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 Mononucleotide

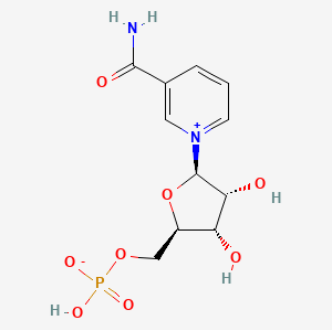
Evidence Summary

Preclinical evidence of NAD+ precursors is compelling. However, clinical trials testing short-term NMN interventions have not produced robust clinical outcomes so far.

Neuroprotective Benefit: Preclinical evidence for neuroprotection is strong. One small randomized controlled trial in healthy older men failed to show cognitive improvement with NMN treatment, but larger studies with longer treatment are needed.

Aging and related health concerns: Clinical trials have shown that NMN increases some components of the NAD+ metabolome, but NMN has shown little effect in improving clinically relevant outcomes thus far.

Safety: Clinical trials have shown that NMN is well-tolerated with mild adverse events, though most studies have been short in duration. Long-term safety needs to be established.

Availability: under clinical development; research grade is available	**Dose**: not established. Clinical trials have tested oral NMN doses ranging from 250 mg daily to 2,000 mg daily.	**Chemical formula:** $C_{11}H_{15}N_2O_8P$ **MW**: 334.22  Source: PubChem
Half-life: not documented	**BBB**: not documented	
Clinical trials: The largest randomized controlled trial of NMN included a total of 108 older adults.	**Observational studies**: none	

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). As people get older, their tissue and cellular NAD+ levels decline, and this decrease has been linked to many age-related disorders (Soma and Lalam, 2022). NAD+ levels can be increased under low energy intake, calorie restriction, fasting, and exercise (Nadeeshani et al., 2021).

NAD+ levels are maintained by several pathways: the de novo pathway, the Preiss-Handler pathway, and the salvage pathway (reviewed in Soma and Lalam, 2022). In the de novo pathway, NAD+ is generated from the amino acid tryptophan. In the Preiss-Handler pathway, nicotinic acid is converted to NAD+ through 3 steps. However, most tissues rely on the salvage pathway where NAD+ is derived from its precursors, nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR). NR can be converted to NMN by NR kinases 1/2 (NRK1/2), then converted to NAD+ by the enzyme NMNAT.

NMN is naturally found in some foods, such as edamame, broccoli, cucumber, and cabbage, but at low levels (0.25-1.88 mg of NMN per 100 g)(Mills et al., 2016). Fruits such as avocado and tomato contain 0.26-1.60 mg of NMN per 100 g.

Although traditionally thought that NMN needed to be converted to NR before entering cells, a potential transporter encoded by the gene Slc12a8 was discovered such that NMN may enter the cell through this transporter, which is highly expressed in the small intestine of mice (Grozio et al., 2019).

Because of the wide-ranging role of NAD+ in aging and health conditions, NMN 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: Preclinical evidence for neuroprotection is strong. One small randomized controlled trial in healthy older men failed to show cognitive improvement with NMN treatment, but larger studies with longer treatment are needed.

Types of evidence:

- 1 clinical trial in healthy older adults
- Numerous reviews
- Numerous laboratory studies

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

No studies in humans have tested whether NMN can prevent dementia or age-related cognitive decline.

In a double-blind randomized controlled trial of 20 healthy older men (65 years or older), NMN treatment (250 mg daily) for 12 weeks significantly increased blood NAD+ levels as well as NAD+ metabolite concentrations, but did not significantly affect overall cognitive function assessed by the Mini-Mental State Examination-Japanese (MMSE-J) and the Japanese version of the Montreal Cognitive Assessment (MOCA-J) (Igarashi et al., 2022). However, the study was likely too small and too short in duration to expect any overt cognitive effects.

Human research to suggest benefits to patients with dementia:
None available.

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 (reviewed in Campbell 2022). 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 a 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 Braidy and Liu, 2020). Restoring NAD+ levels may lead to neuroprotection through numerous mechanisms, including reduced oxidative stress, anti-inflammatory effects, inhibition of apoptosis, and improved mitochondrial function (reviewed in Campbell 2022).

