State of the Science

Clinical Research on Niagen®

ChromaDex Scientific Advisory Board

Dr. Roger Kornberg

Professor of Structural Biology, Stanford University School of Medicine

Nobel Prize Winner, Chemistry

Dr. Rudolph Tanzi

Kennedy Professor of Neurology, Harvard University

Director, Genetics and Aging Research Unit, Massachusetts General Hospital

Dr. Charles Brenner

Chair of the Department of Diabetes and Cancer Metabolism, City of Hope

World's foremost authority on NAD+ metabolism

Dr. Bruce German

Chairman of Food, Nutrition, and Health, University of California, Davis

Leader in food, nutrition, and wellness innovation

Dr. David L. Katz

M.D., M.P.H., FACPM, FACP, FACLM

Founder of Yale-Griffin Prevention Research Center and Past President of the American College of Lifestyle Medicine

Leading expert in nutrition, health promotion, and chronic disease prevention

Dr. Brunie H. Felding

Associate Professor of Molecular Medicine, Scripps Research Institute

Renowned breast cancer researcher focused on NAD+ supplementation

Dr. Vilhelm (Will) Bohr

M.D., Ph.D., D.Sc.

Chief of the Laboratory of Molecular Genetics at the National Institute on Aging

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

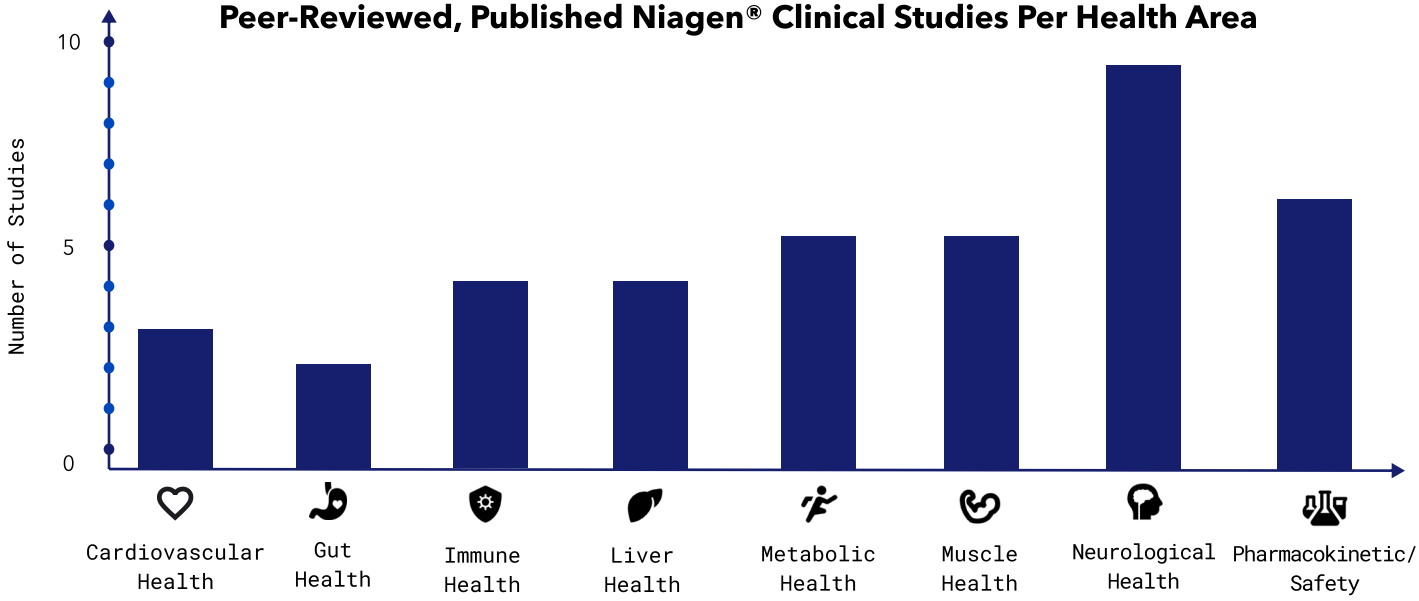
Sir John Walker

FRS, FMedSci

Emeritus Director and Professor MRC Mitochondrial Biology Unit, Cambridge

Nobel Prize Winner, Chemistry

Peer-Reviewed, Published Niagen® Clinical Studies Per Health Area



2 years

is the longest duration of supplementation

Presterud et al., 2023

140 participants

is the largest population studied in a clinical trial

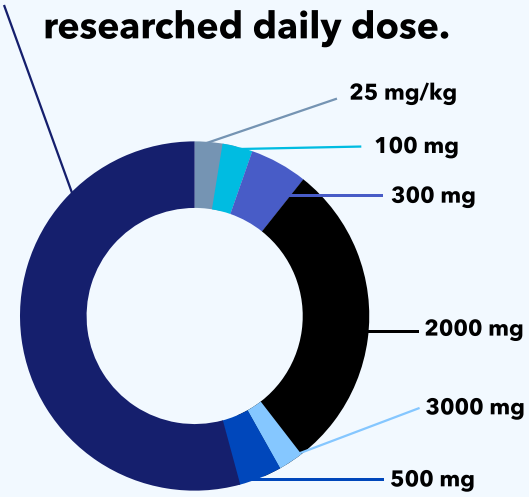
Conze et al., 2019

3000 mg

is the highest dose with established safety

Berven et al., 2023

1000 mg is the most extensively researched daily dose.



