CELLULAR HEALTH

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

Human randomized trials consistently show that oral nicotinamide riboside and nicotinamide mononucleotide raise whole-blood NAD+ metabolites, but clinical endpoints for metabolic, cardiovascular, and muscle function remain mixed over short follow-up windows.

LetsGo Editorial · LetsGo Editorial · 3 November 2026 · 12 min read

A higher whole-blood NAD+ laboratory value confirms that an oral supplement was absorbed and metabolized, not that skeletal muscle mitochondria or vascular endothelium have become biologically younger.

Nicotinamide adenine dinucleotide (NAD+) is an essential pyridine nucleotide present in all living mammalian cells. It functions both as a redox coenzyme in metabolic pathways and as a consumed substrate for enzymes that regulate DNA repair, epigenetic maintenance, and cellular stress responses. Because tissue NAD+ concentrations decline in several rodent models of aging and in specific human tissues—such as skin, brain, and skeletal muscle—during chronological aging or metabolic disease, replenishing NAD+ has become a central hypothesis in cellular health research. Two oral vitamin B3 derivatives, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), dominate clinical trials. Through 2025, dozens of human randomized controlled trials (RCTs) have established that both molecules safely and reliably elevate NAD+ and its breakdown products in whole blood and peripheral blood mononuclear cells (PBMCs). However, a persistent gap separates circulating biomarker changes from functional clinical outcomes. Understanding why blood NAD+ rises sharply while muscle NAD+, insulin sensitivity, and cardiorespiratory fitness often remain unchanged requires examining human hepatic first-pass metabolism, tissue-specific transporter expression, and the distinction between oral precursor guides and commercial intravenous NAD+ infusions.

What it is

NAD+ is a dinucleotide composed of two nucleotides joined through their phosphate groups, with one nucleotide containing an adenine base and the other containing nicotinamide. In mammalian physiology, NAD+ exists in two distinct functional pools: a redox pool that interconverts between oxidized NAD+ and reduced NADH (and the phosphorylated equivalents NADP+ and NADPH) without net consumption, and a signaling pool where NAD+ is cleaved and destroyed by three major enzyme classes. The three NAD+-consuming enzyme families are: 1. Sirtuins (SIRT1 through SIRT7): NAD+-dependent deacylases and deacetylases located in the nucleus (SIRT1, SIRT6, SIRT7), cytoplasm (SIRT2), and mitochondria (SIRT3, SIRT4, SIRT5). Sirtuins remove acetyl and acyl groups from histones and metabolic regulators such as PGC-1alpha and FOXO transcription factors, yielding nicotinamide (NAM) and O-acetyl-ADP-ribose. 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. Ectoenzymes and glycohydrolases (CD38 and CD157) plus SARM1: CD38 is a transmembrane enzyme expressed heavily on immune cells and endothelial cells that hydrolyzes NAD+ into NAM and cyclic ADP-ribose. SARM1 is an inducible NAD+ hydrolase in axons triggered by neuronal injury. Mammalian cells maintain NAD+ levels through three biosynthetic pathways: - The de novo pathway converts dietary tryptophan into quinolinic acid and ultimately

NAD+ via quinolinate phosphoribosyltransferase (QPRT), primarily in the liver and kidneys. - The Preiss-Handler pathway converts dietary nicotinic acid (niacin) into nicotinic acid mononucleotide (NaMN), nicotinic acid adenine dinucleotide (NaAD), and then NAD+ via NAD+ synthetase. - The salvage pathway recycles the nicotinamide (NAM) released by sirtuins, PARPs, and CD38 back into NAD+. Inside the cell, the rate-limiting enzyme nicotinamide phosphoribosyltransferase (NAMPT) converts NAM into NMN. Nicotinamide mononucleotide adenylyltransferases (NMNAT1 in the nucleus, NMNAT2 in the Golgi/cytoplasm, and NMNAT3 in the mitochondria) then adenylate NMN to form NAD+. Oral precursors such as NR and NMN are designed to enter the salvage pathway and bypass the rate-limiting NAMPT enzyme. Inside cells, NR is phosphorylated by nicotinamide riboside kinases (NRK1 and NRK2) to become NMN, which NMNAT enzymes then convert to NAD+. Whether oral NMN enters cells intact via a proposed solute carrier (such as SLC12A8, identified in murine small intestine) or is first dephosphorylated extracellularly by CD73 into NR before entering human cells remains a subject of active biochemical debate.

