# State of the Science

Clinical Research on Niagen®



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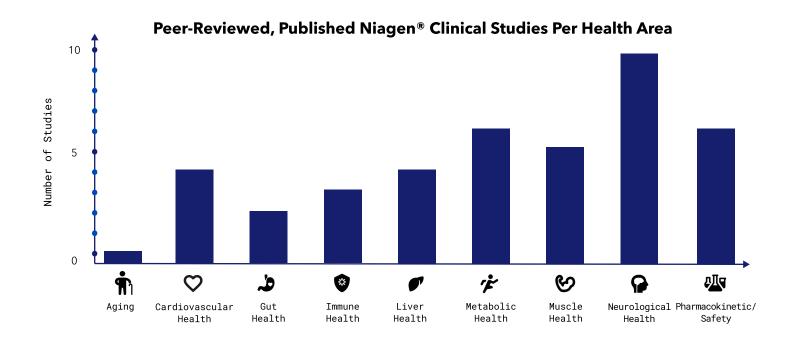
One of the world's most published researchers on aging and neurodegenerative disease



Sir John Walker FRS, FMedSci

Emeritus Director and Professor MRC Mitochondrial Biology Unit, Cambridge

Nobel Prize Winner, Chemistry



#### 2 years

is the longest duration of supplementation

Presterud et al., 2023

## 140 participants

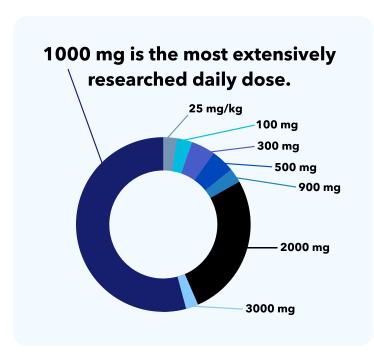
is the largest population studied in a clinical trial

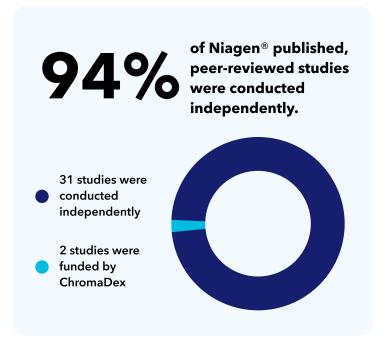
Conze et al., 2019

### 3000 mg

is the highest dose with established safety

Berven et al., 2023





#### **Dosage Key Health Categories** 25 mg/kg • 100 mg 300 mg Aging Immune Health Muscle Health 500 mg 900 mg • 1000 mg Neurological Health 2000 mg 3000 mg Cardiovascular Liver Health Health Pharmacokinetic/ Metabolic Health Gut Health Safety

Table 1. All peer-reviewed, published clinical studies on Niagen®

†Indicates an increase in blood or tissue NAD+ levels and/or NAD+ flux (the rate at which cells make and use NAD+) was observed.

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Trammell et al., 2016†  Nicotinamide Riboside is Uniquely and Orally Bioavailable in Mice and Humans	100 mg 300 mg	24 hours	Pharmacokinetic/ Safety	Randomized, double-blind, single dose, three- arm study in 12 healthy men and women	<ul> <li>Single oral doses of NR significantly and dose-dependently increased NAD+ and related metabolites in peripheral blood mononuclear cells (PBMCs).</li> <li>Mouse pharmacokinetic data demonstrated that NR increased NAD+ levels better than niacin (NA) and stimulated NAD+ consuming activities in the liver more than nicotinamide (NAM).</li> </ul>
Airhart et al., 2017†  An Open-Label, Non-Randomized Study of the Pharmacokinetics of the Nutritional Supplement Nicotinamide Riboside (NR) and Its Effects on Blood NAD+ Levels in Healthy Volunteers	2000 mg	9 days	Pharmacokinetic/ Safety	Non-randomized, open-label study in 8 healthy men and women	<ul> <li>NR supplementation significantly increased blood NAD+ concentrations between baseline and Day 9. On average, NAD+ levels increased 2-fold.</li> <li>No significant changes were observed in blood pressure, body temperature, body weight, white blood cell count, lactate dehydrogenase (LDH), or aspartate aminotransferase (AST).</li> </ul>
Martens et al., 2018†  Chronic Nicotinamide Riboside Supplementation is Well- Tolerated and Elevates NAD+ in Healthy Middle-Aged and Older Adults	1000 mg	6 weeks	Pharmacokinetic/ Safety  Cardiovascular Health	Randomized, double-blind, placebo- controlled, crossover study in 30 healthy, middle-aged, and older men and women	<ul> <li>NR supplementation significantly increased average NAD+ levels by 60% compared to placebo.</li> <li>NR tended to lower blood pressure, especially in subjects with elevated blood pressure (in the stage I hypertension range).</li> <li>NR also tended to decrease aortic stiffness.</li> </ul>