94% of Niagen® published, peer-reviewed studies were conducted independently.

- 29 studies were conducted independently
- 2 studies were funded by ChromaDex

Dosage Key

- 25 mg/kg
- 100 mg
- 300 mg
- 500 mg
- 1000 mg
- 2000 mg
- 3000 mg

Health Categories

- Cardiovascular Health
- Liver Health
- Neurological Health
- Gut Health
- Metabolic Health
- Pharmacokinetic/ Safety
- Immune Health
- Muscle Health

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

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 1000 mg	24 hours	Pharmacokinetic/ Safety	Randomized, double-blind, single dose, three-arm study in 12 healthy men and women	• Single oral doses of NR significantly and dose-dependently increased NAD+ and related metabolites in peripheral blood mononuclear cells (PBMCs). • 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).
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	• NR supplementation significantly increased blood NAD+ concentrations between baseline and Day 9. On average, NAD+ levels increased 2-fold. • No significant changes were observed in blood pressure, body temperature, body weight, white blood cell count, lactate dehydrogenase (LDH), or aspartate aminotransferase (AST).
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 male and female adults	• NR supplementation significantly increased average NAD+ levels by 60% compared to placebo. • NR tended to lower blood pressure, especially in subjects with elevated blood pressure (in the stage I hypertension range). • NR also tended to decrease aortic stiffness.

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	• NR-supplemented subjects had an average 2% absolute reduction in liver fat content compared to a 0.2% absolute reduction in the placebo group. • 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. • NR supplementation tended to decrease circulating levels of alanine aminotransferase (ALT) in the blood.
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** **1000 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.
Dollerup et al., 2019 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	• NR supplementation did not affect fasting or post-glucose challenge concentrations of glucose, insulin, C-peptide, glucagon, GLP-1, or GIP. • β-cell function did not respond to NR intervention and no changes in circulating adipsin or bile acids were observed.
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	• NR supplementation increased the muscle NAD+ metabolome • NR significantly decreased levels of circulating inflammatory markers (IL-6, IL-5, and IL-2, and TNF-α, compared to baseline).

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Dollerup et al., 2019 Nicotinamide Riboside Does Not Alter Mitochondrial Respiration, Content or Morphology in Skeletal Muscle from Obese and Insulin-Resistant Men ***This is the third publication from the Dollerup et al., 2018 group.***	**2000 mg**	12 weeks	Muscle Health Metabolic Health	Randomized, double-blind, placebo-controlled, parallel assignment study in 40 healthy, obese sedentary men	• 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. • Respiration, distribution, and quantity of muscle mitochondria were also unaffected by NR.
Remie et al., 2020 Nicotinamide Riboside Supplementation Alters Body Composition and Skeletal Muscle Acetylcarnitine Concentrations in Healthy Obese Humans	**1000 mg**	6 weeks	Muscle Health Metabolic Health	Randomized, double-blind, placebo-controlled, crossover study in 13 healthy, overweight, or obese, sedentary men and women	• NR significantly increased markers of enhanced NAD+ metabolism in human skeletal muscle (e.g., NAAD and MeNam). • Minor beneficial changes in body 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[a]**	5 days	Liver Health	Acute, single dose, 5-day pilot clinical study in 9 healthy, male subjects	• 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. • Mathematical modeling results showed a global increase in fat metabolism, decreased glucose metabolism, and increased synthesis of NAD+, carnitine, and glutathione.
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 4 Stage D heart failure patients	• NR supplementation increased whole blood NAD+ levels and mitochondrial respiration rate of the heart failure patients' PBMCs. • NR reduced the production and gene expression of proinflammatory cytokines. • The systemic inflammation in heart failure patients was causally linked to mitochondrial function of the PBMCs.

[a] A combination supplement consisting of 1g NR, 20g L-serine, 5g N-acetyl-L-cysteine, and 3g L-carnitine.

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Tinnevelt et al., 2020 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)	• NR-related pathways and metabolites significantly increased after NR supplementation.
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	• NR supplementation had no effect on cold-stimulated BAT activity.
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 volunteers	• 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**[b]	2 weeks	 Immune Health	**Phase II:** Randomized, open-label, placebo-controlled study in 93 patients & **Phase III:** Randomized, double-blind, placebo-controlled study in 309 COVID-19 patients	• 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). • CMA supplementation also improved liver health and markers of inflammation in COVID-19 patients.
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 male subjects	• 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. • Although NR did not increase skeletal muscle NAD+ levels, it increased markers of NAD flux, demonstrating the skeletal muscle bioavailability of NR supplementation.

