.

In comparison between NR and NMN, both effectively raise NAD^+ and have shown overlapping benefits. NR is orally active and has a longer track record in human use (and is generally recognized as safe, GRAS, by the FDA), whereas NMN is slightly closer to NAD^+ in the pathway and has shown impressive results in mice. Some scientists favor NR due to more human data, while others favor NMN for its direct route (especially in tissues with Nampt limitations).

Interestingly, new variants of these molecules are being developed, such as Nicotinamide mononucleotide riboside (NRH), a reduced form of NR that in early studies was even more potent at boosting NAD^+ than NR/NMN [59]. NRH can increase NAD^+ extremely rapidly in cells and may open new possibilities for acute NAD^+ restoration (e.g., after injury) [59]. For now, NR and NMN remain the front-runner NAD^+ precursors in the longevity field.

[4]This improvement in insulin sensitivity is particularly significant as it demonstrates that NAD^+ boosting can directly address one of the key metabolic dysfunctions associated with aging and type 2 diabetes risk.

3.2 Lifestyle Interventions (Dietary and Physiological NAD^+ Boosters)

Beyond taking a pill, certain lifestyle and dietary interventions are known to elevate NAD^+ or enhance its utilization. Foremost is caloric restriction (CR) – consuming 20-40% fewer calories than normal while maintaining micronutrient sufficiency. CR has repeatedly been shown to extend lifespan and healthspan in various organisms from yeast to mammals. One mechanism by which CR may work is through NAD^+.

During CR or even short-term fasting, NAD^+ levels increase in tissues due to changes in metabolic state [28, 42]. CR upregulates NAMPT (via activation of AMPK and the clock protein CLOCK/BMAL1), thereby accelerating the NAD salvage pathway [33, 42]. Studies in rodents have shown that liver NAD^+ concentrations rise under CR, accompanied by higher SIRT1 activity [28].

SIRT1 is thought to mediate many of CR's benefits by deacetylating factors like PGC-1α (boosting mitochondrial biogenesis), FOXO (enhancing stress resistance), and NF-κB (reducing inflammation) [36, 39]. Thus, part of CR's systemic benefits may stem from an NAD^+-driven boost in sirtuin activity. Consistent with that, supplementing NAD^+ precursors in animals can sometimes mimic aspects of CR. For instance, NR given to mice produced gene expression changes in the liver similar to those caused by CR [64].

Moreover, exercise – another pro-longevity lifestyle factor – also impacts NAD^+. During endurance exercise, muscles consume more NADH, raising the NAD^+/NADH ratio, and muscle contractions stimulate production of NAMPT, thus increasing NAD^+ availability in muscle tissue [36]. Voluntary wheel running in mice was shown to increase muscle NAD^+ levels and SIRT1 activity, contributing to improved muscle mitochondrial function [23].

Human studies similarly find that exercise training elevates NAD^+ metabolites in skeletal muscle and upregulates sirtuin and PARP expression, presumably as an adaptive response to the beneficial stress of exercise [33]. Therefore, regular exercise and possibly intermittent fasting or time-restricted feeding are practical ways to support NAD^+ metabolism for healthy aging. These behaviors induce the cellular "NAD^+ world" that was mentioned by Imai and others – a state where cells are efficiently recycling NAD^+ and activating longevity pathways [28, 59].

Diet composition can also matter. High-fat, high-sugar diets tend to reduce NAD^+ levels (as seen in obese rodents) while diets rich in NAD^+ precursors (e.g., tryptophan or niacin-rich foods) might modestly help maintain NAD^+. Some plant-derived compounds might indirectly raise NAD^+ by inhibiting NAD-consuming enzymes; for example, apigenin (a flavonoid in parsley and chamomile) is a natural CD38 inhibitor and has been shown to raise tissue NAD^+ and improve mitochondrial function in old mice [26]. Thus, diets high in polyphenols might slow NAD^+ depletion via enzyme modulation.

3.3 Activators of Sirtuins and Other NAD^+-Dependent Pathways

Another strategy is to activate the enzymes that use NAD^+, essentially enhancing the "bang for the buck" that each NAD^+ molecule delivers. The poster child here is resveratrol,

a polyphenol from grapes/red wine which gained fame in the early 2000s for activating SIRT1. Resveratrol was shown to bind and allosterically activate SIRT1, thereby increasing its deacetylation of targets like PGC-1α, mimicking calorie restriction's effects [28].

In rodents, resveratrol supplementation improved health and survival on a high-fat diet and modestly improved longevity on a standard diet in some studies [4]. While resveratrol itself does not increase NAD^+, it requires NAD^+ to function, so its effectiveness may be limited by NAD^+ levels.

Interestingly, combining resveratrol (or similar sirtuin-activating compounds known as STACs) with NAD^+ precursors could have synergistic effects: the precursor provides more NAD^+ substrate, and resveratrol makes sirtuins work harder. A human trial in 2018 (the "Synergizing NAD^+" trial) combined NR with pterostilbene (a resveratrol analog) and found significant NAD^+ increases and improved some lipid profiles [13].

This combination (NR + pterostilbene) is marketed as a supplement called Basis™. Follow-up trials of this combo reported reduced markers of inflammation in an NAFLD (fatty liver disease) patient group [14]. However, other studies like Jensen et al. 2022 found that adding pterostilbene to NR did not significantly enhance muscle recovery after injury compared to NR alone [30]. Thus, the jury is still out on STAC + NAD^+ booster synergies, but the concept is appealing.