Alzheimer's models: In a mouse model of Alzheimer's disease (APPswe/PS1dE9 mice), NMN treatment (100 mg/kg, s.c., every other day) for 28 days significantly decreased Aβ production, amyloid plaque burden, synapse loss, and inflammatory responses (decreased IL-1β, IL-6, TNF-α)(Yao et al., 2017). Synapse loss, as measured by synaptophysin and PSD-95, was completely prevented in the cortex and hippocampus with NMN treatment. Some of these neuroprotective benefits may be, in part, attributed to NMN-induced inhibition of JNK activation.

In the same mouse model, NMN treatment (100 mg/kg, s.c., every other day) for 28 days decreased full-length mutant APP, restored mitochondrial respiratory function, and decreased SIRT1 activity that was significantly increased with age in transgenic mice (Long et al., 2015). In brain mitochondria isolated from APPswe/PS1dE9 mice, oxygen consumption deficits were reversed by NMN administration. The transgenic mice had increased mitochondrial fragmentation compared to non-transgenic mice, but NMN treatment gave rise to longer mitochondria in the hippocampus, likely through increased fusion or decreased fission.

In a rat model of Alzheimer's disease (intracerebroventricular infusion of Aβ), NMN treatment (500 mg/kg, i.p.) for 10 days improved cognitive function measured by the Morris water maze (Wang et al., 2016). In organotypic hippocampal slice cultures, NMN treatment restored NAD+ levels, decreased reactive oxygen species, and prevented the Aβ-induced inhibition of synaptic plasticity (long-term potentiation).

Vascular cognitive impairment models: In a rat model of vascular cognitive impairment (induced by bilateral common carotid artery occlusion), NMN pretreatment for 14 days significantly prevented cognitive impairment, measured by the Morris water maze and new object recognition tests (Yu et al., 2022). Pretreatment with NMN also increased myelin basic protein (MBP, a marker for myelin) expression and reduced SMI32 (a marker for demyelinated axons) intensity and SMI32/MBP ratio compared with the vehicle group, suggesting that NMN might ameliorate carotid artery occlusion-induced white matter lesions. NMN pretreatment also reduced microglial activation and inhibited microglial phagocytosis.

Aging and other cognitive impairment models: In aged mice (24-month-old C57BL/6 mice), NMN treatment (500 mg/kg/day) for 14 days restored neurovascular coupling responses by increasing endothelial NO-mediated vasodilation, which was associated with improved spatial working memory and gait coordination (Tarantini et al., 2019). In a related study of aged mice, NMN treatment (500 mg/kg/day) for 14 days induced genes in the neurovascular unit that are involved in mitochondrial rejuvenation, anti-inflammatory pathways, and anti-apoptotic pathways (Kiss et al., 2020).

Cerebromicrovascular endothelial cells isolated from aged rats exhibit increased oxidative stress, impaired proliferation and cellular migration, and impaired ability to form capillary-like structures, but NMN treatment significantly improved angiogenic processes and attenuated reactive oxygen species production (Kiss et al., 2019). These effects of NMN were prevented by a SIRT1 inhibitor, EX-527.

In people with diabetes, hypoglycemia-induced brain injury is a potential complication that can lead to neuronal death and cognitive impairment as a consequence of reactive oxygen species production, DNA damage, and depletion of NAD+. In a rat model of insulin-induced severe hypoglycemia, NMN treatment (500 mg/kg/day, i.p.) for one week following the induction of hypoglycemia attenuated spatial learning and memory impairment while reducing neuron death by 83% and preventing disruption of synaptic plasticity as measured by hippocampal long-term potentiation (Wang et al., 2020).

In a mouse model of chemotherapy (cisplatin)-induced cognitive impairment, NMN pretreatment (250 mg/kg/day, i.p.) before 4 cycles of cisplatin administration restored NAD+ levels and prevented the abnormalities in hippocampal neurogenesis, neuronal morphology, and cognitive function (Morris water maze) without affecting tumor growth or anti-tumor efficacy of cisplatin (Yoo et al., 2021).

Brain injury models: In a rat model of moderate-to-severe traumatic brain injury (controlled cortical impact), NMN treatment (43.75 mg/kg, i.p.) one hour after injury significantly attenuated histological damages, neuronal death, and brain edema, and improved neurological and cognitive deficits (Morris water maze) (Zhu et al., 2023). NMN treatment also suppressed activated astrocytes and microglia (GFAP and Iba-1) and inhibited inflammation (NFkB, Jak-STAT, and TNF signaling pathways).

