



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Nicotinamide Riboside

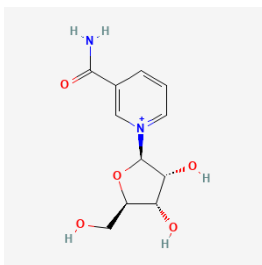
Evidence Summary

NR increases NAD⁺ levels in the blood but has not consistently increased NAD⁺ levels in tissues of interest or improved clinical outcomes. NR has GRAS status and is considered safe up to 300 mg/day.

Neuroprotective Benefit: Laboratory studies have shown neuroprotective benefits with NR. But a few pilot clinical trials completed to date have reported variable outcomes across subjects. Efficacy in various diseases will be evaluated in ongoing trials.

Aging and related health concerns: NR increases blood NAD⁺ levels but does not reliably increase NAD⁺ levels in tissues of interest. NR has shown little effect in improving clinically relevant outcomes such as insulin sensitivity and physical function.

Safety: NR has GRAS status and is considered safe up to 300 mg/day in healthy adults. Clinical trials have generally shown incidences of adverse events that were comparable to placebo.

<p>Availability: sold as supplement</p>	<p>Dose: The EFSA concluded NR is safe up to 300 mg/day for healthy adults. Supplements contain 250-300 mg of NR per serving. In clinical populations, doses of up to 2,000 mg per day have been tested in early phase trials.</p>	<p>Chemical formula: C₁₁H₁₅N₂O₅⁺ MW: 255.25</p>  <p>Source: PubChem</p>
<p>Half-life: 2.7 hours</p>	<p>BBB: increases NAD⁺ in the brain</p>	
<p>Clinical trials: The largest study to date enrolled 140 healthy overweight adults.</p>	<p>Observational studies: None</p>	

What is it?

Nicotinamide adenine dinucleotide (NAD⁺) is a critical coenzyme that, when reduced to NADH, serves as a reducing agent to donate electrons for oxidative phosphorylation and energy production. NAD⁺ is also a critical cofactor for enzymes such as the sirtuins (NAD-dependent deacetylases and master regulator of metabolism), the DNA repair proteins, poly-ADP-ribose polymerases (PARPs), and the cyclic ADP-hydrolases CD38 and CD157 ([Braidy and Liu, 2020](#)). As NAD⁺ is continuously consumed by these enzymes, their activities may become limited when NAD⁺ pools are reduced. The NAD⁺/NADH ratio is a critical component of the redox state of the cell ([Verdin 2015](#)). By some counts, NAD⁺ or the related NADP participates in a quarter of all cellular reactions ([Opitz and Heiland, 2015](#)). There are separate compartments of NAD⁺ in the nucleus, mitochondria, and cytoplasm ([Verdin 2015](#)).

NAD⁺ can be generated from tryptophan *de novo* via multiple enzymatic reactions. However, most tissues rely on the salvage pathways where NAD⁺ is derived from precursors, such as nicotinamide riboside (NR) ([Fletcher and Lavery, 2018](#)). NR can be converted to nicotinamide mononucleotide (NMN) by NR kinases 1/2 (NRK1/2), then converted to NAD⁺ by the enzyme NMNAT. NR can also be converted to nicotinamide (NAM), then converted to NMN by the enzyme NAMPT, then converted to NAD⁺ by NMNAT.

NR is naturally found in some foods (e.g., milk) but in very low quantities (low micromolar range) ([Braidy and Liu, 2020](#)). NR (usually NR chloride) is sold as a dietary supplement alone or in combination with other compounds (e.g., pterostilbene, a sirtuin activator). Because of the wide-ranging role of NAD⁺ in



aging and health conditions, NR and other NAD⁺ precursors have been extensively studied in various conditions, including neurodegenerative diseases, metabolic disorders, cardiovascular diseases, liver disease, and others (reviewed in [Freeberg et al., 2023](#)). Many clinical trials are ongoing.

Neuroprotective Benefit: Laboratory studies have shown neuroprotective benefits with NR. But a few pilot clinical trials completed to date have reported variable outcomes across subjects. Efficacy in various diseases will be evaluated in ongoing trials.

Types of evidence:

- 4 clinical trials (1 in Alzheimer's, 1 in Parkinson's, 1 in ALS, and 1 in healthy people)
- 1 study on human imaging of brain NAD⁺ changes with aging
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No clinical trials have tested the efficacy of NR in preventing dementia or cognitive decline. In a randomized controlled crossover study of 22 healthy older adults, oral NR supplementation (500 mg, twice daily) for 6 weeks did not alter levels of A β 42, p-tau181, total tau, and insulin-related markers (pSer-IRS-1, pAkt, pGSK3 β , and pp70S6K) in neurally-derived extracellular vesicles (NEVs) ([Vreones et al., 2023](#)). However, when the analysis was confined to people with documented NAD⁺ increases ("responders", n=9), NR treatment led to a significant decrease in A β 42 in NEVs. In an exploratory analysis, NR also decreased NEV levels of kinases involved in the insulin cascade (p-JNK, and p-ERK1/2) relative to placebo, suggesting diminished insulin signaling in neurons.

Human research to suggest benefits to patients with dementia:

In a phase 2 double-blind randomized controlled trial of 60 Alzheimer's disease patients, treatment with combined metabolic activators (CMA) that included 1 g of NR, 12.35 g of L-serine, 2.55 g of N-acetylcysteine, and 3.73 g of L-carnitine tartrate was tested ([Yulug et al., 2023](#)). The CMA was dissolved in water and taken orally—1 dose daily for the first 28 days and twice daily thereafter until day 84. CMA treatment showed a significant improvement in cognitive function measured by ADAS-Cog, with a 26% improvement on day 28 (p=0.000003) and a 29% improvement on day 84 (p=0.00001) compared to baseline. The placebo group showed a slight but significant 12% improvement on day 28 (p=0.009) and a



14% improvement on day 84 ($p=0.001$). Although there was no significant difference between groups on day 28 or 84, when the analysis was confined to patients with greater cognitive deficits (higher ADAS-Cog scores), CMA treatment showed a significant improvement in cognitive function on day 84 compared to the placebo group. ($p=0.0073$). These findings suggest that greater responses to the CMA treatment may be observed in more severe Alzheimer's patients. Other primary endpoints, including activities of daily living (ADCS-ADL) and Mini-Mental State Examination (MMSE), were not significantly different between CMA and placebo groups. Brain imaging analysis showed that CMA treatment led to the maintenance of the left whole hippocampal mean volume and the volume of the left molecular layer of the hippocampal body, while significant reductions were observed in the placebo group ($p<0.05$). The left CA1 body and left whole hippocampal body showed a statistical trend for differences between CMA and placebo groups ($p=0.055$ and $p=0.052$, respectively). The CMA was originally developed based on multi-omics data of non-alcoholic fatty liver disease to promote mitochondrial health, alleviate oxidative stress, and improve inflammatory markers ([Zhang et al., 2020](#)). Because the intervention included multiple compounds, it is not possible to pinpoint the specific contribution of NR.