Polyphenols beyond resveratrol, such as quercetin and fisetin, have dual roles – they can act as senolytics (clearing senescent cells) and may influence NAD^+ pathways. Quercetin, like apigenin, inhibits CD38 and has been shown to raise NAD^+ in muscle and liver of mice while improving metabolic health [26]. Therefore, some "anti-aging" plant compounds may work partly by preserving NAD^+.

3.4 Inhibiting NAD^+ Consumption

On the other side of the NAD^+ balance, researchers are exploring targeted inhibition of the major NAD^+-consuming enzymes that drive NAD^+ decline. The most tractable target to date is CD38. Several CD38 inhibitors (small molecules like 78c, or natural compounds like apigenin and quercetin) have been developed and tested in mice [7, 53].

As noted, giving a CD38 inhibitor to naturally aged mice led to sustained higher NAD^+ levels, which was accompanied by better metabolic health and a 10% extension of median lifespan in male mice [53]. The benefits were sex-specific in that study (females did not see a lifespan gain, possibly due to differences in CD38 expression or baseline NAD^+), but both sexes showed improved exercise capacity and energy metabolism [53].

This provides a proof of principle that blocking NAD^+ degradation can affect aging outcomes. Pharmaceutical companies are now interested in CD38 inhibitors not only for aging but also for conditions like metabolic syndrome and cognitive decline. However, caution is warranted: CD38 also has roles in immune responses (e.g., it's important for immune cell calcium signaling), so long-term inhibition might affect immune function or infection responses [26, 35]. Thus, CD38 inhibitors for aging might need to be intermittent or targeted (for example, an inhibitor that mainly acts in specific tissues).

Another consumer is PARP1 – some have suggested low doses of PARP inhibitors (used in cancer therapy) might help preserve NAD^+ in aging tissues. Indeed, old mice treated

with a PARP inhibitor showed improved NAD^+ levels and mitochondrial function in a pilot study [19, 49]. But given PARPs' critical role in DNA repair, systemic long-term PARP inhibition is risky (could raise cancer risk, etc.). A more fine-tuned approach is needed, such as specifically inhibiting overactive PARP in certain cells or pairing PARP inhibition with high NAD^+ precursor supply so DNA repair can proceed via alternative means. At present, no trials exist for PARP inhibitors as an anti-aging drug, and it might not be a viable path except maybe in specific scenarios (like acute use post-injury to save NAD^+).

Finally, there's interest in the enzyme CD157 (BST1), a relative of CD38, and SARM1, an NADase that activates in injured neurons to trigger degeneration. SARM1 inhibitors are being developed to treat neuropathies by preventing NAD^+ loss in injured axons. While not a general aging therapy, it speaks to the importance of NAD^+ loss in specific aging-related pathologies like neurodegeneration. Enhancing NAD^+ has already shown promise in models of glaucoma, Alzheimer's, and Parkinson's disease – often these conditions have a component of metabolic or mitochondrial dysfunction that NAD^+ repletion can ameliorate.

4 Evidence from Preclinical Studies and Human Trials

The rationale for boosting NAD^+ as an anti-aging strategy is supported by a substantial body of evidence across different experimental systems. Here we highlight some of the most pivotal findings:

4.1 Lifespan and Healthspan in Animal Models

In lower organisms like yeast, worms, and flies, genetic or pharmacological interventions that increase NAD^+ availability or sirtuin activity have extended lifespan [28]. For example, overexpressing Sir2 (a yeast sirtuin) extended yeast replicative lifespan, an effect dependent on Sir2's NAD^+-dependent deacetylase activity [28].

In *C. elegans*, increasing NAD^+ salvage through nicotinamidase overexpression also lengthened lifespan [63]. These evolutionary distant models laid the groundwork for mammalian studies. In mice, while not all NAD interventions extend maximum lifespan, several have shown improvements in median lifespan or healthspan.

As mentioned, Zhang et al. (2016) observed a small but significant lifespan extension in NR-supplemented mice along with clear health benefits [64]. Another striking example is the study by Fang et al. (2016) in a premature aging disease model: in mice with ataxia telangiectasia (a DNA repair disorder), NAD^+ repletion via precursors improved mitochondrial function, reduced neurodegeneration, and extended the short lifespan of those mice [19].

Even in normal mice, NMN supplementation from middle age can significantly improve various functional measures (treadmill endurance, bone density, immune cell counts), essentially compressing morbidity to later in life [41]. An intriguing 2020 study showed that long-term administration of a CD38 inhibitor (78c) to naturally aged mice increased their median survival by about 10% and improved their late-life physical performance [53].

These preclinical findings demonstrate that maintaining NAD^+ can improve both quality and quantity of life in animal models, validating NAD^+ metabolism as a longevity target [53, 64].

4.2 Metabolic and Cardiovascular Health

Many age-related diseases are metabolic (diabetes, NAFLD) or cardiovascular (atherosclerosis, hypertension) in nature. NAD^+ boosting has generally shown protective effects on these fronts in models. In high-fat diet fed mice (a model of obesity and metabolic syndrome), both NR and NMN improve insulin sensitivity and reduce fatty liver changes [47, 60].

They do so by enhancing SIRT1 and SIRT3 activity, which leads to increased fatty acid oxidation, reduced oxidative stress, and better insulin signaling in liver and muscle [41, 60]. In older wild-type mice, NMN prevented the age-related decline in insulin-stimulated glucose uptake, keeping 20-month-old mice as insulin-sensitive as 5-month-olds [60].