APOE4 interactions: Unknown.

Aging and related health concerns: Clinical trials have shown that NMN increases some components of the NAD+ metabolome, but NMN has shown little effect in improving clinically relevant outcomes thus far.

Types of evidence:

- 11 double-blind randomized controlled clinical trials
- 1 open-label clinical study
- 6 reviews
- Numerous laboratory studies

Physical performance: SOME BENEFITS BUT INCONSISTENT/INCONCLUSIVE
In a double-blind randomized controlled trial of 80 healthy middle-aged participants, treatment with NMN (300 mg, 600 mg, or 900 mg daily, orally; AbinoNutraNMN) for 60 days significantly raised blood NAD+ levels and increased walking distance on the 6-minute walking test compared to the placebo group (Yi et al., 2023). Subjective health, assessed by the SF-36 scores, was significantly improved on day 30 and day 60 with NMN (600 mg and 900 mg doses) compared to the placebo group ($p<0.05$). The blood biological age (Aging.Ai 3.0 calculator, Insilico Medicine, Inc., Hong Kong and NY) was increased in the placebo group and stayed unchanged in all NMN dose groups, resulting in a significant difference between NMN groups and placebo ($p<0.05$ for all). The Aging.Ai 3.0 calculator is based on a total of 19 clinical laboratory test parameters: albumin, fasting glucose, urea (BUN), total cholesterol, protein total, sodium, creatine, hemoglobin, bilirubin total, triglycerides, HDL cholesterol, LDL cholesterol, calcium,

potassium, hematocrit, MCHC, MCV, platelets, and erythrocytes (RBC). No significant NMN effects were observed for HOMA-IR. The NMN was manufactured by Aba Chemicals Co., Ltd, Shanghai, China in collaboration with Abinopharm, Inc., CT, US, and the 2 companies co-sponsored this trial.

In a double-blind randomized controlled trial of 48 young and middle-aged recreationally trained runners, medium (600 mg daily), and high (1,200 mg daily) doses of NMN treatment (GeneHarbor Biotechnologies Ltd., Hong Kong) for 6 weeks significantly increased oxygen uptake (VO2), percentages of maximum oxygen uptake (VO2max), and power at first ventilatory threshold compared with the placebo group (Liao et al., 2021). However, there was no effect of NMN (any dose) on grip strength, push-up, sit-and-reach, body mass, BMI, body fat %, VO2max, O2-pulse, VO2 related to work rate, and peak power after 6 weeks of treatment. Also, no effects were seen with the low dose NMN (300 mg daily) on any of the measures. The authors speculate that NMN increases ventilatory threshold through an improved ability of O2 utilization by skeletal muscle, as no changes were observed in VO2max, O2 pulse, and change in O2 relative to change in work rate.

In a double-blind randomized controlled trial of 20 healthy older men (65 years or older), NMN treatment (250 mg daily) for 12 weeks significantly increased NAD+ levels as well as NAD+ metabolite concentrations, and improved gait speed (p=0.033) and grip test (p=0.019), but no significant effects were seen on skeletal muscle mass or visceral fat (Igarashi et al., 2022).

In a double-blind randomized controlled trial of 108 older Japanese adults (over 65 years old), NMN treatment (in the morning or in the evening; 250 mg daily; Mitsubishi Corporation Life Sciences Ltd., Japan) for 12 weeks improved physical performance (measured by 5-times sit-to-stand)(Kim et al., 2022). The effect size was largest in the group taking NMN in the evening (after 6pm).

In a double-blind randomized controlled trial of 66 middle-aged and older adults (40-65 years old), NMN treatment (300 mg daily, orally; Uthever) for 60 days did not significantly improve walking endurance (6-minute walking test) or well-being (SF36 questionnaire) compared to placebo (Huang et al., 2022). The NMN treatment increased serum NAD+/NADH levels (by 38%), though the difference between NMN and placebo was not significant.

In aging mice, NMN treatment (100 or 300 mg/kg/day in drinking water) started at 5 months of age and continued for 12 months suppressed age-associated body weight gain, enhanced energy metabolism (increased food intake, oxygen consumption, energy expenditure), increased physical activity, improved insulin sensitivity, and ameliorated eye function and bone density (Mills et al., 2016).