Why it is used

The rationale for exogenous NAD+ precursor supplementation rests on age-associated NAD+ decline. In rodents, tissue NAD+ levels fall by 30% to 50% in old age across liver, muscle, adipose, and brain tissues. In humans, measuring tissue NAD+ requires invasive biopsies or high-field magnetic resonance spectroscopy (31P-MRS or 7T 1H-MRS), making human data sparser than rodent data. Nevertheless, human studies have documented lower NAD+ levels with advancing age in skin, liver, brain (measured via ultra-high-field MRS), and specific skeletal muscle cohorts, where physically inactive older adults show lower muscle NAD+ than young adults, while endurance-trained older adults maintain muscle NAD+ levels comparable to young individuals. Two mechanisms drive age-related NAD+ depletion: reduced biosynthesis (via circadian decline or inflammatory suppression of NAMPT) and accelerated consumption. Chronic low-grade inflammation—often termed inflammaging—and the accumulation of senescent cells secrete pro-inflammatory cytokines (IL-6, TNF-alpha) that upregulate CD38 expression on macrophages and endothelial cells. In preclinical models, CD38 upregulation is the primary driver of tissue NAD+ loss with age, while chronic DNA damage simultaneously increases PARP1 activation. In aged or metabolically impaired mice, restoring NAD+ with high-dose NR or NMN activates SIRT1 and SIRT3, increases mitochondrial biogenesis via PGC-1alpha, improves hepatic and peripheral insulin sensitivity, reverses vascular endothelial dysfunction, and extends healthspan (and in the case of NR in aged C57BL/6J mice, modestly extends median lifespan). The clinical objective in human trials has been to test whether replicating this NAD+ repletion in human blood translates into improved insulin signaling, reduced arterial stiffness, enhanced skeletal muscle bioenergetics, and neuroprotection.

How it helps

Human clinical evidence for NR and NMN differs markedly from preclinical rodent models. Through 2025, human data consist primarily of phase I and phase II randomized, double-blind, placebo-controlled trials ranging from 2 to 24 weeks in duration, enrolling between 12 and 140 participants (healthy middle-aged and older adults, obese insulin-resistant adults, and patients with heart failure, Parkinson's disease, or peripheral artery disease). 1. Non-obvious synthesis: Why blood NAD+ rises while muscle NAD+ and clinical outcomes often do not. A central puzzle in human NAD+ research is the dissociation between circulating NAD+ and peripheral tissue outcomes. Across nearly all human RCTs, oral NR and NMN increase whole-blood or PBMC NAD+ by 40% to 150% and increase urinary or plasma metabolites—specifically nicotinic acid adenine dinucleotide (NaAD), N-methylnicotinamide (MeNAM), N-methyl-2-pyridone-5-carboxamide (Me2PY), and N-methyl-4-pyridone-5-carboxamide (Me4PY)—by several hundred percent. Yet when researchers perform vastus lateralis skeletal muscle biopsies in obese or older men taking NR or NMN for 3 to 12 weeks, steady-state intramuscular NAD+ concentrations rarely change. Quantitative flux tracing in mice and

