CELLULAR HEALTH

Do NAD+ precursors like NMN and NR improve human healthspan or just blood markers?

Why elevating whole-blood NAD+ metabolites in short-term human trials does not automatically translate into tissue rejuvenation or functional aging outcomes.

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Raising NAD+ in a peripheral blood draw is biochemically straightforward; getting that cofactor past hepatic first-pass metabolism into aged skeletal muscle or vascular endothelium to alter clinical function is a separate physiological problem entirely.

Nicotinamide adenine dinucleotide (NAD+) is an essential pyridine nucleotide present in every living mammalian cell. It functions both as a primary electron carrier in mitochondrial oxidative phosphorylation and as an obligate cosubstrate for regulatory enzymes that govern DNA repair, chromatin remodeling, and cellular stress resilience. Across rodent models and limited human tissue biopsies, intracellular NAD+ concentrations decline in specific organs during chronological aging, metabolic syndrome, and chronic inflammation. This observation created a large commercial market for oral NAD+ precursors—specifically nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN)—as well as intravenous NAD+ infusions. Yet human randomized controlled trials (RCTs) published through 2025 reveal a sharp divergence between rodent physiology and human clinical outcomes. While oral precursors reliably elevate NAD+ and its methylated breakdown products in whole blood and peripheral blood mononuclear cells (PBMCs), they rarely increase steady-state NAD+ inside human skeletal muscle, and they have not demonstrated durable improvements in human lifespan, cardiovascular event rates, or broad physical performance. Understanding why a blood marker moves while tissue outcomes remain flat requires examining how humans absorb, degrade, and compartmentalize NAD+ precursors.

What it is

NAD+ (in its oxidized form) and NADH (in its reduced form) compose a fundamental redox couple required for cellular bioenergetics. Within the cytoplasm and mitochondrial matrix, NAD+ accepts hydride ions during glycolysis, fatty acid beta-oxidation, and the tricarboxylic acid (TCA) cycle, converting into NADH. NADH subsequently donates these electrons to Complex I (NADH:ubiquinone oxidoreductase) of the inner mitochondrial membrane to drive proton pumping and adenosine triphosphate (ATP) synthesis. In this bioenergetic role, the molecule is neither created nor destroyed; it cycles continuously between oxidized and reduced states. In a second, distinct role, NAD+ is physically consumed as a substrate by three major classes of non-redox enzymes: 1. Sirtuins (SIRT1 through SIRT7): Class III histone deacetylases that remove acetyl and acyl groups from target proteins—including the mitochondrial biogenesis regulator PGC-1alpha and the transcription factor FOXO3—cleaving NAD+ into nicotinamide (NAM) and O-acetyl-ADP-ribose in the process. 2. Poly(ADP-ribose) polymerases (primarily PARP1 and PARP2): Nuclear enzymes activated by single- and double-strand DNA breaks. PARPs consume large quantities of NAD+ to build ADP-ribose polymers that recruit DNA repair machinery. 3. Cyclic ADP-ribose synthases (predominantly CD38 and CD157): Ectonucleotidases expressed heavily on the surface of macrophages, lymphocytes, and endothelial cells. CD38 hydrolyzes NAD+ (and extracellular NMN) with high catalytic efficiency to generate calcium-mobilizing second messengers, releasing nicotinamide as a byproduct. Because non-redox enzymes continuously destroy the NAD+ molecule,