In dermal fibroblasts as well as in induced pluripotent stem cell-differentiated neural progenitors and astrocytes derived from late-onset Alzheimer's patients, administration of NR and caffeine increased the NAD⁺ pool, transiently increased mitochondrial respiration, and altered gene expression related to the NAD⁺ synthesis/consumption pathways ([Ryu et al., 2022](#)). However, extended treatment led to a reversal of the bioenergetic effects. NR and caffeine also failed to reverse the bioenergetic phenotype associated with late-onset Alzheimer's disease.

There are reports of reduced NAD⁺ synthetic enzyme (NMNATs) in Alzheimer's, tauopathy, Parkinson's, and Huntington's disease ([Ali 2013](#)) and, in one late-onset Alzheimer's patient, copy-number variation was reported in the NAMPT gene (involved in NAD⁺ biosynthesis) ([Villega 2014](#)).

In a phase I double-blind randomized controlled trial in 30 newly diagnosed Parkinson's patients, treatment with NR (1,000 mg daily; Niagen) for 30 days led to a significant but variable increase in cerebral NAD⁺ levels (measured by the 31P-MRS and metabolites in the CSF)([Brakedal et al., 2022](#)). Out of 13 patients receiving NR, 10 patients showed an increase in NAD⁺ levels. In a subgroup of patients who showed increased brain NAD⁺ levels, NR treatment also led to a trend for decreased disease rating scale ($p=0.071$; measured by the MDS-UPDRS). Gene set enrichment analyses of muscle tissue showed that NR treatment upregulated KLF2 (associated with decreased adipogenesis) and induced Nrf2, a transcription factor that regulates antioxidant pathways. In peripheral blood mononuclear cells (PBMCs), NR treatment upregulated biological processes including ribosomal, proteasomal, lysosomal,



and mitochondrial (oxidative phosphorylation) pathways. Various other blood biomarkers were assessed, but there were no effects of NR on serum cytokines or the neurodegeneration marker NfL (serum and CSF) when compared to placebo.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

NAD⁺ is a critical and often rate-limiting factor in many aspects of mitochondrial and cellular function including DNA repair by PARPs, widespread acetylation and epigenetic effects by sirtuins, efficient production of ATP, and other pathways (e.g., [Stein & Imai 2012](#)). NAD⁺ levels decline with age as does the ratio of NAD⁺/NADH, with numerous studies suggesting that blunting this decline with NAD⁺ precursors or genetic manipulations can blunt fundamental features of aging. For example, a pilot study reported that NAD⁺ levels and total NAD in the brain are lower in older adults (aged 59-68) than young adults, as measured by an assay using noninvasive magnetic resonance spectroscopy (MRS) imaging ([Zhu 2015](#)). The levels also decline with the high-fat diet but increase with calorie restriction and fasting ([Stein & Imai 2012](#)), leading some to argue that it can function as a calorie restriction mimetic. The brain is particularly vulnerable to the decline in NAD⁺ levels with aging due to the high energetic demand of neurons, leading to impaired energy production (reviewed in [Braidly and Liu, 2020](#)). Restoring NAD⁺ levels may lead to neuroprotection through numerous mechanisms, including reduced oxidative stress, anti-inflammatory effects, inhibition of apoptosis, and amelioration of mitochondrial dysfunction (reviewed in [Campbell 2022](#)).

Cognitive impairment models: In aged mice, NR treatment (mixed in food; 2.5 g/kg food; equivalent to 400-460 mg/kg; Baikai Chemical Technology Co., Hangzhou, China) for 3 months improved short-term spatial memory measured by the novel object recognition test ([Xie et al., 2019](#)). However, there was no treatment effect in the Y-maze test. NR treatment in aged mice also inhibited the activation of astrocytes.

In aged mice, NR treatment increased neural stem cell proliferation and neurogenesis ([Zhang 2016](#)); however, another study reported that NR treatment failed to increase NAD⁺ levels in the brain ([Canto 2012](#)).

In a mouse model of diabetes (induced by high-fat diet), NR treatment (400 mg/kg/day, oral gavage) for 6 weeks improved spatial working memory and recognition memory, while downregulating inflammation biomarkers (IL-1, TNF- α , IL-6, NLRP3 inflammasome, and caspase-1) ([Lee and Yang, 2019](#)). In NR-treated mice, IL-1 expression in the brain was reduced by 50%, and TNF- α and IL-6 levels were



reduced to levels comparable to control mice. NR treatment also significantly reduced the brain expression of APP and PS1, as well as A β .

Alzheimer's disease models: In a transgenic mouse model of Alzheimer's (Tg2576 mice), NR was reported to blunt cognitive deficits and reduce beta-amyloid production via PGC-1 α activation and increased degradation of BACE1 through ubiquitination and proteasomal pathways ([Gong 2013](#)). Another study in Alzheimer's transgenic mice (APP/PSEN1 mice) suggested that treatment with NR before the onset of symptoms decreased plaque number, improved cognition, and increased mRNA and protein levels of the mitochondrial stress response and oxidative phosphorylation ([Sorrentino et al, 2017](#)).

In the brains of 3xTgAD/Pol β +/- mice, NAD⁺/NADH ratio is significantly reduced, indicating impaired cerebral energy metabolism ([Hou et al., 2018](#)). In 3xTgAD/Pol β +/- mice, supplementation of NR (12 mM in drinking water) for 3 months starting at 16 to 18 months of age restored the NAD⁺/NADH ratio. NR treatment also lessened p-tau pathology, DNA damage, neuroinflammation, and apoptosis of hippocampal neurons, while improving cognitive function (Morris water maze, object recognition, Y-maze, and fear conditioning) and increasing the activity of SIRT3 in the brain. NR treatment did not impact A β accumulation in these mice.

In the brains of APP/PS1 mice with amyloid pathology, levels of NAD⁺ are reduced and markers of inflammation are increased ([Hou et al., 2021](#)). In these mice, NR treatment (12 mM in drinking water; ChromaDex) for 5 months increased brain NAD⁺ levels, improved cognitive functions (measured by the Morris water maze and Y-maze test), improved synaptic plasticity (measured by LTP), reduced expression of proinflammatory cytokines (TNF- α , IL-1 β , CXCL1/KC) and apoptosis (caspase-1), and decreased the activation of microglia and astrocytes. NR treatment also reduced NLRP3 inflammasome expression, DNA damage, apoptosis, and cellular senescence in the brain. The cyclic GMP-AMP synthase stimulator of interferon genes (cGAS-STING), which is associated with DNA damage, inflammation, and cellular senescence, was elevated in APP/PS1 mice but levels were normalized by NR treatment. NR downregulates neuroinflammation, in part, through the cGAS-STING-dependent pathway. NR also increased mitophagy, thereby reducing mitochondrial DNA release into the cytoplasm, and reduced STING-dependent neuroinflammation. NR treatment also promoted the neuroprotective microglial phenotype, promoting microglial phagocytosis of A β .