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Dollerup et al., 2018†  A Randomized Placebo- Controlled Clinical Trial of Nicotinamide Riboside in Obese Men: Safety, Insulin-Sensitivity, and Lipid-Mobilizing Effects	2000 mg	12 weeks	Pharmacokinetic/ Safety  Liver Health  Metabolic Health	Randomized, double-blind, placebo- controlled, parallel assignment study in 40 healthy, obese sedentary men	<ul> <li>NR-supplemented subjects had an average 2% absolute reduction in liver fat content compared to a 0.2% absolute reduction in the placebo group.</li> <li>Of the subset of men who started the trial with greater than 5% liver fat, 69% experienced a reduction in liver fat compared to only 39% of the men taking the placebo.</li> <li>NR supplementation tended to decrease circulating levels of alanine aminotransferase (ALT) in the blood.</li> </ul>
Conze et al., 2019†  Safety and Metabolism of Long-Term Administration of NIAGEN (Nicotinamide Riboside Chloride) in a Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Healthy Overweight Adults	100 mg 300 mg	8 weeks	Pharmacokinetic/ Safety	Randomized, double-blind, placebo- controlled, parallel assignment study in 140 overweight, but otherwise healthy men and women	• NR supplementation significantly and dose-dependently increased whole blood NAD+levels by 22%, 51%, and 142%, respectively, within two weeks. These levels were maintained throughout the remainder of the study.
Effects of Nicotinamide Riboside on Endocrine Pancreatic Function and Incretin Hormones in Nondiabetic Men with Obesity This is the second publication from the Dollerup et al., 2018 group.	2000 mg	12 weeks	Metabolic Health	Randomized, double-blind, placebo- controlled, parallel assignment study in 40 healthy, obese sedentary men	<ul> <li>NR supplementation did not affect fasting or post-glucose challenge concentrations of glucose, insulin, C-peptide, glucagon, GLP-1, or GIP.</li> <li>β-cell function did not respond to NR intervention and no changes in circulating adipsin or bile acids were observed.</li> </ul>
Elhassan et al., 2019†  Nicotinamide Riboside Augments the Aged Human Skeletal Muscle NAD+ Metabolome and Induces Transcriptomic and Anti-inflammatory Signatures	1000 mg	3 weeks	Muscle Health	Randomized, double-blind, placebo- controlled, crossover study in 12 marginally overweight, but otherwise healthy aged men	<ul> <li>NR supplementation increased the muscle NAD+ metabolome</li> <li>NR significantly decreased levels of circulating inflammatory markers (IL-6, IL-5, and IL-2, and TNF-a, compared to baseline).</li> </ul>

