Clinical data
What is Nicotinamide Riboside (NR)?

NR is a pyridine-nucleoside form of vitamin B_3, consisting of nicotinamide (NAM) and ribose. It is also considered a more tolerable form of vitamin B3, as unlike its cousin niacin, this form of vitamin B3 is not associated with unpleasant hot flushing of the face and body.

NR is a biological precursor of the essential coenzyme Nicotinamide Adenine Dinucleotide (NAD+) in the body. NAD+ is one of the most abundant and crucial molecules found in almost every cell in the human body. It is needed for many metabolic pathways and is central to cell signalling and the production of ATP and cellular energy. This is more than just energy to enable the body to exert more power. Rather, it is the energy needed for thousands of chemical processes and functions to enable cells to survive (1).

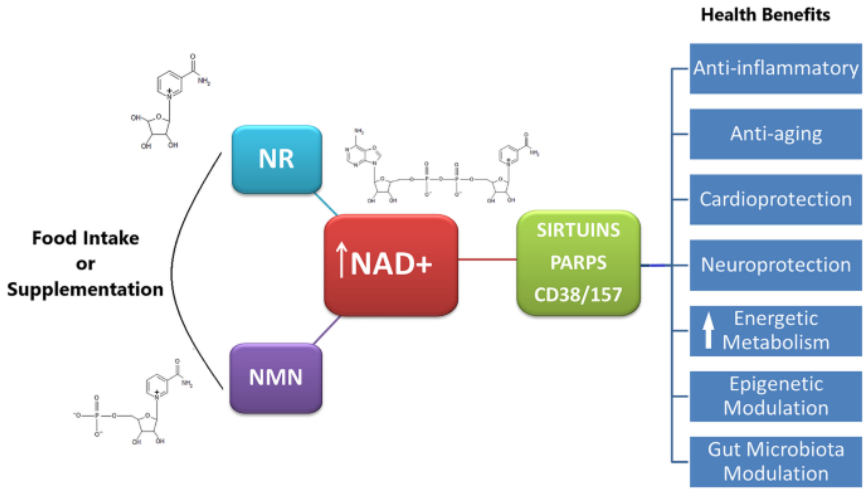
Accumulating research findings on Nicotinamide Riboside (NR) have confirmed its efficacy in various animal and human studies. This includes increasing the activity of the longevity Sirtuin enzymes. These incredible proteins are a group of seven enzymes that wield their unique catalytic powers to influence various cellular processes and potentially hold the key to unlocking the secrets of longevity. Sirtuins stimulate energy production, improve mitochondrial function, repair DNA damage, reduce total cholesterol and fat accumulation levels to promote liver health, reduce neuroinflammation and amyloid production in the brain, prevent axonal degeneration. These diverse functions support the potential of Sirtuins for treating cardiovascular, neurodegenerative, and metabolic disorders (2).

NR Primary Benefits (based on human clinical data)

1. Elevates cellular NAD+ levels in mature adults
2. Supports cellular energy and repair as an essential cofactor for energy production.
3. A bioavailable and non-flushing form of niacin

In vivo mammalian studies

1. Improved insulin sensitivity
2. Improved strength
3. Improved muscle quality
4. Reduced muscle degeneration/senescence
5. Improved neurogenesis, reduced cognitive degeneration, protection against Alzheimer's.
6. Improved metabolism and protection against obesity
7. Effectiveness in the treatment of mitochondrial disease in mice (4).