In APP/PS1 mice, NR treatment (mixed in food; 2.5 g/kg food; equivalent to 400-460 mg/kg; Baikai Chemical Technology Co., Hangzhou, China) for 3 months improved contextual fear memory, but not



short-term spatial memory (novel object recognition) or Y-maze test ([Xie et al., 2019](#)). NR treatment inhibited the accumulation of A β in the cortex (but not in the hippocampus) and the migration of astrocytes to A β .

Amyotrophic lateral sclerosis (ALS): In a double-blind randomized controlled trial of 32 patients with ALS (20 study completers), treatment with EH301 (NR+pterostilbene, 1,200 mg; Elysium Health) for 4 months resulted in significant improvements in the ALS functional rating scale-revised (ALSFRS-R) score ($p < 0.01$), pulmonary function, muscular strength, and in skeletal muscle/fat weight ratio compared to the placebo group ([de la Rubia et al., 2019](#)). NR and pterostilbene are thought to work synergistically to increase NAD⁺ levels and promote sirtuin activity. In the clinical trial, there were some baseline imbalances between the EH301 and placebo groups; the Medical Research Council (MRC) grading scale index and surface electromyogram (EMG) measurements in the right tibia muscles were lower in the EH301 group compared to the placebo group. With regards to ALSFRS-R score, patients in the placebo group had deteriorated significantly relative to their baseline measurements ($p < 0.05$), corresponding to a 3.0- and 5.5-point decline at the 2- and 4-month evaluation, respectively. Everyone in the placebo group except one patient showed disease progression. In contrast, the EH301 group showed a significant improvement in ALSFRS-R score at the 2- and 4-month evaluation, corresponding to a 3.4- and 2.5-point improvement, respectively. Out of 10 patients treated with EH301, 7 showed improvement in the ALSFRS-R scores. With regards to the secondary outcome, MRC grading scale, EH301 treatment for 2 months showed a significant improvement compared to placebo, despite the lower baseline index in the EH301 group; the EH301 group improved by 9.6 points while the placebo group declined by 10.0 points. This was also significant at 4 months, when the difference between EH301 and placebo groups were 23.2 points ($p < 0.01$).

Forced vital capacity (FVC) was significantly improved with EH301 treatment relative to baseline ($p < 0.05$) and relative to placebo ($p < 0.01$) ([de la Rubia et al., 2019](#)). After 2 months of treatment, the EH301 group had a 6.1% increase in FVC, while the placebo group experienced a 3.8% decline. After 4 months of treatment, there was a difference of 19.4% in FVC between EH301 and placebo groups. EH301 treatment for 4 months also led to a significant increase in electrical activity within the right and left tibial muscles relative to baseline ($p < 0.01$ for both) and significantly greater electrical activities in the left biceps, right and left triceps, and left tibial muscles compared to the placebo group. After 2 months of treatment, the EH301 group had an increase in electrical activity in 5 out of 8 muscle groups. After 4 months of treatment, a significant EH301 treatment effect (compared to placebo) was observed for the right and left triceps and the right and left tibial muscles ($p < 0.01$ for all). EH301 treatment also resulted in a significant decrease in fat and a significant increase in skeletal muscle weights, which were

opposite what was observed in the placebo group. These findings suggest that EH301 treatment may improve muscular strength in ALS patients.

After the completion of the ALS trial, all participants were given the option to continue treatment on an open-label extension study, and all participants elected to continue taking EH301 ([de la Rubia et al., 2019](#)). After 1-year post-randomization to EH301, patients did not show significant deterioration in the ALSFRS-R score or muscle function (measured by the MRC grading scale). Also, 6 of the 8 muscle groups investigated (using EMG) did not show deterioration. There was, however, an 11.5% reduction in FVC, suggesting some decline in pulmonary function, though this reduction in FVC at 1-year is less than the reduction in FVC observed in the placebo group at 4 months (16.7% reduction).

In a mouse model of ALS (SOD1G93A mice), treatment with NR+pterostilbene (185 mg/kg of NR orally; 30 mg/kg of pterostilbene in feed) started 4 weeks after birth significantly increased survival, decreased microgliosis/astrogliosis, increased Nrf2-dependent antioxidant defense, increased sirtuin 1 and 3 activity, and ameliorated spinal motor neuron degeneration and ALS-associated loss of neuromotor functions ([Obrador et al., 2021](#)).

Ischemic injury models: In a mouse model of ischemic injury (middle cerebral artery occlusion), NR treatment (300 mg/kg, i.p.) started 20 minutes after reperfusion rescued learning and memory (measured by the Morris water maze), decreased hippocampal infarct volume, and reduced neuronal loss and apoptosis in the hippocampus ([Cheng et al., 2022](#)). In the hippocampus of NR-treated mice, sirtuin-1 activation, NAD⁺ content, and ATP production were increased.

APOE4 interactions: Unknown.

Aging and related health concerns: NR increases blood NAD⁺ levels but does not reliably increase NAD⁺ levels in tissues of interest. NR has shown little effect in improving clinically relevant outcomes such as insulin sensitivity and physical function.

Types of evidence:

- 1 meta-analysis of NAD⁺ precursor supplementation on glucose and lipid biomarkers
- 9 clinical trials
- 3 studies examining NAD⁺ levels in elderly humans
- Numerous laboratory studies

It has been suggested that age-related decreases in NAD⁺ and the NAD⁺/NADH ratio advance aging and age-related diseases because of widespread influence on mitochondrial function, metabolism, senescence, epigenetics, and signaling pathways like sirtuins ([Imai & Guarente 2014](#)). Age-related decreases in NAD⁺ has been reported in rodents and (by small studies) in humans in red-blood cells ([Chaleckis 2016](#)), liver ([Zhou 2016](#)), and the brain ([Zhu 2015](#)). In rodents, NAD⁺ levels decline with the high-fat diet but increase with calorie restriction or fasting ([Stein & Imai 2012](#)), leading some to argue that it can function as a calorie restriction mimetic. Cell culture studies report that the effects of calorie restriction on replicative lifespan require an increase in NAD⁺ (eg. [Yang 2015](#)).

Lifespan: NO BENEFIT IN NIA ITP STUDY

The National Institute on Aging Interventions Testing Program (NIA ITP) is designed to test compounds that are purported to extend lifespan and/or delay onset of age-related diseases. This program is a collaborative effort that uses 1) parallel studies in males and females at 3 different sites, 2) genetically heterogeneous mice (UM-HET3 mice) to guard against conclusions based on a single inbred genotype, and 3) enough samples to provide statistical power. In UM-HET3 mice, treatment with NR (1,000 mg per kg diet; ChromaDex) started at 8 months of age failed to increase lifespan in either males or females ([Harrison et al., 2021](#)). In a separate smaller study, 6- to 10-month-old UM-HET3 mice were fed NR (1,000 mg per kg diet) for 6-6.5 weeks. Oddly, NR treatment resulted in lower levels of nicotinamide and NR in the cortex (p=0.004 and 0.03, respectively), but not in the liver. NR treatment also led to a lower ratio of NAD⁺ to NADH in the cortex (p=0.012).

In a mouse model of ALS (SOD1G93A mice), treatment with NR+pterostilbene (185 mg/kg of NR orally; 30 mg/kg of pterostilbene in feed) started 4 weeks after birth significantly increased survival, while ameliorating ALS-associated loss of neuromotor functions ([Obrador et al., 2021](#)).