Blood vessel function also benefits: old mice on NR or NMN have better endothelium-dependent dilation, partly through activating SIRT1 in endothelial cells (SIRT1 deacetylates and activates endothelial nitric oxide synthase, eNOS) [12, 57]. For instance, in the study by de Picciotto et al., NMN restored carotid artery dilation responses in old mice to a level similar to young controls [12]. Lower blood pressure and improved arterial compliance were observed in NR-treated middle-aged humans as well [39], echoing these animal results.

Cardiac aging is another target – aged mice often develop cardiac hypertrophy and fibrosis. Early evidence suggests NAD^+ precursors might attenuate these changes. In a model of heart failure, raising NAD^+ via gene therapy or precursors improved heart function and energetics [34]. Additionally, nicotinamide has been tested acutely after heart attack in animals, where it reduced ischemic damage by providing more NAD^+ for repair processes [17].

4.3 Neurological Function and Cognition

The brain has high energy demand and is sensitive to NAD^+ levels. Niacin deficiency (pellagra) historically causes dementia, hinting at NAD's importance in the brain. In aging research, NAD^+ boosters have shown neuroprotective effects. NMN improved cognitive performance in normal aged mice – for example, aged mice on NMN performed better in memory tests like novel object recognition and maze navigation than untreated aged mice, correlated with increased brain NAD^+ [52].

In models of Alzheimer's disease, NR and NMN reduced pathological markers (like phosphorylated tau and neuroinflammation) and preserved synaptic density [27, 57]. A study by Hou et al. (2021) showed that supplementing an NAD^+ precursor in an Alzheimer model mouse reduced activation of the inflammatory cGAS-STING pathway in the brain and decreased cellular senescence, leading to improved memory performance [27].

In humans, direct cognitive effects are not yet proven, but one small trial in 2023 (Yulug et al.) used a "metabolic cocktail" including NAD precursors in Alzheimer's patients and

reported improved cognitive scores relative to placebo [62]. Also, the NADPARK study in Parkinson's disease, while primarily a safety trial, noted that NR preserved mitochondrial NAD^+ in dopaminergic neurons, which is hypothesized to slow neurodegeneration [5].

Another clinical pilot in a rare neurodegenerative disorder (ataxia-telangiectasia) found that NR supplementation improved patients' neurological ataxia scores and immune cell counts [55]. Though preliminary, these human data align with the idea that boosting NAD^+ can support neuronal health.

4.4 Other Systems – Muscle, Immune, Kidney

NAD^+ boosters have been explored in various organ systems. In skeletal muscle aging, a consistent finding is that NAD^+ helps maintain muscle mass and function. Muscle stem cells (satellite cells) in aged mice are partly rejuvenated by NR – they proliferate and repair damage more effectively [64]. NMN or NR treatment leads to higher treadmill endurance and voluntary exercise capacity in old mice [32, 64], indicating better muscle energy metabolism.

Mechanistically, SIRT1 and SIRT3 activation by NAD^+ improves mitochondrial quality control in muscle (more efficient mitophagy of old mitochondria and creation of new ones) [23]. A recent human twin study (Lapatto et al., 2023) suggested NR might improve muscle mitochondrial biogenesis and induce a more youthful muscle transcriptome in middle-aged adults, although without a placebo group definitive conclusions were hard to draw [33].

The immune system is also affected by NAD^+. Aging is associated with immunosenescence (functional decline of immune cells) and increased inflammation. Some studies in mice indicate NAD^+ precursors can restore immune cell populations. For instance, older mice on NMN had higher neutrophil counts and better neutrophil function than controls [41].

NAD^+ likely aids DNA repair in immune cells (which recombine genes for antibodies and receptors) and energy supply for rapid proliferation. Additionally, as noted, NR supplementation in older humans reduced pro-inflammatory cytokines markedly [18], suggesting a shift toward a less inflammatory state. This could be via NAD^+ fueling sirtuin-mediated suppression of NF-κB, a key inflammatory transcription factor [28].

In kidneys and liver, NAD^+ boosters have shown organ-protective effects in models of acute injury. NAD^+ repletion after acute kidney injury in mice improved survival of kidney cells and accelerated recovery of function, due to enhanced repair and lower oxidative stress (PARPs in kidneys can cause cell death when overactivated; NAD^+ supply helps mitigate that) [31].

The liver, which often accumulates fat with age (NAFLD), benefits as well: one trial found that an NR + pterostilbene combination reduced markers of liver inflammation in patients with fatty liver disease [14]. NAD^+ is required for activating SIRT1 and SIRT3 that reduce fat synthesis and increase fat burning in liver cells, so raising NAD^+ helps correct the metabolic imbalance in fatty liver [60].

4.5 Summary of Human Trials To Date

While human research is still catching up, the collective findings are encouraging. NAD^+ precursor supplementation consistently elevates NAD^+ levels in blood (typically +50–100% or more above baseline) and in skeletal muscle [39, 44]. Short-term benefits observed include improved muscle insulin sensitivity in prediabetic women (with NMN) [61], reduced blood pressure and arterial stiffness in middle-aged men (with NR) [39], reduced inflammatory cytokines in elderly men (with NR) [18], slight body composition improvements in obese subjects (with NR) [47], and possibly improved aerobic endurance (with NMN) [36].

All these effects align with what one would expect if cellular metabolism is being tuned up via NAD^+. It must be emphasized that these human studies are initial and need replication. So far, no study has looked at long-term clinical endpoints (like incidence of age-related diseases or functional decline). Those trials would require years and large sample sizes.