mammalian cells must constantly synthesize it via three pathways: the de novo kynurenine pathway from dietary tryptophan, the Preiss-Handler pathway from nicotinic acid (niacin), and the salvage pathway. In humans, the salvage pathway accounts for the vast majority of daily NAD+ maintenance. The rate-limiting enzyme of this salvage loop is nicotinamide phosphoribosyltransferase (NAMPT), which recycles free nicotinamide (released by sirtuins, PARPs, and CD38) back into NMN, which is then converted to NAD+ by NMN adenylyltransferases (NMNAT1–3). Oral supplements attempt to bypass the rate-limiting NAMPT enzyme by providing phosphorylated or nucleoside intermediates directly: nicotinamide riboside (NR, which enters the cell via equilibrative nucleoside transporters and is phosphorylated into NMN by nicotinamide riboside kinases NRK1/2) or nicotinamide mononucleotide (NMN, which is either dephosphorylated extracellularly into NR by CD73 before crossing the membrane, or transported via specific solute carriers such as SLC12A8, a mechanism demonstrated in murine small intestine whose quantitative significance in human peripheral tissues remains unconfirmed). Intravenous (IV) NAD+ infusions offered in commercial clinics represent a completely different biochemical class. Because the intact NAD+ dinucleotide is a large, polar, phosphorylated molecule, it cannot passively diffuse across intact mammalian plasma membranes, nor do humans possess a validated plasma membrane transporter for intact NAD+. When infused directly into a vein, extracellular NAD+ must be broken down by cell-surface ectoenzymes (such as CD38 and CD73) into smaller precursors like adenosine, nicotinamide, and NR before entering cells. High extracellular NAD+ and its breakdown product adenosine acutely stimulate purinergic receptors, which explains the immediate autonomic side effects associated with rapid IV drips.

Why it is used

In rodent models, tissue NAD+ concentrations decline by 30% to 50% across liver, skeletal muscle, adipose tissue, and brain between young adulthood and old age. In humans, tissue biopsy and imaging data are sparser and show smaller, more variable reductions: magnetic resonance spectroscopy (MRS) and biochemical assays of human brain, liver, and skeletal muscle indicate declines ranging from 10% to 30% between young adults and older adults, with a major caveat. When older human cohorts are stratified by physical activity in cross-sectional biopsy studies, master athletes and older adults who perform regular aerobic and resistance training exhibit skeletal muscle NAD+ and NAMPT protein levels nearly indistinguishable from those of young adults. Much of the observed human muscular NAD+ decline correlates with disuse and adiposity rather than chronological age alone. Furthermore, mechanistic work in both murine models and human tissues demonstrates that age-related NAD+ depletion is driven less by a failure to synthesize NAD+ and more by accelerated destruction. Chronic low-grade sterile inflammation and the accumulation of senescent cells release pro-inflammatory cytokines (such as TNF-alpha and IL-6) that induce a marked upregulation of CD38 on tissue-resident pro-inflammatory M1 macrophages. Similarly, chronic oxidative DNA damage continually activates nuclear PARP1. Together, hyperactive CD38 and PARP1 act as a metabolic sink, draining the cellular NAD+ pool. Exogenous supplementation with NR or NMN is used to refill this depleted pool with the goal of restoring sirtuin activity, improving mitochondrial oxidative phosphorylation, enhancing mitophagy (the clearance of damaged mitochondria), maintaining endothelial nitric oxide synthase (eNOS) coupling, and supporting genomic stability. In preclinical mouse models of diet-induced obesity, accelerated aging, and heart failure, high-dose NR and NMN reliably restore tissue NAD+, reverse insulin resistance, increase running endurance, and improve vascular elasticity. Whether these rodent outcomes translate to free-living humans has been the focus of recent clinical trials.

How it helps

Randomized, double-blind, placebo-controlled human trials conducted through 2025—typically enrolling 20 to 140 middle-aged or older adults for 4 to 24 weeks—demonstrate one consistent biochemical effect: oral NR and