Muscle/physical performance: MIXED FINDINGS

In a double-blind randomized, placebo-controlled clinical study in 120 healthy individuals between the ages of 60 to 80 years, NR+pterostilbene treatment (regular dose: 250 mg NR, 50 mg pterostilbene, daily, or double dose: 500 mg NR, 100 mg pterostilbene, daily; Basis, Elysium Health) over 8 weeks significantly increased whole blood NAD⁺ levels ([Dellinger et al, 2017](#)). The double dose (but not the regular dose) NR+pterostilbene treatment improved mobility, measured by the 6-minute walk test and 30-second chair test.



In a double-blind controlled cross-over study of 12 young and 12 old people, NR supplementation (500 mg, NAD+ Cell Regenerator™, Life Extension®, Fort Lauderdale, US) increased NADH (by 51% in young, by 59% in old) and NADPH levels (by 32% in young and by 38% in old), decreased F2-isoprostanes (oxidative stress marker) by 18%, and showed a tendency to increase the anti-oxidant, glutathione ($p=0.078$) exclusively in old people ([Dolopikou et al., 2020](#)). Old subjects had higher resting F2-isoprostane levels compared to young subjects. In old subjects, NR treatment failed to improve VO₂max and concentric peak torque, but improved isometric peak torque by 8% ($p=0.048$) and the fatigue index by 15% ($p=0.012$). Also in old subjects, NR supplementation increased lactate dehydrogenase levels compared to placebo ($p=0.024$) and induced a larger increase in blood lactate levels at the end of the fatigue test ($p=0.037$). These changes were not seen in young subjects. In young subjects, NR supplementation showed mixed effects on antioxidant proteins: NR increased SOD levels compared to placebo ($p=0.013$), but decreased GPx levels compared to placebo ($p=0.035$) and showed no effects on catalase levels. In young subjects, NR supplementation failed to improve any physiological measures (VO₂ max, concentric peak torque, isometric peak torque, fatigue).

In a double-blind randomized controlled crossover study of 12 aged men (70-80 years old), NR treatment (250 mg capsules, 2 in the morning, 2 in the evening; ChromaDex) for 21 days resulted in increased muscle NAD+ metabolome (2-fold increase in nicotinic acid adenine dinucleotide and increased nicotinamide clearance products), and downregulation of energy metabolism and mitochondrial pathways, but no significant changes in strength (hand-grip strength or relative strength) or skeletal muscle mitochondrial bioenergetics (complex I- and II-mediated oxidative phosphorylation, maximal respiratory capacity, citrate synthase activity, mitochondrial content, and mtDNA)([Elhassan et al., 2019](#)). NR treatment increased NMN and NAD+ levels in the blood but not in the muscle. NR treatment decreased circulating inflammatory cytokines (IL-6, IL-5, and IL-2, but not significant for TNF- α).

In a monozygotic twin study, 20 twin pairs with BMI discordance were enrolled and treated with escalating doses of NR (250 to 1,000 mg/day) for 5 months ([Lapatto et al., 2023](#)). Overall, NR did not ameliorate adiposity or metabolic health. NR treatment boosted whole-blood NAD+ levels by 2.3-fold in all twins from the BMI-discordant pairs. NR also significantly increased the levels of NMN and N-methyl-4-pyridone-5-carboxamide (Me4py; by 8-fold), suggesting an enhanced elimination of NR's degradation product via methylation. In muscle samples, NR treatment increased mitochondria by 14% (in the intermyofibrillar region of type 1 muscle fibers), increased the cross-sectional area of muscle fiber covered by mitochondria, and increased mitochondrial DNA amount by 30%. NR treatment also led to an increased muscle expression of sirtuin 1, estrogen-related receptor α , transcription factor A (TFAM),



mitofusin 2, and oxidative phosphorylation subunits (cytochrome c oxidase subunit 4, ATP synthase- α), but downregulated complex I subunit. Together, these expression profiles suggest that NR increased muscle biogenesis. The heavier and leaner twins exhibited similar responses to NR with regards to muscle mitochondrial number, mitochondrial DNA, and gene expression, except changes in sirtuin 1 and 3 tended to differ between heavier and leaner cotwins. In white adipose tissue, NR did not significantly influence mitochondrial DNA or gene expression.

In a randomized controlled trial of 32 old people (aged 55-80) subjected to experimental muscle injury, treatment with NR and pterostilbene (500 mg NR and 100 mg pterostilbene, twice daily, orally; Basis, Elysium Health) started 14 days before injury and continued until 30 days after injury did not significantly alter muscle stem cell content, proliferation, cell size, muscle fiber area, central nuclei, or embryonic myosin heavy chain (a protein expressed during muscle development)([Jensen et al., 2022](#)). Whole-blood NAD⁺ levels were increased after NR+pterostilbene treatment, but skeletal muscle NAD⁺ levels were not. Functional recovery, measured as maximal voluntary contractions (MVC) and rate of force development (RFD) of the quadriceps femoris muscle, were decreased after injury but unaffected by the NR+pterostilbene treatment. Thus, NR+pterostilbene treatment did not improve recruitment of the muscle stem cell pool or promote skeletal muscle regeneration after injury.

[Frederick et al \(2016\)](#) reported decreased levels of NAD⁺ and ATP synthesis in an animal model with NAMPT (an enzyme important in the NAD⁺ salvage pathway) knocked out in skeletal muscles. In old mice, there were muscular deficiencies and increased expression of p16ink4a in skeletal muscles, suggesting a senescent phenotype. NR treatment reversed the muscle pathology.

Obesity/metabolic disorders: MIXED, POTENTIAL HARM

In a meta-analysis of NAD⁺ precursor supplementation (NR, NMN, NAM, and nicotinic acid) that included a total of 40 studies, NR did not statistically affect fasting glucose levels, though nicotinic acid significantly increased plasma glucose levels ([Zhong et al., 2022](#)).

In a double-blind randomized controlled trial of 40 obese and insulin-resistant men, NR treatment (1,000 mg, twice daily, orally; Niagen, ChromaDex) for 12 weeks did not improve insulin sensitivity, endogenous glucose production, glucose disposal, or oxidation, and had no effect on resting energy expenditure, lipolysis, oxidation of lipids, or body composition (total body mass, lean mass, total fat mass, fat %, or distribution of visceral and subcutaneous adipose tissue)([Dollerup et al., 2018](#)). A follow-up analysis of the same trial reported that NR treatment did not affect respiration, distribution, or quantity of muscle mitochondria ([Dollerup et al., 2020](#)). NR treatment decreased protein levels of NAMPT (an essential



NAD⁺ biosynthetic enzyme) in skeletal muscle by 14%, but steady-state NAD⁺ levels and gene expression and protein levels of other NAD⁺ biosynthetic enzymes remained unchanged. NR treatment did not affect respiratory capacity of skeletal muscle mitochondria, abundance of mitochondrial associated proteins, mitochondrial fractional area, or network morphology. NR supplementation does not appear to improve skeletal muscle mitochondria in obese and insulin-resistant men.