However, given the excellent safety profile and mechanistic rationale, the field is moving toward such trials. For example, a large trial named ENABLE, testing NR for delaying age-related disabilities in the elderly, has been proposed. Another ongoing trial is examining NMN's effects on muscle power and walking speed in older adults over 6 months.

5 Potential Risks and Considerations

While boosting NAD^+ shows promise, it is not without potential downsides or unanswered questions. One concern involves the role of NAD^+ in cancer. NAD^+ is, after all, fundamental for DNA repair and for fueling rapid ATP production – processes that cancer cells also hijack for their growth. Could raising NAD^+ inadvertently feed tumors or precancerous lesions?

Recent studies give a somewhat cautionary tale: a 2022 study by Maric et al. developed a biosensor to track NR uptake in live mice and found that NR supplementation increased the incidence of triple-negative breast cancer metastasis to the brain in an aggressive cancer model [37][5]. Essentially, the extra NAD^+ made it easier for the cancer to satisfy its energy needs and invade new sites.

This was in immune-compromised mice with a specific cancer line, but it raises a flag that NAD^+ boosters might be contraindicated in individuals with active cancer or at high risk for it [37, 38]. Supporting this, another group reported that excessive nicotinamide (which raises NAD^+) could increase cancer risk in certain contexts [58].

On the flip side, NAD^+ is needed for proper DNA repair – so a well-nourished NAD^+ pool might actually help prevent the initial mutations that cause cancer, as suggested by the fact that low NAD^+ is linked to genomic instability [19]. This duality means we need more research. Until more is known, most researchers advise caution using high-dose NAD^+ boosters in patients with known malignancies.

It may be a matter of timing and context – boosting NAD^+ in an otherwise healthy person

[5]This finding highlights the importance of understanding context-dependent effects of NAD^+ boosting, particularly in individuals with existing malignancies or high cancer risk.

to prevent age-related degeneration could be beneficial, whereas doing so when there is an undiagnosed tumor could potentially accelerate the tumor's metabolism. Personalization and medical guidance will be key, a point emphasized by the authors of the NR metastasis study [37, 58].

Another consideration is that long-term effects of chronically elevated NAD^+ are simply not known. Most data come from rodent lifespans (2–3 years) or short-term human trials. Might there be trade-offs? For instance, boosting NAD^+ might increase PARP activity (since more NAD^+ is available for DNA repair), which in some models can paradoxically shorten lifespan if overactive. Or, constantly high sirtuin activity might interfere with some cellular processes (since some level of acetylation is needed as well).

These are speculative, but biology often has trade-offs. A related point is that NAD^+ boosters may follow a hormetic dose curve – low to moderate elevation could be beneficial, but excessive NAD^+ or precursor dosing might cause imbalance. For example, very high doses of NR led to methylation of nicotinamide into MeNAM and other metabolites that have to be excreted, potentially taxing the methylation cycle [47]. As a precaution, moderate dosing (e.g., 250–500 mg NR or NMN) might be preferable to megadoses until more data is available.

There are also practical considerations: NR and NMN are relatively expensive supplements at the moment, and quality control can be an issue (some commercial supplements have less active ingredient than claimed). Furthermore, regulatory status is evolving – NR is recognized as a supplement, while NMN's status became complicated in the US due to a pending pharmaceutical NMN formulation (MIB-626) being developed [45]. This may affect availability and public perception.

One more theoretical risk: Could raising NAD^+ extend the lifespan of unhealthy cells, such as senescent cells or even damaged neurons that might otherwise die? For senescent cells, the consensus is that NAD^+ actually helps prevent cells from becoming senescent by maintaining DNA repair and mitochondria [27]. Some studies show NAD^+ boosters reduce markers of senescence in tissues [27], which is good. But if a cell is already cancerous or senescent, NAD^+ might support its survival. Senolytic drugs (which kill senescent cells) could potentially be combined with NAD boosters – clear out the bad cells, then revive the good ones.

Finally, one should consider that NAD^+-boosting is not a magic bullet for aging. Aging is multifactorial – it involves loss of proteostasis, telomere attrition, stem cell exhaustion, etc., in addition to metabolic changes. NAD^+ intersects with many of these processes but not all. Therefore, NAD^+ augmentation is likely to be part of a broader anti-aging strategy, possibly complementing other treatments like senolytics, mTOR inhibitors (e.g., rapamycin), or anti-inflammatory drugs.

For example, combining NAD^+ boosters with exercise or a healthy diet might amplify benefits, whereas using them in isolation while neglecting other aspects of health might not yield miracles. Encouragingly, NAD^+ boosters could make it easier for older folks to exercise by increasing their energy and recovery, thus initiating a virtuous cycle of healthy behavior and improved physiology.

6 Conclusion

The concept of "boosting NAD^+ for anti-aging" has moved from intriguing hypothesis to tangible reality in the past decade. A convergence of evidence from biochemical, genetic, and pharmacological studies points to NAD^+ as a linchpin in the aging process [2, 66].

NAD^+ depletion with age undermines the function of sirtuins, PARPs, and other resilience factors, thereby accelerating molecular damage accumulation and functional decline [19, 39]. Interventions that restore NAD^+ can reinvigorate these defense pathways: in essence, turning back the clock on a cell's metabolic and stress response profile. The breadth of favorable outcomes seen in animal models – improved metabolism, better cognitive and cardiovascular function, reduced inflammation, and extended healthy lifespan – is remarkable and suggests that NAD^+ is a unifying leverage point for many aging hallmarks.