NMN increase circulating NAD+ and its metabolites in whole blood and PBMCs by 40% to 150%, alongside 5-fold to 20-fold increases in NAAD and methylated catabolites such as N-methylnicotinamide (MeNAM) and N-methyl-2-pyridone-5-carboxamide (2-Py) in plasma and urine. Two physiological mechanisms explain why a large increase in blood NAD+ rarely produces measurable changes in functional clinical endpoints: 1. The First-Pass Hepatic and Microbiome Bottleneck: Stable-isotope tracing studies in rodents, supported by human metabolite profiling, reveal that orally ingested NR and NMN do not travel intact through the bloodstream to peripheral muscles or the brain in large quantities. A substantial fraction of oral NR and NMN is cleaved by the gut microbiome into nicotinic acid (entering the Preiss-Handler pathway, which explains why NAAD is a sensitive biomarker of NR and NMN ingestion) or degraded by intestinal and hepatic enzymes into plain nicotinamide (NAM). The liver absorbs these precursors, synthesizes NAD+, and exports mostly nicotinamide into the systemic circulation. Erythrocytes and PBMCs circulating through the portal and systemic vasculature readily take up precursors and expand their internal NAD+ pools, making a standard venipuncture blood test highly responsive. 2. Tissue Homeostatic Buffering and the CD38 Sink: When circulating nicotinamide reaches peripheral skeletal muscle, its conversion back to NAD+ is strictly limited by the endogenous enzyme NAMPT. Even when intact NR or NMN reaches peripheral tissues, healthy cells maintain tight feedback inhibition over NAD+ synthesis. Consequently, multiple human RCTs incorporating vastus lateralis muscle biopsies before and after 3 to 12 weeks of NR or NMN supplementation in overweight, insulin-resistant, or older adults have found no statistically significant increase in steady-state intramyocellular NAD+ concentration, mitochondrial copy number, or maximal mitochondrial respiration (measured via high-resolution respirometry), despite high levels of methylated waste products proving the supplement was absorbed and degraded. Where human trials show preliminary signals of benefit, they occur in specific subpopulations or intermediate markers rather than broad functional metrics: - Insulin Sensitivity: At least four RCTs using the hyperinsulinemic-euglycemic clamp in obese or prediabetic men showed no effect of NR on hepatic or peripheral insulin sensitivity. Conversely, one 10-week RCT in 25 postmenopausal women with prediabetes taking oral NMN reported an approximately 25% improvement in skeletal muscle insulin-stimulated glucose disposal and enhanced muscle insulin signaling (phosphorylation of AKT and mTOR), without changes in fasting glucose, HbA1c, or liver fat. - Vascular and Inflammatory Intermediates: Small RCTs (n = 24 to 60, duration 6 to 12 weeks) in middle-aged and older adults have reported modest reductions in circulating inflammatory cytokines (such as IL-6, IL-5, and TNF-alpha) in PBMCs and non-statistically significant trends toward reduced aortic stiffness (carotid-femoral pulse wave velocity) and systolic blood pressure (roughly 3 to 4 mmHg lower in subgroups with elevated starting point pressure), though larger confirmatory trials have failed to replicate the blood pressure reduction. - Submaximal Physical Function: Several 6-to-12-week RCTs of NMN in older adults (n = 40 to 108) reported minor improvements in 6-minute walk distance, gait speed, or chair-stand tests, and one 6-week trial in 48 amateur runners reported an improvement in ventilatory threshold during submaximal exercise without an increase in maximal oxygen uptake (VO2max). Overall, no reliable, reproducible effect size exists for VO2max, muscular strength, body composition, or cognitive performance in healthy humans. For commercial IV NAD+ infusions, controlled human outcome data do not exist. Outside of one small pharmacokinetic pilot study showing that a slow 6-hour IV infusion raises plasma and urinary NAD+ metabolites after an initial 2-hour delay (during which extracellular enzymes clear and process the infused dinucleotide), no randomized, placebo-controlled trials demonstrate that clinic IV NAD+ infusions improve cellular energetics, neurological recovery, or aging biomarkers compared to placebo or oral precursors.

Who should try it

Structured aerobic and resistance exercise is the only intervention proven via human muscle biopsies to increase skeletal muscle NAMPT expression and restore intracellular NAD+ to youthful levels, particularly when paired with energy balance and circadian alignment (as the NAMPT gene is directly regulated by the core circadian clock complex CLOCK:BMAL1). Because clinical trial data for supplements remain largely limited to