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Nicotinamide Riboside Does Not Alter Mitochondrial Respiration, Content or Morphology in Skeletal Muscle from Obese and Insulin- Resistant Men	2000 mg	12 weeks	Muscle Health	Randomized, double-blind, placebo- controlled, parallel assignment study in 40 healthy,	<ul> <li>Protein levels of nicotinamide phosphoribosyltransferase (NAMPT), an essential NAD+ biosynthetic enzyme in skeletal muscle, decreased by 14% with NR. However, NR supplementation did not affect NAD+ metabolite concentrations in skeletal muscle.</li> </ul>
This is the third publication from the Dollerup et al., 2018 group.			Metabolic Health	obese sedentary men	<ul> <li>Respiration, distribution, and quantity of muscle mitochondria were also unaffected by NR.</li> </ul>
Remie et al., 2020†  Nicotinamide Riboside Supplementation Alters Body Composition and Skeletal Muscle	1000 mg	6 weeks	Muscle Health	Randomized, double-blind, placebo- controlled, crossover study in 15 healthy,	<ul> <li>NR significantly increased markers of enhanced NAD+ metabolism in human skeletal muscle (e.g., NAAD and MeNam).</li> <li>Minor beneficial changes in body</li> </ul>
Acetylcarnitine Concentrations in Healthy Obese Humans	Acetylcarnitine Concentrations in Healthy		Metabolic Health	overweight, or obese, sedentary men and women	composition, sleeping metabolic rate, and skeletal muscle acetyl-carnitine concentrations were found.
Zhang et al., 2020  The Acute Effect of Metabolic Cofactor Supplementation: A Potential Therapeutic Strategy Against Non- Alcoholic Fatty Liver Disease	1000 mg <sup>a</sup>	5 days	Liver Health	Acute, single dose, 5-day pilot clinical study in 19 healthy, male subjects	<ul> <li>CMA supplementation significantly decreased blood plasma levels of markers associated with increased liver fat, as well as blood plasma levels of branch chain amino acids.</li> <li>Mathematical modeling results showed a global increase in fat metabolism, decreased glucose metabolism, and increased synthesis of NAD+, carnitine, and glutathione.</li> </ul>
Zhou et al., 2020†  Boosting NAD Level Suppresses Inflammatory Activation of PBMCs in Heart Failure	2000 mg	5-9 days	Cardiovascular Health	Ex vivo and pilot clinical study in 5 Stage D heart failure patients	<ul> <li>NR supplementation increased whole blood NAD+ levels and mitochondrial respiration rate of the heart failure patients' PBMCs.</li> <li>NR reduced the production and gene expression of proinflammatory cytokines.</li> <li>The systemic inflammation in heart failure patients was causally linked to mitochondrial function of the PBMCs.</li> </ul>

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Variable Selection in Untargeted Metabolomics and the Danger of Sparsity	25 mg/kg	4 months	Neurological Health	Comparative study in 14 patients with ataxia- telangiectasia (AT)	<ul> <li>NR-related pathways and metabolites significantly increased after NR supplementation.</li> </ul>
Nascimento et al., 2021  Nicotinamide Riboside Enhances In Vitro Beta- adrenergic Brown Adipose Tissue Activity in Humans	1000 mg	6 weeks	Metabolic Health	Randomized, double-blind, placebo- controlled, crossover study in 8 healthy overweight and obese men and postmenopausal women	<ul> <li>NR supplementation had no effect on cold- stimulated BAT activity.</li> </ul>
Li et al., 2021  NAD+-Boosting Therapy Alleviates Nonalcoholic Fatty Liver Disease via Stimulating a Novel Exerkine Fndc5/Irisin	500 mg	2 weeks	Liver Health	General screening test with 6 healthy human subjects	• NR supplementation increased plasma levels of Fndc5/irisin. A similar increase in plasma Fndc5/irisin was observed after two weeks of exercise, suggesting Fndc5/irisin may be a link between NAD+ and physical exercise.
Altay et al., 2021  Combined Metabolic Activators Accelerates Recovery in Mild-to- Moderate COVID-19	2000 mg <sup>b</sup>	2 weeks	Immune Health	Phase II: Randomized, openlabel, placebocontrolled study in 93 patients & Phase III: Randomized, doubleblind, placebocontrolled study in 309 COVID-19 patients	<ul> <li>After 14 days, CMA supplementation significantly reduced recovery time compared to placebo group in phase II (6.6 vs 9.3 days, respectively), as well as in phase III (5.7 vs. 9.2 days, respectively).</li> <li>CMA supplementation also improved liver health and markers of inflammation in COVID-19 patients.</li> </ul>
Stocks et al., 2021†  Nicotinamide Riboside Supplementation Does Not Alter Whole-Body or Skeletal Muscle Metabolic Responses to a Single Bout of Endurance Exercise	1000 mg	1 week	Muscle Health	Randomized, double-blind, placebo- controlled, crossover study in 8 young, healthy, recreationally active men	<ul> <li>NR did not alter NAD-sensitive signaling pathways in skeletal muscle and did not have any effect on skeletal muscle mitochondrial respiration nor whole-body metabolism.</li> <li>Although NR did not increase skeletal muscle NAD+ levels, it increased markers of NAD flux, demonstrating the skeletal muscle bioavailability of NR supplementation.</li> </ul>

b "Combined metabolic activators" or "CMA," in combination with hydroxychloroquine (HCQ) or favipiravir (FP) for the treatment of patients with COVID-19. The CMA was administered twice per day for 14 days, and each dose consisted of 3.73g L-carnitine tartrate, 1g NR, 12.35g serine, and 2.55g N-acetyl-L-cysteine.