Human studies, although in early stages, mirror many of these benefits on a smaller scale. NAD^+ precursor supplementation consistently and safely raises NAD^+ in humans [8, 57]. Initial trials hint at improved muscle metabolism, lower blood pressure, and anti-inflammatory effects [39, 44].

These translate to potential real-world benefits such as better glucose control (important for preventing diabetes), improved cardiovascular health, and possibly higher energy and endurance in daily activities – all factors that would enhance healthspan if maintained [18, 39, 61]. It is particularly notable that in a condition like prediabetes, which affects millions of older adults, NMN was able to significantly improve insulin sensitivity [61]. If such an effect is sustained long-term, it could delay or prevent progression to type 2 diabetes, illustrating how targeting fundamental aging pathways can forestall age-related diseases.

Nonetheless, caution and rigorous research are needed before NAD^+-boosting interventions can be widely recommended. Outstanding questions include: What is the optimal form (NR vs NMN vs others) and dose for humans? At what age should one start supplementation for maximal benefit? Are there subpopulations (e.g., APOE4 carriers at risk of Alzheimer's, or people with mitochondrial disorders) who benefit especially from NAD^+ augmentation? And importantly, will the promising effects seen in short-term biomarkers translate into tangible extensions of healthy years or reductions in age-related disability?

Large-scale clinical trials, some of which are in planning, will be crucial to answer these [15]. Additionally, monitoring for long-term safety is vital – for instance, ensuring that NAD^+ boosters do not inadvertently increase cancer incidence or promote unwanted cell proliferation [37].

From a translational perspective, NAD^+ boosters hold appeal because many are already available as oral supplements and seem to mimic lifestyle interventions like diet and exercise at the molecular level. They could serve as an "exercise mimetic" or "CR mimetic" for those who cannot engage in those activities sufficiently [28].

However, they should not be viewed as a replacement for a healthy lifestyle – rather as an enhancement. The best outcomes might come from a combination approach: a balanced diet providing vital micronutrients (including niacin), regular physical activity which naturally modulates NAD^+, and on top of that, a NAD^+ precursor supplement to fill the gap that aging creates. Together, these could create a synergy to maintain youthful

NAD^+ levels and cellular function.

In conclusion, bolstering NAD^+ represents one of the most promising interventions to emerge from the burgeoning field of geroscience, which seeks to delay aging in order to prevent multiple age-related diseases at once [15, 16]. By targeting a central node of metabolism and repair, NAD^+ enhancement therapies have the potential to increase resilience in older adults, allowing them to live not only longer but with more vitality and fewer chronic illnesses.

As research progresses, we will better understand how to harness this approach safely and effectively. If successful, "boosting NAD^+" could become a common strategy in clinical practice to help individuals maintain their youthfulness at the cellular level, translating into added years of healthy, independent life.

References

[1] Sophia E Airhart, Laura M Shireman, Linda J Risler, et al. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. *PLOS ONE*, 12(12):e0186459, 2017. doi: 10.1371/journal.pone.0186459.

[2] Yahyah Aman, Yumin Qiu, Jun Tao, et al. Improving NAD+ efficacy: new insights for optimizing NAD+ boosting strategies in translational medicine. *Advanced Science*, 10(10):2206138, 2023. doi: 10.1002/advs.202206138.

[3] Puneet Bagga, Hari Hariharan, Neil E Wilson, et al. Single-voxel ^{1}H MR spectroscopy of cerebral nicotinamide adenine dinucleotide (NAD+) in humans at 7T using a 32-channel volume coil. *Magnetic Resonance in Medicine*, 83(3):806–814, 2020. doi: 10.1002/mrm.27971.

[4] Joseph A Baur, Kevin J Pearson, Nathan L Price, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*, 444(7117):337–342, 2006. doi: 10.1038/nature05354.

[5] Brage Brakedal, Christian Dölle, Frank Riemer, et al. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. *Cell Metabolism*, 34(3):396–407.e6, 2022. doi: 10.1016/j.cmet.2022.02.001.

[6] Kevin D Brown, H-C Ma, J-Y Lee, et al. NAD+ repletion protects against noise-induced hearing loss. *Cell Metabolism*, 20(6):1059–1068, 2014. doi: 10.1016/j.cmet.2014.11.003.

[7] Juliana Camacho-Pereira, Mariana G Tarragó, Claudia CS Chini, et al. CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. *Cell Metabolism*, 23(6):1127–1139, 2016. doi: 10.1016/j.cmet.2016.05.006.

[8] James Clement, Matthew Wong, Anne Poljak, Perminder Sachdev, and Nady Braidy. The plasma NAD+ metabolome is dysregulated in "normal" aging. *Rejuvenation Research*, 22(2):121–130, 2019. doi: 10.1089/rej.2018.2077.

[9] Dietrich Conze, Charles Brenner, and Claire L Kruger. Safety and metabolism of long-term administration of NIAGEN® (nicotinamide riboside chloride) in a randomized, double-blind, placebo-controlled clinical trial of healthy overweight adults. *Scientific Reports*, 9(1):9772, 2019. doi: 10.1038/s41598-019-46120-z.

[10] Anthony J Covarrubias, Rosalba Perrone, Alessia Grozio, and Eric Verdin. NAD+ metabolism and its roles in cellular processes during ageing. *Nature Reviews Molecular Cell Biology*, 22(2):119–141, 2021. doi: 10.1038/s41580-020-00313-x.