blood metabolite elevation, oral NAD+ precursors are secondary interventions. An adult aged 40 to 65 may consider a time-limited trial of an oral NAD+ precursor after exercise, sleep architecture, and glycemic control are established, specifically when NAD+ turnover is stressed—such as in documented metabolic inflexibility or elevated systemic inflammation after addressing primary causes. Any supplementation trial should use predefined starting point and 12-week follow-up biomarkers. Trade-offs, Side Effects, and Contraindications: - Oral Precursors (NR and NMN): Well tolerated in short-term human RCTs lasting up to 24 weeks. Reported side effects are mild and infrequent, including gastrointestinal discomfort, nausea, mild headache, and transient fatigue. Unlike high-dose niacin (nicotinic acid), NR and NMN do not activate the GPR109A receptor on dermal Langerhans cells and do not cause prostaglandin-mediated skin flushing. - The Methylation Trade-Off: Every molecule of NAD+ consumed by sirtuins, PARPs, or CD38 releases nicotinamide. Excess nicotinamide that is not salvaged is cleared by the liver via the enzyme nicotinamide N-methyltransferase (NNMT), which transfers a methyl group from S-adenosylmethionine (SAMe) to form MeNAM for urinary excretion. High-dose oral precursor supplementation increases hepatic methylation demand. In individuals with marginal folate, vitamin B12, or betaine status, or variants in methylation-pathway enzymes, this clearance pathway can deplete methyl donors and elevate plasma homocysteine. - Oncology and Senescence Considerations: Rapidly dividing cells rely heavily on NAMPT and NAD+ to fuel glycolysis (the Warburg effect) and PARP-mediated DNA repair; consequently, oncology trials actively test NAMPT inhibitors to starve tumors. In rodent models, while NAD+ replenishment prevents DNA damage in healthy tissues, administering high-dose NAD+ precursors after an aggressive tumor is established can support tumor cell proliferation or increase the pro-inflammatory senescence-associated secretory phenotype (SASP) of existing senescent cells. Active malignancy or a history of high-risk hormone- or metabolism-sensitive cancer is a clinical contraindication to exogenous NAD+ loading. - Opportunity Cost and IV NAD+ Risks: Oral precursors carry a recurring monthly financial cost that yields lower physiological return than structured exercise programming. IV NAD+ infusions carry high financial and time costs alongside immediate, rate-dependent adverse effects during administration—including severe abdominal cramping, nausea, chest tightness, flushing, bradycardia or tachycardia, and lightheadedness driven by extracellular purinergic receptor activation and adenosine release—plus standard venipuncture risks (phlebitis, local infection) without RCT validation.

Measurements that show improvement

Elevated whole-blood NAD+ on a consumer dried-blood-spot test confirms only that the supplement was absorbed into portal circulation and taken up by erythrocytes or leukocytes; it does not demonstrate that skeletal muscle, brain, or cardiac tissue has improved its bioenergetic capacity. Evaluating whether a cellular health intervention produces physiological adaptation requires tracking downstream functional and metabolic markers over an 8-to-12-week window: - Intracellular Blood NAD+ (Whole Blood or PBMC LC-MS/MS): An increase of 40% to 150% from starting point confirms biochemical compliance and salvage pathway flux, but should not be interpreted in isolation as a functional outcome. - High-Sensitivity C-Reactive Protein (hs-CRP): Because inflammatory macrophage CD38 expression is a primary driver of NAD+ destruction, tracking hs-CRP (targeting a reduction toward < 1.0 mg/L) indicates whether the underlying inflammatory drain on the NAD+ pool is resolving. - Fasting Insulin, HbA1c, and HOMA-IR: To test whether sirtuin activation is improving metabolic flexibility, track reductions in fasting insulin (toward < 6 uIU/mL) and HbA1c; exercise and dietary carbohydrate control produce much larger effect sizes on these markers than precursors. - Plasma Homocysteine: Measured at starting point and 8 to 12 weeks after initiating oral precursors to verify that clearance of excess nicotinamide via NNMT is not depleting hepatic methyl donors and driving homocysteine upward (target < 8 to 10 umol/L). - Hepatic Transaminases (ALT, AST) and Uric Acid: Monitored to verify the absence of hepatotoxicity or altered purine and nucleotide catabolism. - Cardiopulmonary Exercise Testing (VO2max and Ventilatory Threshold / Zone 2 Power Output): The functional readout of skeletal muscle mitochondrial density and Complex I redox capacity. An upward shift in watts produced at a fixed blood lactate (< 2.0 mmol/L) or heart rate, or an increase