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Veenhuis et al., 2021  Nicotinamide Riboside Improves Ataxia Scores and Immunoglobulin Levels in Ataxia Telangiectasia  This is the second publication from the Tinnevelt et al., 2020 group.	25 mg/kg	4 months	Neurological Health	Open-label proof- of-concept study in 24 patients with AT	<ul> <li>NR supplementation improved ataxia scores (SARA and ICARS). However, this improvement disappeared after NR withdrawal, indicating a temporary, symptomatic effect of NR in AT.</li> <li>NR also markedly increased serum immunoglobin G (IgG) in immunodeficient patients.</li> <li>This is the first clinical study to investigate the effects of NR in patients with AT, and most notably, the first clinical NR trial in children under the age of 18.</li> </ul>
Zeybel et al., 2021  Combined Metabolic Activators Therapy Ameliorates Liver Fat in Nonalcoholic Fatty Liver Disease Patients	2000 mg <sup>c</sup>	10 weeks	Liver Health	Randomized, single-blind, placebo- controlled, phase Il study in 31 patients with nonalcoholic fatty liver disease (NAFLD)	<ul> <li>CMA significantly decreased liver fat by 10%, and improved liver function, as seen through the significant reductions in serum ALT (39%), AST (30%), and uric acid (12%) levels.</li> <li>CMA reduced plasma levels of inflammatory proteins, suggesting a decrease in liver inflammation.</li> <li>Fecal and salivatory sample analyses showed that CMA supplementation caused beneficial changes in the microbiome.</li> </ul>
Wu et al., 2022†  Boosting NAD+ Blunts Toll-Like Receptor-4 Induced Type-I Interferon in Control and Systemic Lupus Erythematosus Monocytes	1000 mg	1 week	Immune Health	Ex Vivo:  Monocytes were extracted from young, healthy subjects and patients with systemic lupus erythematosus (SLE) and then treated with NR  In Vivo: Randomized, double-blind, placebocontrolled, pilot study in 35 young, healthy subjects	<ul> <li>Ex Vivo: <ul> <li>NR reduced cytokine expression and type-l interferon (IFN) signaling (which plays an important role in the human immune response) in monocytes from healthy subjects and SLE patients.</li> </ul> </li> <li>In Vivo: <ul> <li>NR supplementation increased whole blood NAD+ levels, as well as levels of related NAD+ metabolites.</li> </ul> </li> <li>NR supplementation also replicated the effects observed with ex-vivo NR administration, resulting in a similar reduction in type-l IFN signaling in the young, healthy subjects.</li> </ul>