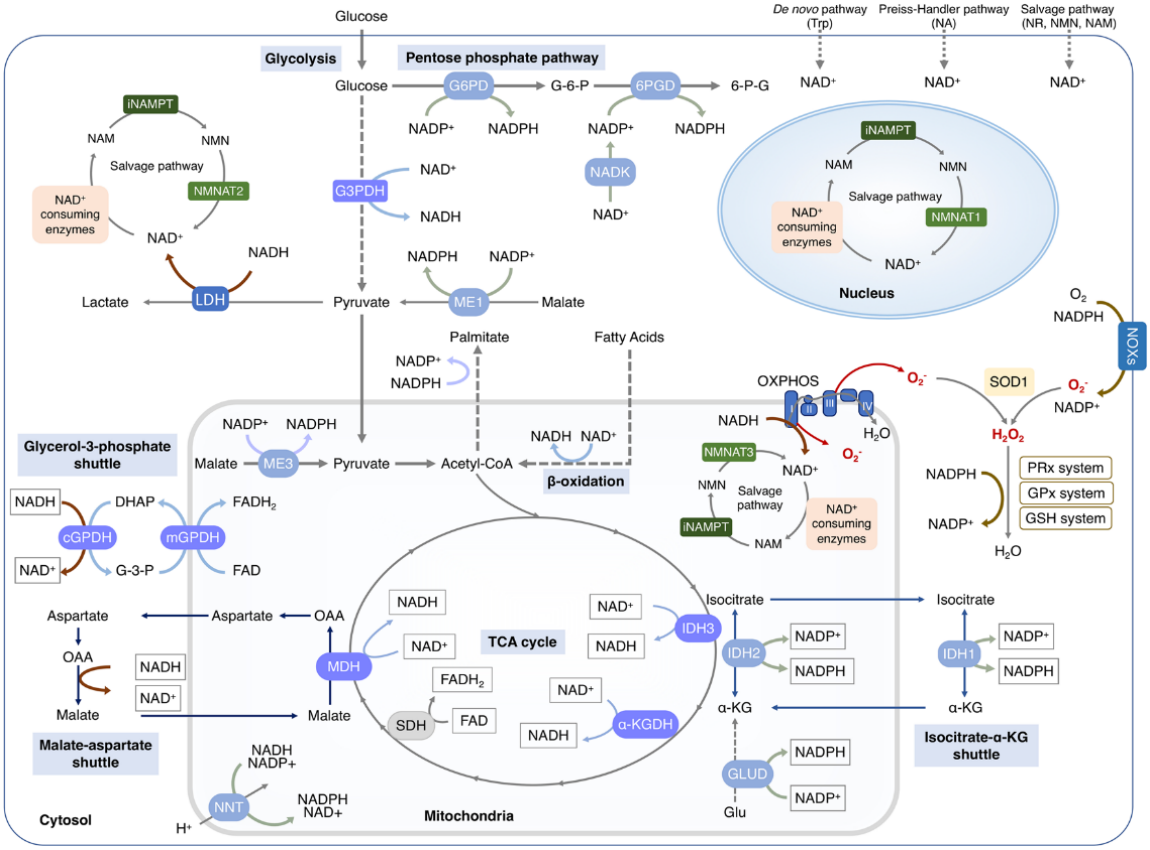


Whole body benefits of optimal NAD+ levels (5)

The importance of Nicotinamide adenine dinucleotide (NAD+) to all cells

Approximately 200 enzymes rely on NAD+ as an electron acceptor for vital chemical reactions. NAD+ is the ultimate energy source for cells: By accepting electrons, NAD+ gets "charged up" and becomes NADH, ready to donate its stored energy for various cellular functions. NAD+ is necessary for oxidative reactions in the cytosol and mitochondria, playing a fundamental role in cellular health. It is also required for carbohydrate oxidation during adenosine triphosphate. (ATP) production.

Research indicates that systemic NAD+ levels decrease due to reduced synthesis rates. The substantial demand for NAD+, crucial for cellular processes, can be restored by supplementing NAD+ precursors such as NR. Additionally, fasting, caloric restriction and exercise, have demonstrated the ability to significantly elevate NAD+ levels in the body (2).



Intracellular metabolic pathways of NAD+ metabolism (3)

In addition to its crucial function as a coenzyme in energy metabolism, the important role of NAD+ has expanded to be a co-substrate for various enzymes including Sirtuins, PARPs, CD157, CD73, CD38 and SARM1, all of which impact DNA repair, cellular aging and epigenetic adaptation (3).

What are Sirtuins?