pharmacokinetic studies in humans explain this bottleneck. Orally ingested NR and NMN undergo extensive degradation in the gastrointestinal tract and first-pass metabolism in the liver. Furthermore, the microbiome converts a significant portion of oral precursors into nicotinic acid and nicotinamide before absorption. What enters the portal vein is largely metabolized by hepatocytes into NAM, which is released into systemic circulation. Skeletal muscle relies heavily on its own endogenous NAMPT enzyme to convert circulating NAM into NAD+, and mature muscle fibers maintain tightly regulated homeostatic feedback loops. When excess NAD+ precursors or NAM arrive at resting skeletal muscle, the excess is methylated by nicotinamide N-methyltransferase (NNMT) into MeNAM and oxidized into Me2PY/Me4PY for renal excretion, rather than expanding the functional intramuscular NAD+ pool. By contrast, nucleated blood cells (PBMCs) and the liver readily expand their NAD+ pools in response to oral supplementation. 2. Metabolic and insulin sensitivity outcomes. In human RCTs of overweight or obese men and women (typically 6 to 12 weeks, 20 to 40 participants per arm), oral NR has consistently shown no significant effect on hepatic or peripheral insulin sensitivity as measured by the gold-standard hyperinsulinemic-euglycemic clamp, nor has it altered HbA1c, fasting glucose, or hepatic lipid content. For NMN, one 10-week RCT in 25 postmenopausal women with prediabetes reported roughly a 25% improvement in skeletal muscle insulin sensitivity (glucose disposal rate during a clamp) and increased muscle insulin signaling (AKT and mTOR phosphorylation), without changing liver fat or whole-body fat mass. However, other NMN trials in middle-aged men and women using oral glucose tolerance tests or HOMA-IR have shown null effects on glycemic control. 3. Cardiovascular and endothelial function. A 6-week crossover RCT of NR in 24 healthy middle-aged and older adults reported a trend toward lower systolic blood pressure (roughly 3 to 4 mmHg reduction in the subgroup with elevated starting point blood pressure) and lower carotid-femoral pulse wave velocity (a measure of aortic stiffness), though larger subsequent analyses have not established a definitive antihypertensive effect size. A 6-month RCT in patients with peripheral artery disease (PAD) found that NR improved 6-minute walk distance compared to placebo in exploratory analyses, suggesting a potential microvascular or bioenergetic benefit in ischemic tissue where starting point NAD+ is actively depleted. 4. Neurological and inflammatory markers. In small phase I/II trials in Parkinson's disease (30 days of oral NR, 30 participants), supplementation raised cerebral NAD+ levels measured by 31P-MRS and decreased inflammatory cytokines in serum and cerebrospinal fluid, alongside altered cerebral metabolic network patterns on FDG-PET. Similarly, multiple human trials in older adults and heart failure cohorts show that oral NR reduces PBMC mitochondrial reactive oxygen species and lowers circulating pro-inflammatory cytokines (such as IL-6, IL-1beta, and TNF-alpha) when starting point systemic inflammation is elevated. 5. Oral precursors vs. Intravenous (IV) NAD+ drips. Commercial infusion clinics frequently market intravenous NAD+ for fatigue and recovery. An IV NAD+ drip is a completely different intervention from oral NR or NMN guides. Mammalian cells (outside of specialized transport in limited experimental contexts) lack transporters to import the large, charged, intact NAD+ molecule across the plasma membrane. When intact NAD+ is infused intravenously, extracellular ectoenzymes (such as CD38 and CD73) must degrade it in the bloodstream into NMN, NR, adenosine, and nicotinamide before cells can absorb the fragments. Furthermore, rapid IV infusion of intact NAD+ triggers acute purinergic receptor activation and vagal responses, causing chest tightness, abdominal cramping, nausea, headache, and lightheadedness during the drip. Published human pharmacokinetic data on IV NAD+ are sparse, consisting mainly of small pilot studies (fewer than 15 participants) showing that infused NAD+ is rapidly cleared or sequestered from plasma within the first two hours before urinary excretion of metabolites rises. No randomized controlled trial has shown that IV NAD+ improves human healthspan markers or tissue NAD+ levels more effectively than oral precursors.