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	• NR supplementation improved ataxia scores (SARA and ICARS). However, this improvement disappeared after NR withdrawal, indicating a temporary, symptomatic effect of NR in AT. • NR also markedly increased serum immunoglobin G (IgG) in immunodeficient patients. • 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.
Zeybel et al., 2021 Combined Metabolic Activators Therapy Ameliorates Liver Fat in Nonalcoholic Fatty Liver Disease Patients	**2000 mg[c]**	10 weeks	 Liver Health	Randomized, single-blind, placebo-controlled, phase II study in 31 patients with nonalcoholic fatty liver disease (NAFLD)	• 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. • CMA reduced plasma levels of inflammatory proteins, suggesting a decrease in liver inflammation. • Fecal and salivatory sample analyses showed that CMA supplementation caused beneficial changes in the microbiome.
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, placebo-controlled, pilot study in 35 young, healthy subjects	**Ex Vivo:** • NR reduced cytokine expression and type-I interferon (IFN) signaling (which plays an important role in the human immune response) in monocytes from healthy subjects and SLE patients. **In Vivo:** • NR supplementation increased whole blood NAD+ levels, as well as levels of related NAD+ metabolites. • NR supplementation also replicated the effects observed with ex-vivo NR administration, resulting in a similar reduction in type-I IFN signaling in the young, healthy subjects.

[c] One dose of 3.73g L-carnitine tartrate, 1g NR, 12.35g serine, and 2.55g N-acetyl-L-cysteine for the first 14 days and two doses for the next 56 days.

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	• NR supplementation significantly increased cerebral NAD+ levels, altered brain metabolic pattern, and decreased levels of inflammatory cytokines in the cerebrospinal fluid of PD patients. • Moreover, patients experienced a mild but significant clinical improvement, and this correlated with the change in the brain's metabolic pattern.
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)	• High-dose NR supplementation was safe and well-tolerated, significantly, and dose-dependently (nearly) doubled whole blood NAD+ levels, and increased PBMC mitochondrial respiration. • NR also decreased expression of inflammatory markers, such as NLRP3.
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 males and female adults	• NR supplementation significantly increased NAD+ in plasma derived human neuronal extracellular vesicles (NEVs), suggesting an increase in neuronal NAD+ levels. • 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.
Lapatto et al., 2023 Nicotinamide Riboside Improves Muscle Mitochondrial Biogenesis, Satellite Cell Differentiation, and Gut Microbiota in a Twin Study	**1000 mg**	5 months	Muscle Health Gut Health	Nonrandomized, open-label, parallel-assignment study in 22 BMI-discordant (one leaner, one heavier) identical twin pairs	• In the BMI-discordant twin pairs, NR supplementation was well-tolerated and increased whole blood NAD+ levels. • 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.

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[d]**	8 weeks	 Neurological Health	Randomized, double-blind, placebo-controlled, phase II study in 47 Alzheimer's disease (AD) patients	• CMA supplementation improved cognitive function by 29% in AD patients. Patients with high ADAS-Cog scores (worsened cognitive function) showed improvement with CMA supplementation. • 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.
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	• NR supplementation had no impact on DNA methylation in PD patients, including in those with common mutations in the MTHFR gene. • 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.
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[e]**	6 weeks	 Metabolic Health	Randomized double-blind, placebo-controlled, crossover study in 24 chronic kidney disease (CKD) patients	• NR supplementation showed a trend towards improved energy metabolism and submaximal exercise efficiency, suggesting better carbohydrate utilization for energy. • NR decreased plasma levels of NAD-dependent citric acid cycle intermediates, suggesting improved mitochondrial metabolism. • NR reduced short and medium-chained plasma triglycerides with a high degree of saturation (tightly packed), suggesting favorable changes in lipid metabolism. • CoQ10 reduced certain types of triglycerides and increased plasma free fatty acids.

[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 next 56 days.

[e] Patients were given NR (1000mg/day) or CoQ10 (1200mg/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	**Ex Vivo:** • NAD+/NADH ratio was reduced in psoriatic T cells compared to cells from healthy subjects. • NR treatment reduced immune responsiveness in CD4+ T cells from healthy subjects and psoriasis patients. **In Vivo:** • 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.
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	• Long-term NR supplementation was safe and well tolerated, with no serious adverse events. • Compared to historical controls, NR supplementation significantly improved motor coordination and eye movements in AT patients. • This is the second clinical NR trial including children under the age of 18 and the longest NR supplementation study to date.
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)	• 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. • Cognitive function measures remained stable in both NR and placebo groups throughout the study. • Global methylation analyses trended towards a modest NR-associated increase in DNA methylation.

Publication	Dose	Duration	Health Area	Study Design	Key Outcomes
Berven et al., 2023 NR-SAFE: A Randomized, Double-Blind Safety Trial of High Dose Nicotinamide Riboside in Parkinson's	3000 mg	4 weeks	Pharmacokinetic/ Safety Neurological Health	Randomized, double-blind, placebo-controlled, phase I clinical study in 20 idiopathic PD patients	• High-dose NR supplementation was safe and well-tolerated with no related adverse events. • NR did not alter whole blood homocysteine, or other major methyl donor groups, suggesting no impact on methyl donor group pool. • NR significantly improved clinical symptoms of PD, suggesting augmenting NAD+ levels may have a symptomatic anti-Parkinson's effect.

Clinical Research on Niagen®

NIAGEN®