The Silent Information Regulator (SIR) genes (Sirtuins) are genes that contain the code to create a family of 7 proteins, called Sirtuins. Sirtuins primarily promote cellular resilience and longevity. They also help to maintain NAD+ levels and protects the cells from damage (6).

How do sirtuin enzymes function?

The sirtuin enzymes remove acetyl groups from lysine residues on various cells proteins through a process called deacetylation. This modification alters the function of the cell proteins impacting metabolism, gene expression and response to cell stress. The sirtuin proteins are able to silence specific regions of the DNA, prevented unwanted gene expression. This process is crucial for maintaining gene stability and regulating cell differentiation. Sirtuins are present in virtually all species and seven sirtuin genes - SIRT1 to SIRT7 - have been identified in humans (7).

Sirtuins and NAD+ must exist in synergy. Sirtuins are NAD+ dependent histone deacetylases and require NAD+ as a vital cofactor for their enzymatic activity on cell proteins. Sirtuins can detect changes in metabolism and energy homeostasis and are involved in various biological processes such as:

- cell survival
- senescence
- proliferation
- apoptosis,
- DNA repair
- DNA expression
- cell metabolism

Sirtuins are also activated by caloric restriction, fasting, moderate intensity exercise and certain antioxidants such as quercetin, resveratrol and green tea. Sirtuins have been considered potential targets for the treatment of human age-related pathologies including neurodegenerative diseases, cardiovascular diseases, respiratory conditions, and cancer (7).

	Substrates/targets			Function
	Modification	**Activation**	**Inhiibition**	
SIRT1	H3K9ac, H3K26ac, H3K16ac, H1K26, H1K9, H3K56, H3K14, H4K16, α-tubulin, p53	Suv39h1, N-Myc, ER, Sirt6, ADAM-10, LKB1, AMPK, NBS1, XPA, MnSOD, WRN, Ku70, FOXO1/3, PGC-1a, PPARα, FXR	NF-KB, p300, p66^{shc}, mTOR, HIF-1a, TNF-1a, Histone acctylation, SREBP-1c	Glucose metabolism, fatty-acid and cholesterol metabolism, differentiation, insulin secretion, and neuroprotection, stress responses, DNA repair, vascular protection and other cellular processes
SIRT2	α-tubulin, H3K56ac, H4K16ac,	FOXO, c-Myc, G6PD, PEPCK	NF-KB, p53, FoxO1	Cell-cycle control, carbohydrate and lipid metabolism, tubulin and transcription factors deacetylation and anti-inflammatory
SIRT3	H3K9, H4K16, H3K56ac, H4K14ac,	Ku70, Mn-SOD, FOXO3a, DH2, FAO, GDH, complexI/III, IDH2	p53, HIF-1a, Ros, lipogcncasis	regulation of mitochondrial enzymes deacetylation, ATP production, reactive oxygen species (ROS) management, b-oxidation, ketogenesis, cell death, and carbohydrate and lipid metabolism
SIRT4			GDH, AMPK, ROS, PDH	Insulin secretion, glutamine and fatty acid metabolism and regulate the ATP homeostasis
SIRT5	CPS1	SOD1	GLS	Urea cycle, regulation of ATP synthesis, metabolism, apoptosis and intracellular signaling, regulation of ammonia detoxification, fatty acid oxidation
SIRT6	H2BK12, H3K9ac H3K56ac, WRN	FOXO, PARP1, CtIP, P53, DNA-PKcs, CCNDBP1	NF-KB, RELA, TNF-a, IGF-1, HIF-1a, Myc, c-Jun, PGC-1a, GCN5	Telomeres and telomeric functions, DNA repair, metabolic homeostasis, inflammation, stress responses, and genomic stability
SIRT7	H2A, H2B, H3 (H3K18)	FOXO	RNA-POLY-merase, HIF-1a/2a	regulates the transcription of rDNA and mediate histone desuccinylation

Actions of Sirtuins (7)

What are PARPs?

Like Sirtuins, PARPs, (Poly (ADP-ribose) polymerases) are a class of 17 protein enzymes involved in cell processes and due to the high NAD+ requirements, tends to deplete NAD+ in the cells.