Cardiovascular disease: INCONCLUSIVE

In a double-blind randomized controlled trial of 36 healthy middle-aged participants, NMN treatment (125 mg twice daily; DHC Corporation) for 12 weeks significantly increased serum nicotinamide and tended to decrease pulse wave velocity values (measure of arterial stiffness), though it was not statistically significant (Katayoshi et al., 2023). The levels of serum NAD+ and NMN were below the lower limit of quantification and could not be compared between NMN and placebo groups. Ankle-brachial index and brachial-ankle pulse wave velocity were measured to evaluate blood flow and arterial stiffness, respectively. A meta-analysis of longitudinal studies have reported that high brachial-ankle pulse wave velocity is associated with a 3-fold risk of cardiovascular events (Vlachopoulos et al., 2012). The average brachial-ankle pulse wave velocity values in the NMN treatment group tended to decrease by 25.1 ± 14.5 cm/s, but this difference was not significant compared to placebo (p=0.097)(Katayoshi et al., 2023).

In a subgroup analysis of subjects with above-average BMI or blood glucose levels, NMN treatment significantly decreased brachial-ankle pulse wave velocity values compared to the placebo group (Katayoshi et al., 2023). There were no effects of NMN on other biomarkers, including BMI, blood glucose levels, urinary 8-hydroxydeoxyguanosine (8-OHdG), SIRT1 mRNA expression in the blood, and advanced glycation end products (AGEs) in the skin.

In a double-blind randomized controlled trial of 66 middle-aged and older adults (40-65 years old), NMN treatment (300 mg daily, orally; Uthever) for 60 days did not significantly alter pulse pressure, systolic blood pressure or diastolic blood pressure (Huang et al., 2022).

In a double-blind randomized controlled trial of 30 healthy subjects, NMN treatment (250 mg daily; Mitsubishi Corporation Life Sciences Limited, Tokyo, Japan) for 12 weeks significantly increased blood NAD+ levels but this increase varied across individuals and correlated with baseline pulse rate (Okabe et al., 2022). However, NMN treatment did not significantly alter body weight, BMI, systolic blood pressure, diastolic blood pressure, or pulse rate.

In a double-blind randomized controlled trial of 20 healthy older men (65 years or older), NMN treatment (250 mg daily) for 12 weeks significantly increased NAD+ levels as well as NAD+ metabolite concentrations, but no significant effects were seen on triglyceride, LDL-cholesterol, HDL-cholesterol, and C-peptide levels (Igarashi et al., 2022).

In an open-label, single-arm exploratory study of 10 healthy volunteers, an intravenous dose of NMN (300 mg in 100 mL saline) increased blood NAD+ levels and decreased triglyceride levels, but did not affect total cholesterol, LDL cholesterol, HDL cholesterol, electrocardiograms, pulse, and blood pressure (Kimura et al., 2022).

In a study of old mice, NMN treatment (300 mg/kg, daily, in drinking water) for 8 weeks restored endothelium-dependent dilation, reduced aortic pulse-wave velocity, normalized O2 production, decreased nitrotyrosine, reversed collagen-1, increased elastin, and restored SIRT1 activity (di Picciotto et al., 2016). In isolated aortas, NMN incubation increased NAD+ levels by 3-fold and manganese superoxide dismutase (MnSOD) by 50%.

Diabetes: NO BENEFIT

In a double-blind randomized controlled trial of 14 older men with diabetes and impaired physical performance, NMN treatment (250 mg daily) for 24 weeks did not significantly improve grip strength, walking speed, or blood sugar (measured by HbA1c)(Akasaka et al., 2023). There was a trend for decreased prevalence of frailty (p=0.066; but baseline frailty was different between groups) and a preservation of central retinal thickness (p=0.051) with NMN treatment compared to placebo.

In double-blind randomized controlled trials of healthy people, NMN treatment did not significantly alter measures of glucose metabolism (e.g., fasting glucose, HbA1c, HOMA-IR)(Okabe et al., 2022; Igarashi et al., 2022; Huang et al., 2022).