In a double-blind randomized controlled crossover study of 12 aged men, NR treatment (250 mg capsules, 2 in the morning, 2 in the evening; ChromaDex) for 21 days did not significantly alter body weight, blood pressure, lipid profile, fasting glucose, insulin, oral glucose tolerance test, or homeostatic model assessment of insulin resistance (HOMA-IR)([Elhassan et al., 2019](#)).

In a monozygotic twin study, 20 twin pairs with BMI discordance were enrolled and treated with escalating doses of NR (250 to 1,000 mg/day) for 5 months, which led to a 2.3-fold increase in whole-blood NAD⁺ levels ([Lapatto et al., 2023](#)). NR treatment led to an increase in body weight (by ~3 kg) and whole-body fat percentage in both the leaner and heavier twins compared to baseline. NR treatment also led to an upregulation of PPAR γ , the essential transcription factor controlling adipogenesis. NR treatment also led to a decrease in insulin sensitivity, measured by glucose, insulin, C-peptide, and HOMA-IR, while remaining within normal reference ranges in all twins. The leaner cotwins had an increased HbA1c compared to the heavier cotwins after NR treatment. Basal metabolic rate was significantly increased due to the increase in body weight, though no marked changes in food intake or physical activity were seen. Also, NR slightly but significantly increased the levels of total plasma homocysteine (an amino acid linked to heart disease and dementia), especially in the leaner counterparts, but not beyond the normal range. There were no significant effects of NR on lean tissue (muscle) mass, bone mass, liver fat content, or adipocyte number, diameter, volume, and weight. NR treatment showed no changes in blood lipid values except for the small, clinically not meaningful decrease in high-density lipoprotein and triglycerides. There were also no significant effects of NR on blood pressure, pulse rate, or the inflammation marker, hsCRP. In BMI-concordant twin pairs, NR's effects on body composition and metabolic health did not significantly differ from the effects of placebo.

Hyperlipidemia: NO EFFECT IN HEALTHY PEOPLE

In a meta-analysis of NAD⁺ precursor supplementation (NR, NMN, NAM, and nicotinic acid) that included a total of 40 studies, NR did not statistically affect levels of triglyceride, total cholesterol, LDL cholesterol, or HDL cholesterol, though nicotinic acid significantly reduced triglyceride, total cholesterol, and LDL cholesterol and increased HDL cholesterol ([Zhong et al., 2022](#)). Effects of NR on lipids cannot be ruled out due to the relatively few studies included in the meta-analysis. Overall, this meta-analysis



found that NAD⁺ precursors have little effect in healthy people but may have greater benefits in patients with cardiovascular disease and dyslipidemia.

In a double-blind randomized controlled trial of 40 obese and insulin-resistant men, NR treatment (1,000 mg, twice daily, orally; Niagen, ChromaDex) for 12 weeks did not affect total cholesterol, HDL, or LDL, but led to an increase in triglycerides (from 1.5 ± 0.1 mM/L at pretreatment to 1.8 ± 0.2 at posttreatment, but within normal reference range of < 2 mmol/L)([Dollerup et al., 2018](#)).

Cardiovascular diseases: UNCLEAR

In a non-randomized clinical trial of 30 patients with heart failure (reduced ejection fraction), NR treatment (1,000 mg twice daily) for 12 weeks doubled whole-blood NAD⁺ levels, and the magnitude of increase correlated with increases in peripheral blood mononuclear cell basal and maximal mitochondrial respiration, and decreases in inflammation (NLRP3 expression)([Wang et al., 2022](#)). Correlations between the extent of NAD⁺ level increase and other proinflammatory markers (IL-1 β , IL-6, IL-18, and TNF- α) were not significant, though directionally similar to NLRP3. Exploratory analyses reported a lack of effect of NR on functional capacity (6-minute walk test), quality of life, left ventricular (LV) systolic function, LV filling pressure, LV end-diastolic volume, and LV end-systolic volume. It is currently not known whether oral supplementation of NR increases NAD⁺ levels in the myocardium. This question is being addressed in an ongoing clinical trial of NR pretreatment in patients receiving LV assist device implantation (NCT04528004).

A double-blind placebo-controlled randomized cross-over study in 24 healthy middle-aged and older adults reported that NR (500 mg twice daily) for 6 weeks resulted in lowering of systolic blood pressure (by 9 mmHg) in a subset of patients with stage 1 hypertension (120-139/80-89), but it was an exploratory analysis and no statistical inferences could be made ([Martens et al., 2018](#)).

In a double-blind randomized, placebo-controlled clinical study in 120 healthy individuals between the ages of 60 to 80 years, NR+pterostilbene treatment (regular dose: 250 mg NR, 50 mg pterostilbene, daily; Basis, Elysium Health) over 8 weeks resulted in an increase in total cholesterol with the regular dose NR+pterostilbene on day 30 (by 3%) and day 60 (by 3.5%), compared to placebo ([Dellinger et al., 2017](#)). The increase in cholesterol was more pronounced in people with higher BMI (overweight category, 25-32). Larger increases in total cholesterol and LDL cholesterol were observed in the double dose NR+pterostilbene group (500 mg NR, 100 mg pterostilbene, daily).

Liver disease: LITTLE BENEFIT

In a double-blind randomized controlled trial of 111 patients with non-alcoholic fatty liver disease (NAFLD), treatment with NR+pterostilbene (250 mg NR and 50 mg pterostilbene or 500 mg NR and 100 mg pterostilbene daily) for 6 months did not significantly alter the primary endpoint of hepatic fat fraction compared to placebo ([Dellinger et al., 2022](#)). Of prespecified secondary outcomes, the lower-dose NR+pterostilbene (250 mg/50 mg) resulted in a decrease in liver enzymes ALT and GGT and the toxic lipid ceramide 14:0 when compared to placebo. No effects were observed with the higher-dose NR+pterostilbene (500 mg/100 mg). Total cholesterol, triglycerides, and LDL levels were not significantly altered after 6 months of NR+pterostilbene treatment.

Kidney disease: UNKNOWN

In a double-blind randomized controlled trial of 24 hospitalized patients with acute kidney injury, treatment with escalating doses of NR+pterostilbene (250/50 mg, 500/100 mg, 750/150 mg, and 1,000/200 mg; twice daily for 2 days at each dose; Basis, Elysium) showed a trend for increase in blood NAD⁺ levels but only the dose of 500 mg NR and 100 mg pterostilbene taken twice daily for 2 days resulted in a significant increase in NAD⁺ levels (by 47%)([Simic et al., 2020](#)). Across all doses, NR+pterostilbene increased NAD⁺ levels by 37% at 48 hours (p=0.002). However, there was a wide interindividual variability in NAD⁺ levels posttreatment. In contrast, placebo-treated patients showed a 50% reduction in whole-blood NAD⁺ levels at 48 hours compared to baseline.