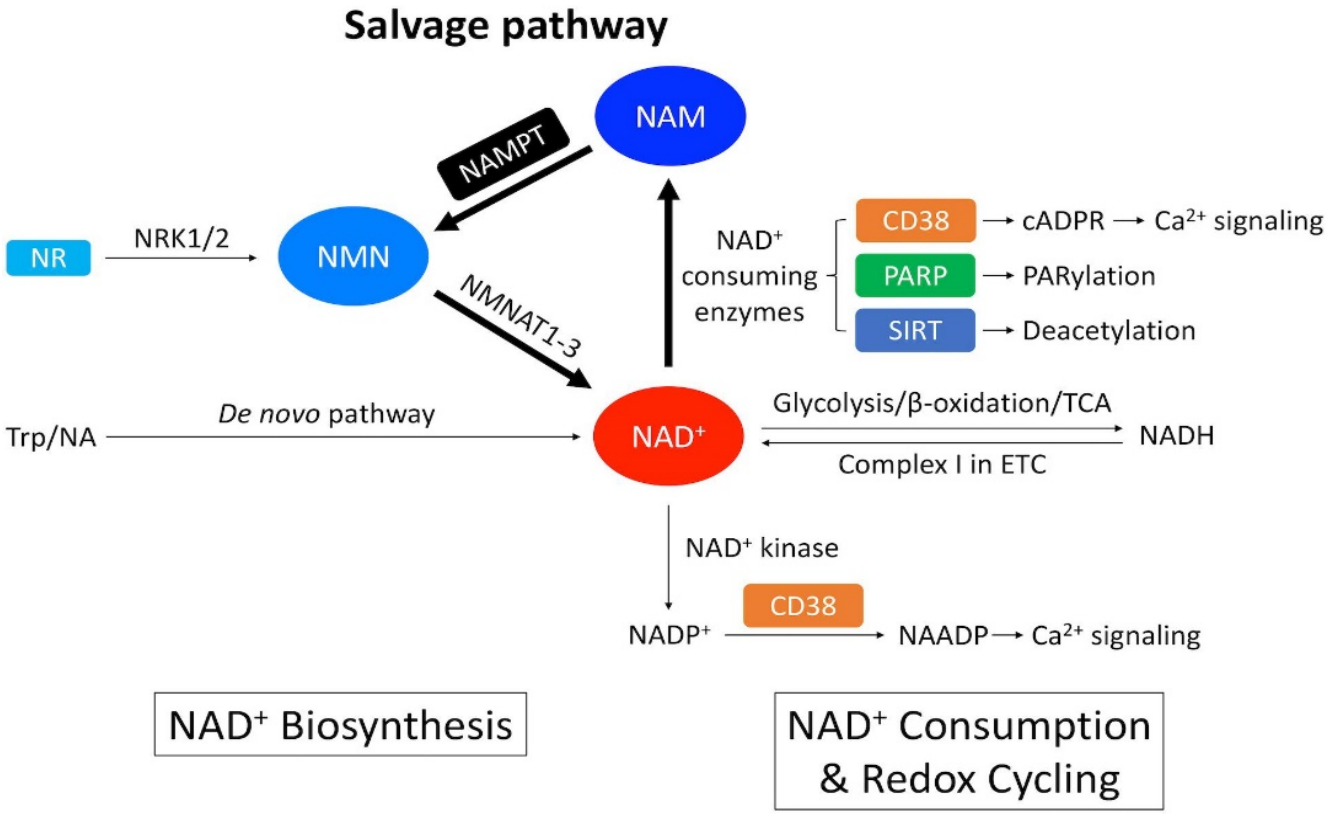
However, these enzymes modify proteins by adding ADP-ribose chains, a process called ADP-ribosylation. This modification can influence protein function, signalling, DNA repair, genomic stability and programmed cell death (apoptosis). PARP-1 belongs to the PARP family, and plays a crucial role in cellular responses to diverse stresses, including DNA damage and inflammation and its functions encompass DNA repair, modulation of inflammation, and regulation of specific gene activities. Research suggests that its activity is linked to longer lifespan in mammals and humans, playing an important role in longevity (8).