in VO2max (mL/kg/min), demonstrates peripheral mitochondrial adaptation. - Nocturnal Heart Rate Variability (HRV) and Resting Heart Rate (RHR): Tracked via wearable photoplethysmography or ECG straps over rolling 30-day averages. A sustained rise in nocturnal rMSSD and a reduction in RHR reflect improved autonomic recovery, whereas an acute drop following an intervention signals metabolic or sympathetic stress. - Composite Biological Age Clocks: Multi-system blood biomarker panels or second- and third-generation epigenetic clocks (such as GrimAge or DunedinPACE) integrate inflammatory, renal, hepatic, and metabolic drift. If a precursor raises blood NAD+ while pace-of-aging and metabolic markers remain unchanged at 12 to 24 weeks, resources are better redirected toward resistance training, Zone 2 aerobic volume, or sleep interventions.

Products and services

These LetsGo products and services sit next to this subject. They are not a prescription. A link is not evidence that the product causes the change discussed above. - [Grokki longevity programme](/programs/grokki/longevity) — A coached plan that can track the markers named in this article. - [LetsGo supplement shelf](/supplements) — Bottles LetsGo stocks for members. Read the label before the first order. A link is not a dose.

Practical takeaways

- Perform progressive resistance training (2 to 4 sessions per week) and Zone 2 aerobic conditioning (150 to 180 minutes per week at blood lactate < 2.0 mmol/L) for 12 weeks to upregulate endogenous skeletal muscle NAMPT and increase VO2max.
- Measure hs-CRP and visceral adipose tissue at starting point; reduce hs-CRP below 1.0 mg/L via caloric balance and physical activity to suppress macrophage CD38 expression before spending money on exogenous NAD+ precursors.
- If conducting a 12-week trial of oral NR or NMN, measure starting point and 12-week fasting insulin (target < 6 uIU/mL), HbA1c, hs-CRP, ALT, AST, and plasma homocysteine (target < 10 umol/L).
- Discontinue oral NR or NMN at 12 weeks if fasting insulin, HOMA-IR, hs-CRP, or submaximal ventilatory threshold show no improvement, even if whole-blood NAD+ rises by 40% to 150%, or immediately if plasma homocysteine rises above 10 umol/L.
- Avoid commercial IV NAD+ infusions for general healthspan; they lack randomized controlled trial evidence for clinical benefit and induce acute purinergic adverse effects including bradycardia, chest tightness, and abdominal cramping.

Safety note

Oral NAD+ precursors are contraindicated in individuals with active malignancies or unexplained suspicious masses due to the reliance of rapidly proliferating cells on NAD+-dependent glycolysis and DNA repair. High-dose precursor use increases hepatic methyl-group consumption via NNMT and requires caution in individuals with hyperhomocysteinemia or severe hepatic or renal impairment. Intravenous NAD+ infusions can induce acute autonomic, cardiovascular, and gastrointestinal reactions and should not be treated as equivalent to oral dietary supplements.

Disclaimer

This article is for educational purposes only and does not constitute medical advice, diagnosis, or treatment. Always consult a qualified physician or healthcare provider before starting any new supplement, intravenous infusion, or diagnostic regimen, particularly if you have existing medical conditions or take prescription medications.

Human clinical trials through 2025 have clarified the boundary between biochemical target engagement and clinical healthspan. Oral NAD+ precursors reliably raise circulating NAD+ metabolites in blood draws, proving

that the human salvage and Preiss-Handler pathways readily process exogenous nucleosides in the gut, liver, and blood cells. Yet first-pass hepatic clearance, strict tissue homeostatic buffering, and accelerated NAD+ destruction by inflammatory CD38 enzymes prevent most of that oral payload from increasing steady-state NAD+ or mitochondrial function inside human skeletal muscle. Rather than relying on precursor capsules or unvalidated intravenous drips to override sedentary physiology, adults achieve reliable restoration of cellular bioenergetics by suppressing chronic inflammatory NAD+ sinks and driving endogenous NAMPT expression through structured physical training.