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Brakedal et al., 2022†  The NADPARK Study: A Randomized Phase I Trial of Nicotinamide Riboside Supplementation in Parkinson's Disease	1000 mg	30 days	Neurological Health	Randomized, double-blind, placebo- controlled, phase I study in 30 Parkinson's disease (PD) patients	<ul> <li>NR supplementation significantly increased cerebral NAD+ levels, altered brain metabolic pattern, and decreased levels of inflammatory cytokines in the cerebrospinal fluid of PD patients.</li> <li>Moreover, patients experienced a mild but significant clinical improvement, and this correlated with the change in the brain's metabolic pattern.</li> </ul>
Wang et al., 2022†  Safety and Tolerability of Nicotinamide Riboside in Heart Failure With Reduced Ejection Fraction	2000 mg	12 weeks	Cardiovascular Health	Randomized, double-blind, placebo- controlled study in 30 patients with Stage C heart failure with reduced ejection fraction (HFrEF)	<ul> <li>High-dose NR supplementation was safe and well-tolerated, significantly, and dose- dependently (nearly) doubled whole blood NAD+ levels, and increased PBMC mitochondrial respiration.</li> <li>NR also decreased expression of inflammatory markers, such as NLRP3.</li> </ul>
Vreones et al., 2022†  Oral Nicotinamide Riboside Raises NAD+ and Lowers Biomarkers of Neurodegenerative Pathology in Plasma Extracellular Vesicles Enriched for Neuronal Origin	1000 mg	6 weeks	Neurological Health	Randomized, double-blind, placebo- controlled, crossover study in 22 healthy, middle-aged, and older men and women	<ul> <li>NR supplementation significantly increased NAD+ in plasma derived human neuronal extracellular vesicles (NEVs), suggesting an increase in neuronal NAD+ levels.</li> <li>In NEVs, NR also decreased levels of Aβ42, an Alzheimer's disease biomarker, as well as biomarkers pJNK and pERK1/2, which are involved in insulin resistance and neuroinflammatory pathways.</li> </ul>
Lapatto et al., 2023†  Nicotinamide Riboside Improves Muscle Mitochondrial Biogenesis, Satellite Cell Differentiation, and Gut Microbiota in a Twin Study		5 months	Wuscle Health	Nonrandomized, open-label, parallel- assignment study in 20 BMI- discordant (one leaner, one heavier) identical twin pairs	<ul> <li>In the BMI-discordant twin pairs, NR supplementation was well-tolerated and increased whole blood NAD+ levels.</li> <li>NR also increased muscle mitochondrial biogenesis and improved gut microbiota composition, as seen through an increase in the abundance of Faecalibacterium prausnitzii—one of the most beneficial bacteria found in the microbiome of healthy humans.</li> </ul>
	1000 mg	5 months	Gut Health		

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Yulug et al., 2023  Combined Metabolic Activators Improve Cognitive Functions in Alzheimer's Disease Patients: A Randomized, Double-Blinded, Placebo- Controlled Phase-II Trial	2000 mg <sup>d</sup>	8 weeks	Neurological Health	Randomized, double-blind, placebo- controlled, phase II study in 69 Alzheimer's disease (AD) patients	<ul> <li>CMA supplementation improved cognitive function by 29% in AD patients. Patients with high ADAS-Cog scores (worsened cognitive function) showed improvement with CMA supplementation.</li> <li>CMA also improved serum markers related to AD, as well as markers of liver and kidney health in AD patients, as seen through significant decreases in levels of ALT and uric acid.</li> </ul>
Gaare et al., 2023  Nicotinamide Riboside Supplementation is Not Associated with Altered Methylation Homeostasis in Parkinson's Disease	1000 mg	30 days	Neurological Health	Randomized, double-blind, placebo- controlled, phase I study in 29 newly diagnosed PD patients	<ul> <li>NR supplementation had no impact on DNA methylation in PD patients, including in those with common mutations in the MTHFR gene.</li> <li>NR also resulted in minor changes in the activity of metabolic pathways and patterns of DNA methylation. However, these changes were not harmful and did not disrupt normal DNA methylation.</li> </ul>
Peluso et al., 2023  Oral Supplementation of Nicotinamide Riboside Alters Intestinal Microbial Composition in Rats and Mice, But Not Humans  This is the fourth publication from the Dollerup et al., 2018 group.	2000 mg	12 weeks	Gut Health	Randomized, double-blind, placebo- controlled, parallel assignment study in 40 healthy, obese sedentary men	NR supplementation did not affect the diversity or abundance of gut bacteria in humans. However, NR increased (albeit not significantly) the ratio of Firmicutes and Proteobacteria, suggesting a potential positive effect.
Ahmadi et al., 2023  Randomized Crossover Clinical Trial of Coenzyme Q10 and Nicotinamide Ribosome in Chronic Kidney Disease	1000 mg°	6 weeks	Metabolic Health	Randomized double-blind, placebo- controlled, crossover study in 25 chronic kidney disease (CKD) patients	<ul> <li>NR supplementation showed a trend towards improved energy metabolism and submaximal exercise efficiency, suggesting better carbohydrate utilization for energy.</li> <li>NR decreased plasma levels of NAD-dependent citric acid cycle intermediates, suggesting improved mitochondrial metabolism.</li> <li>NR reduced short and medium-chained plasma triglycerides with a high degree of saturation (tightly packed), suggesting favorable changes in lipid metabolism.</li> <li>CoQ10 reduced certain types of triglycerides and increased plasma free fatty acids.</li> </ul>

d One dose of 12.35g L-serine, 1g NR, 2.55g N-acetyl-L-cysteine, and 3.73g L-carnitine tartrate for the first 28 days and two doses for the

e Patients were given NR (1000 mg/day) or CoQ10 (1200 mg/day).