Obesity: INCONCLUSIVE

In a double-blind randomized controlled trial of 31 overweight or obese older adults (55-80 years old), NMN treatment (1,000 mg once daily or twice daily; MIB-626 tablet microcrystalline formulation from Metro International Biotech) for 14 days resulted in a significant increase in blood NMN and blood NAD+ levels, but did not alter fasting glucose levels, insulin, HOMA-IR, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, uric acid, or free fatty acids (Pencina et al., 2023). However, the trial was not large or long enough in duration to properly investigate NMN's effects on glucose metabolism and lipid biomarkers. The dose selection was based on pharmacokinetic data of their single-ascending dose study that suggested that 250, 500, and 750 mg of NMN failed to consistently raise NAD+ levels. Blood NMN levels were 1.7-times and 3.7-times higher compared to baseline with 1,000 mg once daily and 1,000 mg twice daily NMN. This study was funded by a research grant from Metro International Biotech.

In a double-blind randomized controlled trial of 25 overweight or obese postmenopausal women with prediabetes, NMN treatment (250 mg daily; Oriental Yeast Co., Ltd., Tokyo, Japan) for 10 weeks increased insulin-stimulated glucose disposal and skeletal muscle insulin signaling (increased phospho-AKT and phospho-mTOR), but did not significantly alter handgrip strength, torque, fatigue from exercise, fat mass, fat-free mass, intraabdominal adipose tissue volume, intrahepatic triglyceride content, plasma glucose, insulin, free fatty acid, lipid, adiponectin, or leptin (Yoshino et al., 2021). The authors noted that the improvement in muscle insulin sensitivity is similar to the improvement observed after ~10% weight loss and after 12 weeks of treatment with the insulin-sensitizing agent, troglitazone. NMN treatment did not alter muscle NAD+ or nicotinamide content after 10 weeks, but NMN treatment increased NMN metabolites (increased muscle N-methyl-nicotinamide, methyl-2-pyridone-5-carboxamide, and N-methyl-4-pyridone-5-carboxamide), suggesting increased NAD+ turnover. NMN supplementation also upregulated the expression of platelet-derived growth factor receptor β and other genes related to muscle remodeling.

Osteoporosis: POTENTIAL BENEFIT BASED ON PRECLINICAL STUDIES
In a mouse model of osteoporosis (ovariectomy-induced), NMN treatment (400 mg/kg/day, intragastrically) for up to 2 months attenuated senescent cell induction in growth plates and partially prevented osteoporosis, while enhancing bone healing capacity (Lu et al., 2023). In human primary osteoblasts, NMN restored NAD+/NADH levels and ameliorated TNF-α-mediated senescence induction and the impaired osteogenic differentiation.

Sleep: NO BENEFIT
In a double-blind randomized controlled trial of 108 older Japanese adults (over 65 years old), NMN treatment (in the morning or in the evening; 250 mg daily; Mitsubishi Corporation Life Sciences Ltd., Japan) for 12 weeks did not significantly improve sleep quality (Kim et al., 2022). Drowsiness was improved in the group receiving NMN in the evening, but it was also improved in the group receiving placebo in the evening.

Telomere length: MAY INCREASE
In a non-blinded non-controlled clinical study of 8 healthy men aged 45-60 years old, NMN supplementation (300 mg/day) for 90 days significantly increased telomere length in peripheral blood mononuclear cells (Niu et al., 2021). The increase compared to baseline was observed after 30, 60, and 90 days. A larger randomized controlled double-blind study is needed to confirm these findings.

Safety: Clinical trials have shown that NMN is well-tolerated with mild adverse events, though most studies have been short in duration. Long-term safety needs to be established.

Types of evidence:

- 11 randomized controlled clinical trials
- 2 non-randomized clinical trials
- 1 review
- Numerous laboratory studies

Clinical studies in healthy people:
In a double-blind randomized controlled trial of 80 healthy middle-aged participants, treatment with NMN (300 mg, 600 mg, or 900 mg daily, orally; AbinoNutraNMN) for 60 days was well-tolerated based on adverse events, laboratory values, and clinical measures (Yi et al., 2023). The only parameters that were statistically different from placebo groups were mean corpuscular hemoglobin concentration and LDL cholesterol in the NMN 900 mg group (baseline, 132.80 ± 39.70; day 60, 146.00 ± 36.90), and uric acid nitrogen in the NMN 600 mg group. No clinically meaningful abnormalities were observed in vital signs, physical findings, or clinical lab parameters. A total of 9 adverse events were reported, 6 of which were in the placebo group and 3 were in the NMN 300 mg group; no adverse events were observed in the NMN 600 or 900 mg groups. All adverse events were mild or moderate.