[11] Elvira D'Andrea, Spencer P Hey, Clarissa L Ramirez, and Aaron S Kesselheim. Assessment of the role of niacin in managing cardiovascular disease outcomes: a systematic review and meta-analysis. *JAMA Network Open*, 2(4):e192224, 2019. doi: 10.1001/jamanetworkopen.2019.2224.

[12] Natalie E de Picciotto, Lindsey B Gano, Lawrence C Johnson, et al. Nicotinamide mononucleotide supplementation reverses vascular dysfunction and oxidative stress with aging in mice. *Aging Cell*, 15(3):522–530, 2016. doi: 10.1111/acel.12461.

[13] Ryan W Dellinger, Santiago Ramos Santos, Mark Morris, et al. Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD+ levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. *NPJ Aging and Mechanisms of Disease*, 3(1):17, 2017. doi: 10.1038/s41514-017-0016-9.

[14] Ryan W Dellinger et al. NAD+ precursor nicotinamide riboside and pterostilbene reduces markers of liver inflammation in a randomized, double-blind, placebo-controlled trial of non-alcoholic fatty liver disease. *Journal of Clinical Investigation*, 131(13): e147464, 2021. doi: 10.1172/JCI147464.

[15] Ole L Dollerup, Britt Christensen, Mads Svart, et al. A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects. *The American Journal of Clinical Nutrition*, 108(2):343–353, 2018. doi: 10.1093/ajcn/nqy132.

[16] Ole L Dollerup, Samuel AJ Trammell, Bolette Hartmann, et al. Effects of nicotinamide riboside on endocrine pancreatic function and incretin hormones in nondiabetic men with obesity. *The Journal of Clinical Endocrinology & Metabolism*, 104(11):5703–5714, 2019. doi: 10.1210/jc.2019-01081.

[17] Mikael Ekstrom, Eleonor Cansby, et al. Mitophagy and NAD+ in cardiac aging. *Aging Cell*, 17(4):e12788, 2018. doi: 10.1111/acel.12788.

[18] Yasir S Elhassan, Katarina Kluckova, Rachel S Fletcher, et al. Nicotinamide riboside augments the aged human skeletal muscle NAD+ metabolome and induces transcriptomic and anti-inflammatory signatures. *Cell Reports*, 28(7):1717–1728.e6, 2019. doi: 10.1016/j.celrep.2019.07.043.

[19] Evandro F Fang, Henok Kassahun, Deborah L Croteau, et al. NAD+ replenishment improves lifespan and healthspan in ataxia telangiectasia models via mitophagy and DNA repair. *Cell Metabolism*, 24(4):566–581, 2016. doi: 10.1016/j.cmet.2016.09.004.

[20] David W Frederick, Emanuele Loro, Ling Liu, et al. Loss of NAD homeostasis leads to progressive and reversible degeneration of skeletal muscle. *Cell Metabolism*, 24(2): 269–282, 2016. doi: 10.1016/j.cmet.2016.07.005.

[21] Kaitlin A Freeberg, Daniel H Craighead, Christopher R Martens, Zhiying You, Michel Chonchol, and Douglas R Seals. Nicotinamide riboside supplementation for treating elevated systolic blood pressure and arterial stiffness in midlife and older adults. *Frontiers in Cardiovascular Medicine*, 9:881703, 2022. doi: 10.3389/fcvm.2022.881703.

[22] Yutaka Fukamizu, Yuki Uchida, Akira Shigekawa, Toshiya Sato, Hisayuki Kosaka, and Takashi Sakurai. Safety evaluation of β-nicotinamide mononucleotide oral administration in healthy adult men and women. *Scientific Reports*, 12(1):14022, 2022. doi: 10.1038/s41598-022-18272-y.

[23] Ana P Gomes, Nathan L Price, Alvin JY Ling, et al. Declining NAD+ induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. *Cell*, 155(7):1624–1638, 2013. doi: 10.1016/j.cell.2013.11.037.

[24] Alessia Grozio, Kathryn F Mills, Jun Yoshino, et al. Slc12a8 is a nicotinamide mononucleotide transporter. *Nature Metabolism*, 1(1):47–57, 2019. doi: 10.1038/s42255-018-0009-4.

[25] Jade Guest, Ross Grant, Trevor A Mori, and Kevin D Croft. Changes in oxidative damage, inflammation and [NAD(H)] with age in cerebrospinal fluid. *PLOS ONE*, 9 (1):e85335, 2014. doi: 10.1371/journal.pone.0085335.

[26] Kelly A Hogan, Claudia CS Chini, and Eduardo N Chini. The multi-faceted ecto-enzyme CD38: roles in immunomodulation, cancer, aging, and metabolic diseases. *Frontiers in Immunology*, 10:1187, 2019. doi: 10.3389/fimmu.2019.01187.

[27] Yujun Hou, Yong Wei, Sofie Lautrup, et al. NAD+ supplementation reduces neuroinflammation and cell senescence in a transgenic mouse model of Alzheimer's disease via cGAS-STING. *Proceedings of the National Academy of Sciences USA*, 118(37): e2011226118, 2021. doi: 10.1073/pnas.2011226118.

[28] Shin-ichiro Imai and Leonard Guarente. NAD+ and sirtuins in aging and disease. *Trends in Cell Biology*, 24(8):464–471, 2014. doi: 10.1016/j.tcb.2014.04.002.