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Han et al., 2023  Boosting NAD Preferentially Blunts Th17 Inflammation via Arginine Biosynthesis and Redox Control in Healthy and Psoriasis Subjects	1000 mg	1 week	Immune Health	Ex Vivo: CD4+ T cells were extracted from 12 mild- moderate psoriasis patients and healthy subjects and then treated with NR In Vivo: Randomized, double-blind, placebo- controlled, pilot study in 25 young, healthy subjects	<ul> <li>Ex Vivo: <ul> <li>NAD+/NADH ratio was reduced in psoriatic T cells compared to cells from healthy subjects.</li> </ul> </li> <li>NR treatment reduced immune responsiveness in CD4+ T cells from healthy subjects and psoriasis patients.</li> </ul> <li>In Vivo: <ul> <li>NR supplementation replicated the immune-modulating effects observed with ex-vivo NR administration, resulting in a decrease in inflammatory markers while enhancing antioxidant gene expression in immune cells.</li> </ul> </li>
Presterud et al., 2023†  Long-Term Nicotinamide Riboside Use Improves Coordination and Eye Movements in Ataxia Telangiectasia	500 mg	2 years	Neurological Health	Open-label, single arm, observational intervention study in 10 patients with AT	<ul> <li>Long-term NR supplementation was safe and well tolerated, with no serious adverse events.</li> <li>Compared to historical controls, NR supplementation significantly improved motor coordination and eye movements in AT patients.</li> <li>This is the second clinical NR trial including children under the age of 18 and the longest NR supplementation study to date.</li> </ul>
Orr et al., 2023†  A Randomized Placebo-Controlled Trial of Nicotinamide Riboside in Older Adults with Mild Cognitive Impairment	1000 mg	10 weeks	Neurological Health	Randomized, double-blind, placebo- controlled, phase II, pilot study in 20 primarily Hispanic older adults with mild cognitive impairment (MCI)	<ul> <li>NR-supplemented subjects exhibited reduced cerebral blood flow, particularly in the default mode network (DMN), suggesting less degeneration in brain regions that typically require higher blood flow.</li> <li>Cognitive function measures remained stable in both NR and placebo groups throughout the study.</li> <li>Global methylation analyses trended towards a modest NR-associated increase in DNA methylation.</li> </ul>

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Berven et al., 2023 <sup>†</sup> NR-SAFE: A  Randomized, Double-			Pharmacokinetic/ Safety	Randomized, double-blind, placeblo-	<ul> <li>High-dose NR supplementation was safe and well-tolerated with no related adverse events.</li> <li>NR did not alter whole blood homocysteine, or other major methyl donor groups, suggesting no impact on methyl donor group pool.</li> <li>NR significantly improved clinical symptoms of PD, suggesting augmenting NAD+ levels may have a symptomatic anti-Parkinson effect.</li> </ul>
Blind Safety Trial of High Dose Nicotinamide Riboside in Parkinson's	3000 mg	4 weeks	eks  Neurological Health	controlled, phase I study in 20 idiopathic PD patients	
McDermott et al., 2024  Nicotinamide Riboside for Peripheral Artery Disease: The NICE Randomized Clinical Trial			Aging	Randomized, double-blind, placebo- controlled, phase II study in 90 peripheral artery disease (PAD) patients	<ul> <li>NR supplementation significantly improved treadmill walking time and the six-minute walking distance (by 17.6 meters), a clinically meaningful change.</li> <li>NR effectively improved walking</li> </ul>
	TUUU mg	6 months	Cardiovascular Health		<ul> <li>performance in individuals with PAD, while resveratrol did not enhance the benefits of NR.</li> <li>NR combined with resveratrol did not significantly improve the six-minute walk distance compared to placebo.</li> </ul>
Nanga et al., 2024 <sup>†</sup> Acute Nicotinamide Riboside Supplementation Increases Human Cerebral NAD+ Levels In Vivo	900 mg	4 hours	Neurological Health	Open-label, pilot study in 10 healthy subjects	<ul> <li>NR supplementation significantly increased brain NAD+ levels by about 16% compared to baseline.</li> </ul>

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