In the largest double-blind randomized controlled trial to date, 108 older Japanese adults (over 65 years old) were enrolled and received NMN (in the morning or in the evening; 250 mg daily; Mitsubishi Corporation Life Sciences Ltd., Japan) or placebo for 12 weeks (Kim et al., 2022). There were no reported side effects from NMN in this study.

In a double-blind randomized controlled trial of 48 young and middle-aged recreationally trained runners, NMN treatment (300, 600, or 900 mg daily, orally; GeneHarbor Biotechnologies Ltd., Hong Kong) for 6 weeks did not result in overt abnormalities on the echocardiogram (Liao et al., 2021). None of the participants reported any adverse events.

In a double-blind randomized controlled trial of 31 healthy men and women (age 20-65), NMN treatment (1,250 mg daily, orally) for 4 weeks did not result in clinically significant changes in anthropometry, hematology, biochemistry, urinalysis, and body composition (Fukamizu et al., 2022). No severe adverse events were observed during the study. There were 5 adverse events observed during the study period: 1 person in the placebo group had loose stool and 4 people in the NMN group had a

common cold, high blood pressure, loose stool, and acne vulgaris. The investigator determined that there was no direct causal relationship between NMN and any of the adverse events.

In a double-blind randomized controlled trial of 66 middle-aged and older adults (40-65 years old), NMN treatment (300 mg daily, orally; Uthever) for 60 days did not result in any clinically meaningful changes in safety laboratory tests (Huang et al., 2022). One participant in the NMN group and one participant in the placebo group had mild dyslipidemia, which was resolved with medication.

In a double-blind randomized controlled trial of 36 healthy middle-aged participants, NMN treatment (125 mg twice daily, orally; DHC Corporation) for 12 weeks was well-tolerated and did not cause any adverse events (Katayoshi et al., 2023). No significant changes were observed in measures of hematology, clinical chemistry, or hormones.

In a double-blind randomized controlled trial of 30 healthy subjects, NMN treatment (250 mg daily, orally; Mitsubishi Corporation Life Sciences Limited, Tokyo, Japan) for 12 weeks did not cause any abnormalities in physiological or laboratory tests (Okabe et al., 2022). There were 7 and 8 participants who complained about some symptoms in the placebo and NMN group, respectively, but there were no serious adverse events in either group. No participant discontinued treatment in the NMN group.

In a double-blind randomized controlled trial of 20 healthy older men (65 years or older), NMN treatment (250 mg daily) for 12 weeks was well-tolerated, and no serious adverse events occurred (Igarashi et al., 2022). No significant differences were observed between NMN and placebo groups with regards to hematological and blood chemistry parameters, including liver enzymes and renal function markers. All clinical laboratory values were within the normal range in the NMN group.

In an open-label, single-arm exploratory study of 10 healthy volunteers, an intravenous dose of NMN (300 mg in 100 mL saline) did not lead to any abnormalities with regards to urinalysis, blood cell counts, electrocardiograms, and chest radiographs (Kimura et al., 2022). There were no changes in liver, pancreas, heart, and kidney metabolism markers.

Clinical studies in patient populations:
In a double-blind randomized controlled trial of 31 overweight or obese older adults (55-80 years old), NMN treatment (1,000 mg once daily or twice daily; MIB-626 tablet microcrystalline formulation from Metro International Biotech) for 14 days was well-tolerated and the frequency of adverse events was similar to placebo (Pencina et al., 2023). One participant in the NMN 1,000 mg twice-daily group had

diarrhea between Days 8 and 14. Clinical laboratory values were not significantly different between NMN and placebo groups. Two participants, one in the NMN 1,000 mg daily group and one in the placebo group, experienced mild AST and ALT elevations on Day 14; these levels returned toward baseline after discontinuation of the study in both participants. There were no clinically significant changes from baseline in vital signs or QTc interval in any group.

In a double-blind randomized controlled trial of 25 overweight or obese postmenopausal women with prediabetes, NMN treatment (250 mg daily; Oriental Yeast Co., Ltd., Tokyo, Japan) for 10 weeks did not result in any abnormalities in blood tests (Yoshino et al., 2021). No adverse events were reported in this study.