Glaucoma: UNKNOWN

Glaucoma is an optic neuropathy characterized by the death of retinal ganglion cells, which leads to progressive visual field loss. Currently, the only approved treatment to prevent or delay progression in glaucoma is to decrease intraocular pressure. In a review of NAD⁺ precursors as potential treatments for glaucoma, authors discuss their roles in protecting against reactive oxygen species and maintenance of mitochondrial function, reducing the vulnerability of retinal ganglion cells to external stressors ([Silva et al., 2023](#)). NR supplementation in glaucoma patients is currently being tested in a clinical trial ([Leung et al., 2022](#)).

Peripheral neuropathy: POTENTIAL BENEFIT BASED ON RODENT MODELS

In a mouse model of peripheral neuropathy (induced by cisplatin), NR treatment (500 mg/kg, i.p., daily) alleviated neuropathy by protecting differentiated dorsal root ganglion neurons ([Acklin et al., 2022](#)). Interestingly, neuroprotection mediated by SIRT2 activation did not inhibit the cisplatin-mediated cytotoxic activity against cancer cells, and in fact, appeared to sensitize cancer cells to cisplatin.



In a rat model of peripheral neuropathy (tumor-bearing rats receiving paclitaxel), NR treatment (200 mg/kg, daily, oral gavage; ChromaDex) for 28 days significantly decreased hypersensitivity to tactile and cool stimuli, as well as place-escape avoidance behaviors ([Hamity et al., 2020](#)). Survival was 90+% in NR-treated rats after 28 days, while it was around 50% in vehicle-treated rats. NR treatment also blunted the loss of intraepidermal nerve fibers in tumor-bearing rats, as well as in tumor-naive rats. Similar to the study above in mice, NR treatment decreased tumor growth (measured by Ki67-positive tumor cells) in rats receiving chemotherapy. NR treatment did not alter tumor growth in rats that were not treated with paclitaxel. Thus, NR may enhance tumor-suppressing effects of chemotherapy.

Safety: NR has GRAS status and is considered safe up to 300 mg/day in healthy adults. Clinical trials have generally shown incidences of adverse events that were comparable to placebo.

Types of evidence:

- 10 clinical trials
- 2 reports from the European Food Safety Authority
- 1 rat oral toxicity study

In 2015, ChromaDex's NR product received new dietary ingredient (NDI) status from the FDA for use in supplements with a daily dose of 180 mg ([ProactiveInvestors.co.uk](#)). In August 2016, NR chloride received generally recognized as safe (GRAS) status in the US for addition to vitamin waters, protein shakes, nutrition bars, gum, chews, and powdered beverages as a source of vitamin B3 (with the intended maximum use level of 0.027% by weight) ([FDA.gov](#)). The NDI status was updated in 2017 with a new proposed intake level of 300 mg daily ([NutritionalOutlook.com](#)).

In 2019, the European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods and Allergens concluded that NR chloride is safe up to 300 mg/day for healthy adults, and up to 230 mg/day for pregnant and lactating women ([EFSA Panel on Nutrition, 2019](#)). The production process, composition, specifications, batch-to-batch variability, and stability of NR did not raise safety concerns. NR is obtained through chemical synthesis and contains over 90% NR chloride, with the remaining components being residual solvents, reaction by-products, and degradation products. NR was found to be stable for at least 36 months when stored under ambient conditions. Animal and human data showed that NR administration contributed to the nicotinamide body pool. No safety concerns were raised based on human studies and no concerns were seen regarding genotoxicity, based on bacterial reverse

mutagenicity test, the *in vivo* mammalian erythrocyte micronucleus test, and the *in vitro* mammalian chromosome aberration test.

In a 90-day oral toxicity study Sprague Dawley rats, NR administration (300, 500, and 1,200 mg/kg/day, orally) did not cause any mortality or clinical observations attributable to NR ([Marinescu et al., 2020](#)). A small but statistically significant decrease in body weight (by 13%) was observed on day 92 in male (but not female) rats at the highest dose (1,200 mg/kg/day). There were no adverse changes in clinical observations, ophthalmological examinations, hematology, coagulation, urinalysis, and macro- and microscopic histopathology findings with NR administration. The no-observed-adverse-effect-level (NOAEL) was determined to be 500 mg/kg/day for male rats and 1,200 mg/kg/day for female rats. Based on these findings, the human upper limit can be derived using the 100-fold safety factor, accounting for a 10-fold human variability and 10-fold extrapolation from rodents to humans, while using the average human weight of 60 kg. The upper limit in humans is 300 mg/day for men and 720 mg/day for women. A NOAEL of 300 mg/kg/day was derived from other repeated dose toxicity studies with rats and dogs ([EFSA Panel on Nutrition, 2021](#)). A NOAEL of fertility and reproductive performance of 675 mg/kg/day in males and 1,088 mg/kg/day in females and a NOAEL for maternal and embryo/fetotoxicity of 325 mg/kg/day were derived from reproductive and developmental toxicity studies in rats.

In 2021, EFSA Panel on Nutrition, Novel Foods and Allergens assessed the safety and extension of use of NR in 'meal replacement products' and 'nutritional drink mixes' at levels up to 300 mg/day for the general population, and in 'food for special medical purposes' and 'total diet replacement for weight control' at levels up to 500 mg/day in adults ([EFSA Panel on Nutrition, 2021](#)). Due to the lack of tolerable upper intake level (UL) for nicotinamide in infants and the narrow margin of exposure between the estimated intake in infants and the lower confidence bound of the benchmark doses estimated by modelling, the Panel concludes that the safety of NR has not been established for use in 'meal replacement products' and 'nutritional drink mixes' under the proposed conditions of use. For 'food for special medical purposes' and 'total diet replacement for weight control', the proposed maximum use level corresponds to an intake of 210 mg nicotinamide per day, which is below the current upper limit for nicotinamide of 900 mg/day for adults. The Panel considers that the NR is as safe as pure nicotinamide for use in 'food for special medical purposes' and 'total diet replacement for weight control'. However, the Panel noted that intakes of nicotinamide (or its precursors) at levels that are substantially higher than the physiological requirement might cause adverse effects, based on experimental data. Several possibilities have been proposed by which high intake of nicotinamide and/or its precursors could lead to adverse health effects, including 1) through affecting methyl group transfers in a variety of metabolic pathways and epigenetic mechanisms; 2) through modulating NAD+

metabolism; 3) through an elevated circulation and renal excretion of nicotinamide metabolites; and 4) the potential toxicity of these metabolites.

Clinical studies in healthy people:

A randomized three-arm cross over trial (100mg, 300mg, and 1000mg NR) in 12 healthy adults reported that NR increased levels of many NAD⁺ metabolites and suggested that nicotinic acid adenine dinucleotide (NAAD) is a unique biomarker for NR supplementation, as it is below detectable levels without supplementation ([Trammell et al, 2016](#)).