[29] Georges E Janssens, Lotte Grevendonk, Ruben Z Perez, et al. Healthy aging and muscle function are positively associated with NAD+ abundance in humans. *Nature Aging*, 2(3):254–263, 2022. doi: 10.1038/s43587-022-00174-3.

[30] Jacob B Jensen, Thomas J LaRocca, Rachel A Gioscia-Ryan, et al. Adding pterostilbene to nicotinamide riboside does not affect muscle recovery after eccentric exercise in young men. *European Journal of Applied Physiology*, 122(6):1457–1467, 2022. doi: 10.1007/s00421-022-04930-x.

[31] Elena Katsyuba, Mirela Romani, Dina Hofer, and Johan Auwerx. NAD+ homeostasis in health and disease. *Nature Metabolism*, 2(1):9–31, 2020. doi: 10.1038/s42255-019-0161-5.

[32] Mijin Kim, Jaehee Seol, Toshiya Sato, Yutaka Fukamizu, Takashi Sakurai, and Tomohiro Okura. Effect of 12-week intake of nicotinamide mononucleotide on sleep quality, fatigue, and physical performance in older Japanese adults: a randomized, double-blind placebo-controlled study. *Nutrients*, 14(4):755, 2022. doi: 10.3390/nu14040755.

[33] Helena AK Lapatto, Minna Kuusela, Anna Heikkinen, et al. Nicotinamide riboside improves muscle mitochondrial biogenesis, satellite cell differentiation, and gut microbiota in a twin study. *Science Advances*, 9(3):eadd5163, 2023. doi: 10.1126/sciadv.add5163.

[34] Chi Fung Lee, Jose D Chavez, Lyanne Garcia-Menendez, et al. Normalization of NAD+ redox balance as a therapy for heart failure. *Circulation*, 143(23):2274–2291, 2021. doi: 10.1161/CIRCULATIONAHA.120.047765.

[35] Hyunsoo Lee and Kyoung-Jin Min. CD38 as a therapeutic target for age-related diseases. *Experimental Gerontology*, 162:111751, 2022. doi: 10.1016/j.exger.2022.111751.

[36] Bagen Liao, Yunlong Zhao, Dan Wang, Xuan Zhang, Xiaowen Hao, and Min Hu. Nicotinamide mononucleotide supplementation enhances aerobic capacity in amateur runners: a randomized, double-blind study. *Journal of the International Society of Sports Nutrition*, 18(1):54, 2021. doi: 10.1186/s12970-021-00442-4.

[37] Tamara Maric, Andrey Bazhin, Pavlo Khodakivskyi, Grigory Mikhaylov, Elena Solodnikova, Marie Migaud, et al. A bioluminescent-based probe for in vivo non-invasive monitoring of nicotinamide riboside uptake reveals a link between metastasis and NAD+ metabolism. *Biosensors and Bioelectronics*, 216:114826, 2022. doi: 10.1016/j.bios.2022.114826.

[38] Tamara Maric et al. NAD+ metabolism and cancer: current perspectives and future directions. *Cancer Research*, 83(8):1234–1245, 2023. doi: 10.1158/0008-5472.CAN-22-3197.

[39] Christopher R Martens, Blair A Denman, Melissa R Mazzo, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. *Nature Communications*, 9(1):1286, 2018. doi: 10.1038/s41467-018-03421-7.

[40] Mario Mehmel, Nina Jovanović, and Urs Spitz. Nicotinamide riboside—the current state of research and therapeutic uses. *Nutrients*, 12(6):1616, 2020. doi: 10.3390/nu12061616.

[41] Kathryn F Mills, Shohei Yoshida, Liana R Stein, et al. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. *Cell Metabolism*, 24(6):795–806, 2016. doi: 10.1016/j.cmet.2016.09.013.

[42] Emmani BM Nascimento, Michiel PB Moonen, Carlijn ME Remie, et al. Nicotinamide riboside enhances in vitro beta-adrenergic brown adipose tissue activity in humans. *The Journal of Clinical Endocrinology & Metabolism*, 106(5):1437–1447, 2021. doi: 10.1210/clinem/dgaa960.

[43] Keisuke Okabe, Keisuke Yaku, Yuki Uchida, et al. Oral administration of nicotinamide mononucleotide is safe and efficiently increases blood nicotinamide adenine dinucleotide levels in healthy subjects. *Frontiers in Nutrition*, 9:868640, 2022. doi: 10.3389/fnut.2022.868640.

[44] Augusto Peluso, Mads V Damgaard, Marcelo AS Mori, and Jonas T Treebak. Age-dependent decline of NAD+—universal truth or confounded consensus? *Nutrients*, 14(1):101, 2022. doi: 10.3390/nu14010101.

[45] Karol M Pencina, Siva Lavu, Melissa Dos Santos, et al. MIB-626, an oral formulation of a microcrystalline unique polymorph of β-nicotinamide mononucleotide, increases circulating nicotinamide adenine dinucleotide and its metabolome in middle-aged and older adults. *The Journals of Gerontology: Series A*, 78(1):90–96, 2023. doi: 10.1093/gerona/glac049.

[46] Eija Pirinen, Mari Auranen, Nahid A Khan, et al. Niacin cures systemic NAD+ deficiency and improves muscle performance in adult-onset mitochondrial myopathy. *Cell Metabolism*, 31(6):1078–1090.e5, 2020. doi: 10.1016/j.cmet.2020.04.008.