Who should try it

Because human trials show that healthy, physically active adults with normal starting point NAD+ levels experience minimal functional change from oral precursors, NAD+ supplementation is best viewed as a targeted conditional intervention rather than a universal foundation. Populations where emerging human evidence

suggests potential utility include: - Older adults (typically over age 55 to 60) with documented systemic low-grade inflammation (elevated hs-CRP or inflammatory cytokines) or bioenergetic decline. - Individuals with specific metabolic or ischemic states characterized by accelerated NAD+ consumption, where clinical trials are ongoing (such as post-viral fatigue states, heart failure with reduced ejection fraction, or peripheral artery disease), under physician supervision. Populations where opportunity cost is high and foundational interventions are superior: - Sedentary middle-aged adults seeking improvements in VO2max, insulin sensitivity, or body composition. In human muscle biopsy studies, 12 weeks of resistance or aerobic exercise training increases skeletal muscle NAMPT protein expression by roughly 15% to 30% and directly restores intramuscular NAD+ to youthful levels—an outcome oral NR and NMN have failed to match consistently in resting human muscle. Contraindications, side effects, and trade-offs: - Side effects: Oral NR and NMN are generally well tolerated in human trials up to several months. Mild gastrointestinal symptoms (nausea, bloating, diarrhea), muscle cramping, and occasional skin warmth occur in a small percentage of participants. Unlike nicotinic acid (niacin), neither NR nor NMN activates the GPR109A receptor on Langerhans cells, so neither causes the classic prostaglandin-mediated niacin flush. - Methylation demand: Because excess nicotinamide is cleared via methylation by NNMT using S-adenosylmethionine (SAMe) as the methyl donor, chronic high intake of NAD+ precursors theoretically increases demand on the one-carbon metabolism pathway and increases homocysteine production, although overt methyl depletion has not been widely observed in short-term clinical trials. - Oncology considerations: Preclinical mouse models show that while NAD+ repletion supports DNA repair via PARPs in healthy cells (potentially preventing tumorigenesis), once a tumor is established, cancer cells rely heavily on NAMPT and high NAD+ turnover to sustain rapid proliferation (the Warburg effect) and evade senescence. In addition, elevated NAD+ supports the pro-inflammatory senescence-associated secretory phenotype (SASP) via HMGA proteins and AMPK inhibition in certain preclinical models. Consequently, individuals with active malignancy, a recent history of cancer, or high-grade pre-cancerous lesions are generally advised by longevity physicians to avoid exogenous NAD+ precursors. - Vascular metabolites: Recent large observational human metabolomic cohorts have linked high circulating levels of the terminal breakdown products 2PY and 4PY with vascular inflammation (VCAM-1 expression) and major adverse cardiovascular events. Whether exogenous NR or NMN supplementation carries long-term vascular risk via 2PY/4PY accumulation remains unknown and unstudied in long-term outcome trials. - Cost: Quality-tested oral NR or NMN represents a recurring monthly expense of roughly $50 to $120, while clinic IV NAD+ infusions cost $300 to $1,000 per session with no randomized outcome data.

Measurements that show improvement

Because subjective energy is highly susceptible to placebo effects, evaluating an NAD+ intervention requires objective biomarkers tracked before and 8 to 12 weeks after initiating a guide. 1. Direct NAD+ Quantification: - Intracellular PBMC NAD+ or Dried Blood Spot (DBS) Whole-Blood NAD+: Measured via liquid chromatography-tandem mass spectrometry (LC-MS/MS) or validated enzymatic colorimetric assays. A meaningful response to oral NR or NMN is a 40% to 100% increase from starting point intracellular concentrations (typically moving from a lower starting point into the upper quartile of the laboratory reference range, often expressed around 30 to 50 micromolar in whole blood depending on the assay). - Note on Plasma NAD+: Standard cell-free plasma NAD+ is present at nanomolar concentrations (roughly 100-fold lower than intracellular RBC or PBMC levels) and is easily confounded by sample hemolysis. Intracellular or whole-blood assays are required for reliable tracking. 2. Downstream Metabolic, Inflammatory, and Methylation Markers: - High-sensitivity C-reactive protein (hs-CRP): Direction of interest is a decrease toward <1.0 mg/L in individuals starting with elevated starting point systemic inflammation. - Fasting Insulin and HOMA-IR (alongside HbA1c): Direction of interest is a reduction in fasting insulin (ideally toward <6–8 uIU/mL) and HOMA-IR (<1.5), though readers should recognize that most human trials show minimal change from NAD+ precursors alone without concurrent exercise or caloric restriction. - Plasma Homocysteine: Tracked as a safety marker for methylation