NAD+ Metabolism

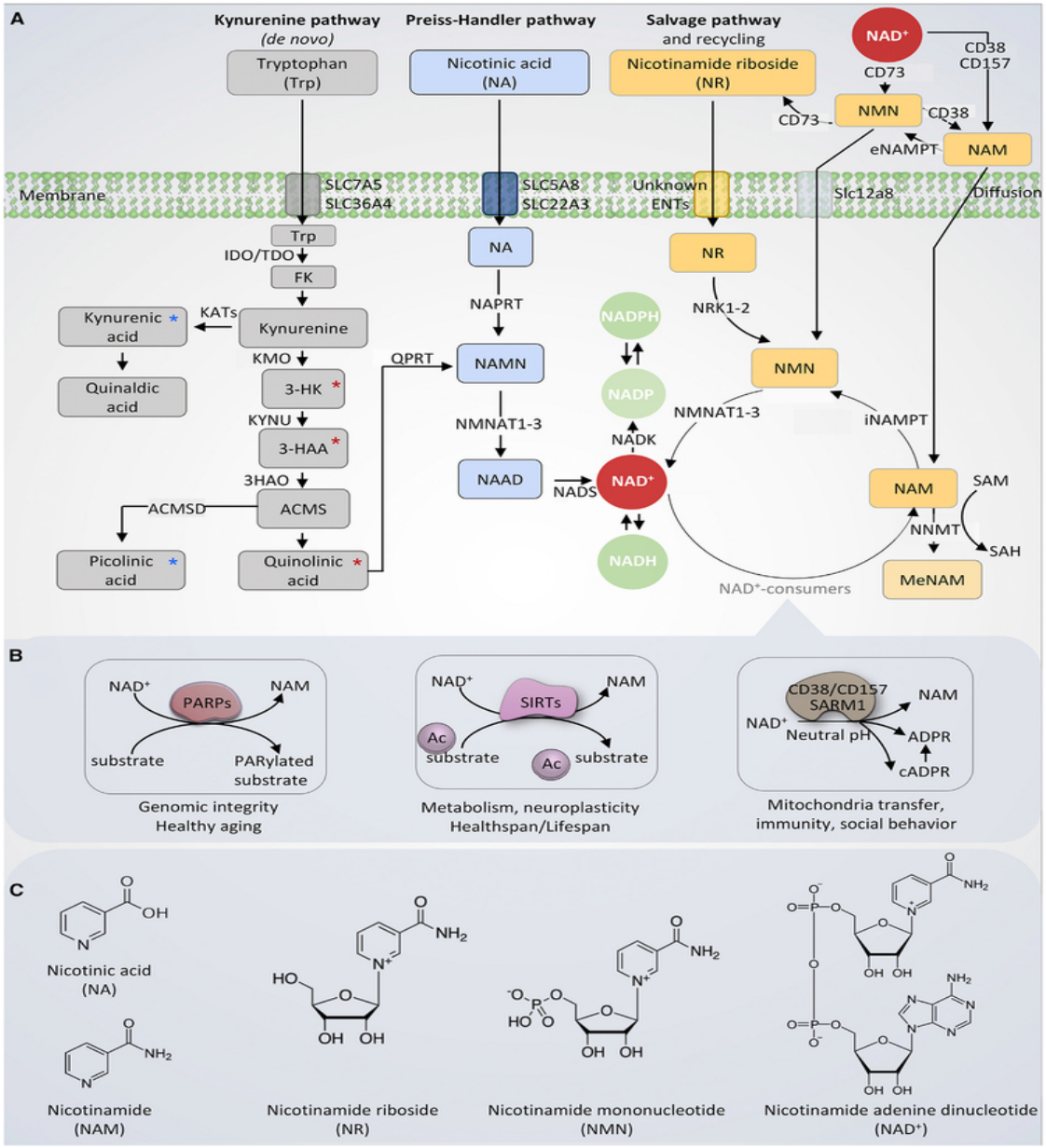
Biosynthesis can compensate depleted levels of NAD^+ via the salvage pathways from four precursors,

1. Nicotinamide (NAM)
2. Nicotinic acid/Niacin (NA),
3. Nicotinamide riboside (NR)
4. Nicotinamide. mononucleotide (NMN) (2)

In the diagram below, NR, NA or NAM is converted to NMN under the influence of the enzyme nicotinamide phosphoribosyltransferase (NAMPT). The enzyme nicotinamide mononucleotide adenylyltransferase (NMNAT aka NMN transferase) then converts NMN to NAD+. The salvage pathways are the main source of NAD+ for cells (2).