In a double-blind randomized controlled trial of 14 older men with diabetes and impaired physical performance, NMN treatment (250 mg daily) for 24 weeks was well-tolerated with no severe adverse events (Akasaka et al., 2023). One patient in the placebo group discontinued the study due to acute heart failure as a serious adverse event. One patient in the NMN group discontinued treatment after the 12-week visit due to diarrhea. These events were deemed not related to the study medication. Adverse events occurred in comparable frequencies between placebo and NMN groups.

Laboratory studies:
In an acute and subchronic (90-day) safety study in rats, a high purity form of NMN (NMN-C®) at doses up to 1500 mg/kg/day was not mutagenic or genotoxic and appeared to be safe based on body weight, food and water consumption, biochemical and blood parameters, and organ histology (Cros et al., 2021). In this study, a no-observable adverse effect level (NOAEL) for NMN-C® was determined to be over 1,500 mg/kg/day in rats.

In a subacute toxicity study in beagle dogs, NMN (1,340 mg/day, oral gavage) administration for 14 days resulted in a mild increase in blood creatinine levels, suggesting mild adverse effects on the kidneys of dogs (You et al., 2020).

In aging mice, NMN treatment (100 or 300 mg/kg/day in drinking water) started at 5 months of age and continued for 12 months did not generate any serious adverse effects or obvious toxicity (Mills et al., 2016).

In the Ames test (bacterial reverse mutation test), NMN did not increase revertant mutant colonies at any of the treatment concentrations tested (313, 625, 1250, 2500, and 5000 µg/plate)(Fukamizu et al., 2022).

Theoretical concerns:
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). In a mouse model of chemotherapy (cisplatin)-induced cognitive impairment, NMN pretreatment (250 mg/kg/day, i.p.) before 4 cycles of cisplatin administration restored NAD+ levels without affecting tumor growth or anti-tumor efficacy of cisplatin (Yoo et al., 2021).

NAD+ depletion via NAMPT inhibitors has also 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 the day, suggesting the possibility that supplementation might disrupt healthy circadian signaling (Peek et al 2013).

Drug interactions:
Drug or supplement interactions with NMN have not been well-studied to date.

Sources and dosing:

MIB-626, a pharmaceutical grade tablet of NMN is under clinical development by Metro International Biotech.

Although NMN used to be sold as a dietary supplement, at the end of 2022, the FDA announced that NMN can no longer be sold as a dietary supplement in the US due to its authorization as an investigational new drug (Freeberg et al., 2023).

NMN is contained in some foods, such as edamame, broccoli, cucumber, and cabbage, but at low levels (0.25-1.88 mg of NMN per 100 g)(Mills et al., 2016). Fruits such as avocado and tomato contained 0.26-1.60 mg of NMN per 100 g.

Research underway:

There are currently 10 clinical trials testing NMN, based on ClinicalTrials.gov. These studies are in people with type 2 diabetes, hypertension, ovarian insufficiency, polycystic ovary syndrome, COVID-19, and in healthy people. There are 4 additional studies testing MIB-626, a pharmaceutical-grade NMN: one in Alzheimer's disease, one in type 2 diabetes, one in Friedreich ataxia, and one in COVID-19. The clinical trial in Alzheimer's patients is a double-blind randomized controlled trial enrolling 50 patients and will test a dose of 1,000 mg MIB-626 twice daily for 90 days (NCT05040321). The primary outcome is the change in CSF levels of MIB-626. Secondary outcomes include changes in CSF levels of MIB-626 metabolites, change in NAD+ levels in the brain (MRS), change in NAD+ levels in peripheral blood mononuclear cells, and changes in biomarkers of aging (HbA1c, IGF1, T3, IL-6, TNF-α, and urinary F2-isoprostane).

Search terms:

Pubmed, Google: NMN, nicotinamide mononucleotide

- + meta-analysis, + Alzheimer, + cognitive, +APOE4, + clinical trial, + aging

Websites visited for NMN, nicotinamide mononucleotide:

- Clinicaltrials.gov
- Examine.com
- DrugAge
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com
- PubChem
- DrugBank.ca
- ConsumerLab.com
- Cafepharma (0)
- Pharmapro.com (0)

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