pool strain. Direction of interest is maintaining stability (<8–10 umol/L); a rise in homocysteine following NAD+ precursor initiation suggests increased methyl group consumption by NNMT. - Liver Enzymes (ALT, AST) and Uric Acid: Tracked for hepatic safety and purine/nucleotide turnover stability. 3. Functional Physiological Markers: - Resting Heart Rate (RHR) and Heart Rate Variability (HRV via nocturnal RMSSD): Tracked continuously over 4-week rolling averages to assess autonomic recovery. - Resting Blood Pressure and Pulse Wave Velocity (PWV): In adults with borderline elevated systolic pressure, a reduction of 3 to 4 mmHg systolic or a decrease in carotid-femoral PWV reflects improved endothelial compliance. - VO2max and Grip Strength: Tracked via cardiopulmonary exercise testing (CPET) and hand dynamometry. If whole-blood NAD+ doubles over 12 weeks while VO2max, zone 2 power output, hs-CRP, and fasting insulin remain completely static, the intervention is moving a surrogate blood marker without altering physiological function. Within a physician-led framework such as a LetsGo program, intracellular NAD+ testing is paired with a comprehensive cardiometabolic and inflammatory panel (including ApoB, hs-CRP, fasting insulin, and homocysteine) and composite BioAge tracking to verify whether a supplement is producing systemic resilience or merely excreting methylated metabolites.

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

- Treat whole-blood NAD+ as a pharmacokinetic compliance marker, not a guaranteed healthspan outcome: a higher blood NAD+ number confirms absorption, but does not prove that skeletal muscle or vascular tissues have rejuvenated.
- Prioritize resistance and aerobic exercise to raise tissue NAD+: exercise directly increases intramuscular NAMPT expression in humans, solving the tissue uptake bottleneck that limits oral supplements.
- Measure starting point and 12-week follow-up biomarkers if trialing an oral precursor: pair an intracellular whole-blood or PBMC NAD+ test with hs-CRP, fasting insulin, and homocysteine to check both efficacy and methylation safety.
- Avoid commercial IV NAD+ infusions for routine longevity purposes: they lack randomized human outcome data, cannot enter cells intact without extracellular degradation, and carry acute infusion side effects and high financial cost.
- Screen for contraindications before starting: individuals with active cancer, a recent history of malignancy, or unexplained elevated cardiovascular inflammation markers should consult a physician and generally avoid exogenous NAD+ precursors.

Safety note

Oral NAD+ precursors (NR and NMN) are dietary supplements, not FDA-approved drugs for disease treatment. Because NAD+ fuels cellular proliferation and DNA repair pathways utilized by tumor cells, individuals with active cancer or a history of malignancy should not use NAD+ precursors without explicit oncological clearance. Monitor plasma homocysteine when supplementing long-term to ensure nicotinamide clearance does not deplete methyl donors.

Disclaimer

This article is for educational and informational purposes only and does not constitute medical advice, diagnosis, or

treatment. Always consult a qualified physician or healthcare provider before starting any new supplement, diagnostic guide, or health intervention.

Human clinical trials through 2025 confirm that oral nicotinamide riboside and nicotinamide mononucleotide reliably elevate whole-blood and PBMC NAD+ concentrations. However, because of hepatic first-pass metabolism and tight homeostatic regulation in peripheral tissues, a higher blood NAD+ reading does not automatically translate into increased skeletal muscle NAD+ or measurable gains in insulin sensitivity and cardiorespiratory fitness. High-agency adults evaluating NAD+ interventions should anchor their cellular health strategy in structured exercise—which directly upregulates endogenous muscle NAMPT—and use objective intracellular NAD+, inflammatory, and metabolic biomarkers to verify whether oral supplementation provides measurable physiological value.