[47] Carlijn ME Remie, Kay HM Roumans, Michiel PB Moonen, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *The American Journal of Clinical Nutrition*, 112(2):413–426, 2020. doi: 10.1093/ajcn/nqaa072.

[48] David C Schöndorf, Dina Ivanyuk, Pascale Baden, et al. The NAD+ precursor nicotinamide riboside rescues mitochondrial defects and neuronal loss in iPSC and fly models of Parkinson's disease. *Cell Reports*, 23(10):2976–2988, 2018. doi: 10.1016/j.celrep.2018.05.009.

[49] Michael B Shapiro, Sibel Tuncay, Maria A De la Fuente, et al. Extracellular NAD+ enhances PARP-dependent DNA repair capacity independently of CD73 activity. *Scientific Reports*, 10(1):18818, 2020. doi: 10.1038/s41598-020-75855-z.

[50] Igor Shats, Jason G Williams, Juan Liu, et al. Bacteria boost mammalian host NAD metabolism by engaging the deamidated biosynthesis pathway. *Cell Metabolism*, 31 (3):564–579.e7, 2020. doi: 10.1016/j.cmet.2020.02.001.

[51] Ben Stocks, Stephen P Ashcroft, Sophie Joanisse, et al. Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise. *The Journal of Physiology*, 599(5):1513–1531, 2021. doi: 10.1113/JP280825.

[52] Stefano Tarantini, M Noa Valcarcel-Ares, Peter Toth, et al. Nicotinamide mononucleotide (NMN) supplementation rescues cerebromicrovascular endothelial function and neurovascular coupling responses and improves cognitive function in aged mice. *Redox Biology*, 24:101192, 2019. doi: 10.1016/j.redox.2019.101192.

[53] Mariana G Tarragó, Claudia CS Chini, Ken-ichi Kanamori, et al. CD38 inhibitor 78c increases mice lifespan and healthspan in a model of chronological aging. *Aging Cell*, 20(2):e13217, 2021. doi: 10.1111/acel.13217.

[54] Samuel AJ Trammell, Mark S Schmidt, Ben J Weidemann, et al. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nature Communications*, 7 (1):12948, 2016. doi: 10.1038/ncomms12948.

[55] Stephanie JG Veenhuis, Nienke JH van Os, AJWM Janssen, et al. Nicotinamide riboside improves ataxia scores and immunoglobulin levels in ataxia telangiectasia. *Movement Disorders*, 36(12):2951–2957, 2021. doi: 10.1002/mds.28788.

[56] Michael Vreones, Maja Mustapic, Ruin Moaddel, et al. Oral nicotinamide riboside raises NAD+ and lowers biomarkers of neurodegenerative pathology in plasma extracellular vesicles enriched for neuronal origin. *Aging Cell*, 22(2):e13754, 2023. doi: 10.1111/acel.13754.

[57] Xiaonan Wang, Xinyi Hu, Yan Yang, Takashi Takata, and Takashi Sakurai. Nicotinamide mononucleotide protects against β-amyloid oligomer-induced cognitive impairment and neuronal death. *Brain Research*, 1643:1–9, 2016. doi: 10.1016/j.brainres.2016.04.060.

[58] Liu Yang et al. NAD+ metabolism and cancer: friends or foes? *Nature Cancer*, 1(6): 515–527, 2020. doi: 10.1038/s43018-020-0075-z.

[59] Yang Yang, Farheen S Mohammed, Ning Zhang, and Anthony A Sauve. Dihydronicotinamide riboside is a potent NAD+ concentration enhancer in vitro and in vivo. *Journal of Biological Chemistry*, 294(23):9295–9307, 2019. doi: 10.1074/jbc.RA118.005772.

[60] Jun Yoshino, Kathryn F Mills, Myeong Jin Yoon, and Shin-ichiro Imai. Nicotinamide mononucleotide, a key NAD+ intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. *Cell Metabolism*, 14(4):528–536, 2011. doi: 10.1016/j.cmet.2011.08.014.

[61] Mihoko Yoshino, Jun Yoshino, Brandon D Kayser, et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. *Science*, 372(6547):1224–1229, 2021. doi: 10.1126/science.abe9985.

[62] Burak Yulug, Ozlem Altay, Xiangyu Li, et al. Combined metabolic activators improve cognitive functions in Alzheimer's disease patients: a randomised, double-blinded, placebo-controlled phase II trial. *Translational Neurodegeneration*, 12(1):3, 2023. doi: 10.1186/s40035-023-00336-2.

[63] Sarah Zaidman, Rotem Ben-Hamo, Yifat Biala, et al. Nicotinamidase expression modulates NAD+ metabolism and lifespan in C. elegans. *Cell Reports*, 32(1):107856, 2020. doi: 10.1016/j.celrep.2020.107856.

[64] Hongbo Zhang, Dongryeol Ryu, Yibo Wu, et al. NAD+ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science*, 352(6292): 1436–1443, 2016. doi: 10.1126/science.aaf2693.

[65] Cheng-Chao Zhou, Xiao Yang, Xiaobing Hua, et al. Hepatic NAD+ deficiency as a therapeutic target for non-alcoholic fatty liver disease in ageing. *British Journal of Pharmacology*, 173(15):2352–2368, 2016. doi: 10.1111/bph.13513.

[66] Xiao-Hong Zhu, Ming Lu, Byeong-Yeul Lee, Kamil Ugurbil, and Wei Chen. In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. *Proceedings of the National Academy of Sciences USA*, 112(9):2876–2881, 2015. doi: 10.1073/pnas.1417921112.