In the largest double-blind randomized controlled trial to date, 140 healthy overweight adults (40-60 years old) were treated with NR (100, 300, and 1000 mg; NIAGEN) or placebo for 8 weeks ([Conze et al., 2019](#)). NR dose-dependently and significantly increased whole-blood NAD⁺ after 2 weeks by 22%, 51%, and 142% compared to baseline with 100, 300, and 1000 mg doses of NR, respectively. At 8 weeks, NAD⁺ levels were increased compared to baseline by 10%, 48%, and 139%, respectively. There were no significant differences in adverse events between the NR and placebo-treated groups and there were no serious adverse events. Of the reported adverse events, those that were deemed possibly related to NR included leg pain, high blood pressure, nausea (2), muscle pain, sore back, and muscle soreness; all of these were mild in intensity. There were no reports of flushing, which is common with other NAD⁺ precursors (e.g., niacin, nicotinic acid). NR also did not elevate LDL cholesterol or homocysteine levels, and there were no significant effects regarding clinical chemistry parameters, blood pressure, mean heart rate, or body weight.

In a non-randomized open-label pharmacokinetic study of 8 healthy volunteers, an escalating dose of NR (250 mg daily up to 1000 mg twice daily) over an 8-day period was well-tolerated with no adverse events ([Airhart et al., 2017](#)). The increase in NR levels was highly variable, ranging from -10% to +127%. NAD⁺ abundance in whole blood (measured by mass spectrometry) increased 2-fold on average. Slight but significant decrease was seen for hematocrit (-2%), hemoglobin (-0.4 g/dL), and platelet count (-20,000/ μ L). There were no significant changes in blood pressure, body temperature, body weight, white blood cell count, lactate dehydrogenase, aspartate aminotransferase, sodium, chloride, urea nitrogen, creatinine, or white blood cell differential.

A double-blind placebo-controlled randomized cross-over study in 24 healthy middle-aged and older adults reported that NR (500 mg twice daily) for 6 weeks was safe and well-tolerated with no serious adverse events ([Martens et al, 2018](#)). All self-reported adverse events were mild in severity and included nausea, flushing, leg cramps, and increased bruising during the NR condition, and headache, skin rash,



flushing, fainting, and drowsiness during the placebo condition. There were no meaningful differences between NR and placebo for hematology, blood chemistry (e.g., markers of renal function and liver enzymes), or blood lipid profiles.

In a double-blind randomized controlled crossover study of 12 aged men (70-80 years old), NR treatment (250 mg capsules, 2 in the morning, 2 in the evening; ChromaDex) for 21 days was well-tolerated, with no adverse effects regarding hematological or clinical biochemistry safety parameters ([Elhassan et al., 2019](#)). There were 4 participants (33.3%) who self-reported a noticeable increase in libido while on NR, while there were no such reports on placebo.

In a monozygotic twin study, 20 twin pairs with BMI discordance were enrolled and treated with escalating doses of NR (250 to 1,000 mg/day) for 5 months, which was well-tolerated, though led to a decline in muscle satellite cell number and possibility for impaired glucose metabolism ([Lapatto et al., 2023](#)). Side effects of NR included muscle pain, gastrointestinal irritation, sweating, nausea, and headache but not cutaneous flushing typically caused by niacin. No side effects were reported by placebo-treated twins. There were no significant alterations in safety parameters including the kidney function marker creatinine, liver enzymes, and complete blood count.

In a double-blind randomized, placebo-controlled clinical study in 120 healthy individuals between the ages of 60 to 80 years, NR+pterostilbene treatment (regular dose: 250 mg NR, 50 mg pterostilbene, daily, or double dose: 500 mg NR, 100 mg pterostilbene, daily; Basis, Elysium Health) over 8 weeks was well tolerated with no serious adverse events ([Dellinger et al, 2017](#)). There were no significant differences in the incidence of adverse events across treatment groups. There was one adverse event mild in intensity possibly related to the NR+pterostilbene at the regular dose (nausea) and 5 adverse events possibly related to the double dose NR+pterostilbene (moderate fatigue, mild headache, moderate dyspepsia, moderate abdominal discomfort, and diarrhea), and one adverse event possibly related to the placebo product (pruritus). Whole blood NAD⁺ levels increased at the regular dose (by ~40%) and with double the regular dose (by ~90%) at 4 weeks. Levels were maintained with the regular dose over 8 weeks. In the double dose, levels were initially higher after four weeks (by ~90%) and returned to levels seen with the regular dose (~55%) after 8 weeks. There were no changes in liver function tests except a significant decrease was observed in alanine transaminase in the regular dose NR+pterostilbene group, suggesting improvement in liver function. There were no changes in blood pressure or hematology and clinical chemistry parameters. There was an increase in total cholesterol with the regular dose NR+pterostilbene on day 30 (by 3%) and day 60 (by 3.5%), compared to placebo. The increase in cholesterol was more pronounced in people with higher BMI (overweight category, 25-

32). Larger increases in total cholesterol and LDL cholesterol were observed in the double dose NR+pterostilbene group. The double dose NR+pterostilbene group showed improvements in mobility, measured by the 6-minute walk test and 30-second chair test.

In a randomized controlled trial of 32 old people (aged 55-80) subjected to experimental muscle injury, treatment with NR and pterostilbene (500 mg NR and 100 mg pterostilbene, twice daily, orally; Basis, Elysium Health) started 14 days before injury and continued until 30 days after injury was well-tolerated ([Jensen et al., 2022](#)). Two participants in the placebo group reported constipation. Transient reflux and transient loose stools were reported by one subject each in the NR+pterostilbene group. These adverse events were all mild in severity. Blood biochemistry showed no difference between treatment and placebo after 14 days.

Clinical trials in patient populations:

In a double-blind randomized controlled trial of 40 obese and insulin-resistant men, NR treatment (1,000 mg, twice daily, orally; Niagen, ChromaDex) for 12 weeks did not result in any serious adverse events and safety blood test results were normal ([Dollerup et al., 2018](#)). There were reports of mild adverse reactions from 4 participants in the NR group (pruritus, excessive sweating, bloating, and transient changes in stool) and from 2 participants in the placebo group (reflux and periodic loose stools).

In a non-randomized clinical trial of 30 patients with heart failure (reduced ejection fraction), NR treatment (1,000 mg twice daily) for 12 weeks appeared to be safe and well-tolerated ([Wang et al., 2022](#)). There were no between-group differences in treatment-emergent adverse events. There was one serious adverse event in a participant randomized to placebo (hospitalization for heart failure exacerbation and pancreatitis). A few out-of-range lab values were seen. One participant in the NR group had creatinine levels above 1.5x but under 3x the baseline on 2 occasions. One participant in the placebo group had alanine aminotransferase levels over 3x but under 5x the baseline. No significant changes in other laboratory or clinical variables were observed.

In a phase 2 double-blind randomized controlled trial of 60 Alzheimer's disease patients, an 84-day treatment with combined metabolic activators (CMA) that included 1 g of NR and other compounds resulted in no severe adverse events ([Yulug et al., 2023](#)). There were 5 patients in the treatment arm who reported adverse events: 2 patients had diarrhea, 1 had nausea, 1 had dizziness, and 1 had pruritis. Also, CMA treatment for 84 days resulted in reduced alanine aminotransferase (ALT), uric acid, platelets, basophil % and absolute numbers of basophil and neutrophil compared to baseline. These changes in clinical parameters are generally considered to be improvements.

In a double-blind randomized controlled trial of 32 patients with ALS (20 study completers), treatment with NR+pterostilbene (1,200 mg; Elysium Health) for 4 months did not result in any adverse events attributed to the investigational product ([de la Rubia et al., 2019](#)). Adverse events including mild headache, moderate dyspepsia, and moderate diarrhea were reported by 4 participants in the placebo group and 5 participants of the NR+pterostilbene group.

In a double-blind randomized controlled trial of 111 patients with non-alcoholic fatty liver disease (NAFLD), treatment with NR+pterostilbene (250 mg NR and 50 mg pterostilbene or 500 mg NR and 100 mg pterostilbene daily) for 6 months resulted in adverse events that were mostly gastrointestinal issues ([Dellinger et al., 2022](#)). There were no severe adverse events.

In a double-blind randomized controlled trial of 24 hospitalized patients with acute kidney injury, treatment with escalating doses of NR+pterostilbene (250/50 mg, 500/100 mg, 750/150 mg, and 1,000/200 mg; twice daily for 2 days at each dose; Basis, Elysium) was well-tolerated and did not alter any safety laboratory tests, including creatinine, estimated glomerular filtration rate (eGFR), electrolytes, liver function tests (ALT, AST, ALP), and blood counts ([Simic et al., 2020](#)). Three out of 20 patients receiving NR+pterostilbene at the two lower doses reported minor gastrointestinal side effects (bloating and gas, indigestion with upper abdominal discomfort). No side effects were reported with placebo or with the two higher doses of NR+pterostilbene. There were no serious adverse events in this study.

Theoretical concerns for cancer:

In a mouse model of cancer (triple-negative breast cancer), NR supplementation resulted in a significant increase in cancer prevalence and metastases to the brain ([Maric et al., 2023](#)). In contrast, two rodent models of peripheral neuropathy induced by chemotherapeutic agents reported that NR treatment appeared to enhance the tumor-suppressing effects of cisplatin/paclitaxel ([Acklin et al., 2022](#); [Hamity et al., 2020](#)).

The depletion of NAD⁺ via NAMPT inhibitors has been proposed as a strategy to treat cancer, which might suggest concern for NAD⁺ precursors. However, such inhibitors have so far met with limited success in clinical trials and the mechanism – reduced PARP activity to reduce genomic stability in cancer cells – may in contrast reduce the risk of incident cancer by increasing genomic stability in normal cells ([Montecucco, 2013](#), [Sauve 2007](#)).



Other considerations:

There are several other theoretical concerns. NAD⁺ depletion via NAMPT inhibitors has been proposed as a potential therapy for inflammatory and cardiovascular diseases ([Montecucco, 2013](#)). NAD⁺ in the extracellular space may encourage bone breakdown (e.g., [Iqbal & Zaidi 2014](#)). Thus, increasing NAD⁺ may theoretically increase the risk of cardiovascular diseases, osteoporosis, and inflammation+. However, these concerns are theoretical at this point with no robust data in humans. Also, NAD⁺ levels may change at different times of day, raising concern that supplementation might disrupt healthy circadian signaling ([Peek et al 2013](#)).

Sources and dosing:

The EFSA concluded that NR chloride is safe up to 300 mg/day for healthy adults, and up to 230 mg/day for pregnant and lactating women ([EFSA Panel on Nutrition, 2019](#)). NR has a shelf-life of 36 months and is ideally stored in refrigerated conditions. NR is available in supplement form from companies such as ChromaDex and Elysium. These products contain 250-300 mg of NR per serving. From a biological perspective, the goal should be to supplement enough to reverse the age-dependent decrease, not to cause artificially high NAD⁺ levels as most of the rodent studies have achieved (e.g., [Zhang et al., 2016](#)). In clinical populations (e.g., obesity, heart failure), doses of up to 2000 mg per day have been tested in early phase trials (e.g., [Dollerup et al., 2018](#)).

NR is unlikely to have much benefit in people whose NAD⁺ levels have not fallen, for example in younger healthy adults. The pilot studies in humans to-date do not adequately inform when NAD⁺ levels are likely to fall but tentatively suggest a very slow decline starting in the 20's without reaching significance until after the 40's ([Zhu et al., 2015](#)). In mice, NAD⁺ levels have a circadian rhythm with a peak in NAD⁺ levels at the end of the rest cycle (e.g., [Peek et al., 2013](#)). This circadian regulation of NAD⁺ levels needs to be confirmed for humans but, if true, suggests that NR should be taken at the same time each day, perhaps immediately on waking.

Most studies have reported NR-induced increases in blood NAD⁺ levels, but these increases have not been observed in all studies and have often not been observed in tissues of interest. Within each study, high variability in NAD⁺ levels were observed across subjects. Interindividual differences in intestinal transport, gut microbiome, and metabolism of NR (and other NAD⁺ precursors) may underlie the variability in outcomes ([Freeberg et al., 2023](#)). Thus appropriate dosing may be different for each person.

Research underway:

There are over 40 ongoing clinical trials testing NR, based on [ClinicalTrials.gov](https://clinicaltrials.gov). Of those testing NR in neurodegenerative diseases, there are 3 studies in Alzheimer's disease ([NCT05617508](https://clinicaltrials.gov/ct2/show/study/NCT05617508); [NCT04430517](https://clinicaltrials.gov/ct2/show/study/NCT04430517); [NCT05245903](https://clinicaltrials.gov/ct2/show/study/NCT05245903)), 2 studies in Parkinson's disease ([NCT05589766](https://clinicaltrials.gov/ct2/show/study/NCT05589766); [NCT03568968](https://clinicaltrials.gov/ct2/show/study/NCT03568968)), 2 studies in amyotrophic lateral sclerosis ([NCT05095571](https://clinicaltrials.gov/ct2/show/study/NCT05095571); [NCT04562831](https://clinicaltrials.gov/ct2/show/study/NCT04562831)), 1 study in multiple sclerosis ([NCT05740722](https://clinicaltrials.gov/ct2/show/study/NCT05740722)), 1 study in mild cognitive impairment ([NCT03482167](https://clinicaltrials.gov/ct2/show/study/NCT03482167)), and 1 study in chemotherapy-induced peripheral neuropathy ([NCT04112641](https://clinicaltrials.gov/ct2/show/study/NCT04112641)). There is also one study testing NR for cognition and sleep ([NCT05500170](https://clinicaltrials.gov/ct2/show/study/NCT05500170)).

The biological mechanisms behind the wide individual variations in the NR-induced increase in NAD⁺ levels and the pharmacokinetics and metabolism of NR in human subjects are not clearly defined and are an active area of research.

Search terms:

Pubmed, Google: nicotinamide riboside

Websites visited for nicotinamide riboside:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [Examine.com](https://www.examine.com)
- [DrugAge](https://www.drugage.com)
- [Geroprotectors](https://www.geroprotectors.com)
- Drugs.com (0)
- WebMD.com (0)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- [DrugBank.ca](https://www.drugbank.ca)
- Labdoor.com (0)
- [ConsumerLab.com](https://www.consumerlab.com)



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