The NAD+ Salvage Pathway



(NAD+) Production and Catabolism in Mammalian Cells (9)

NR Cellular Bioavailability

The literature shows that NR is considered safe and is very well tolerated. Human studies showed that taking up to 2000mg per day had no harmful side effects and the average daily dose is 300mg per day is shown to be beneficial (10).

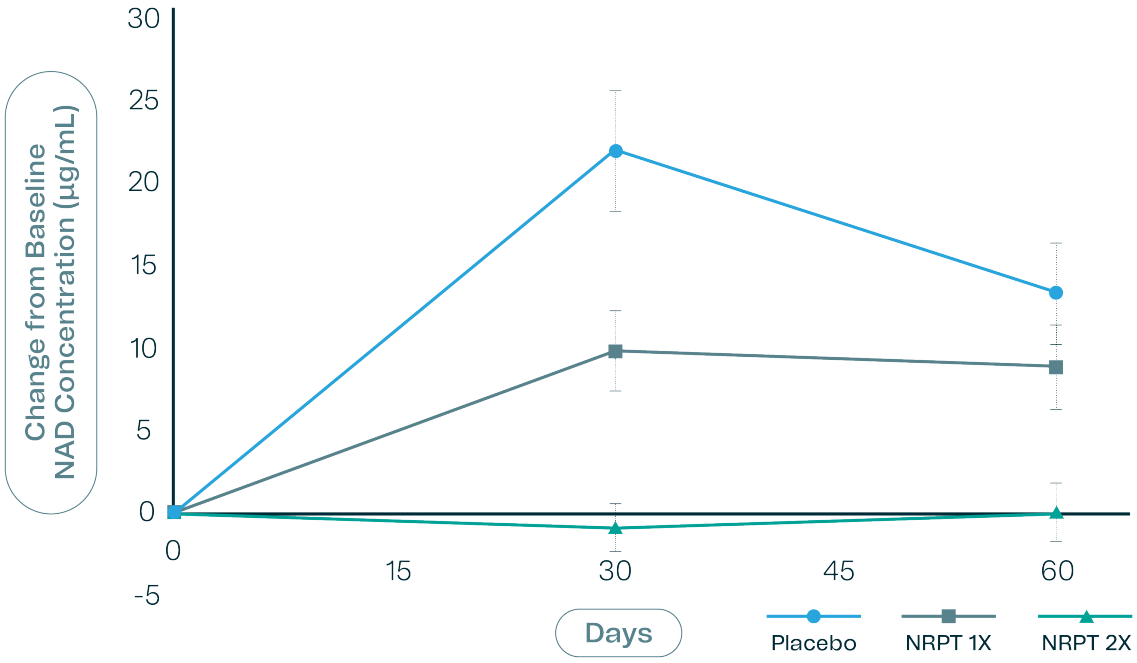
1. In vivo trial to investigate the impact of nicotinamide riboside (NR)

- 2 x 6-week randomised, double-blind, placebo-controlled, crossover clinical trial.
- Sixty healthy individuals
- Ages 55 to 79, including both middle-aged and older men and women

- The findings demonstrated that NR is well-tolerated and proficiently elevates NAD+ levels and enhances NAD+ metabolism in humans (11).

2. Human clinical trial involving NR and pterostilbene, a naturally occurring analogue of the polyphenol resveratrol

- Results revealed that a single oral dose of NR led to a notable up to 2.7-fold increase in blood NAD+ levels.
- In a randomised, double-blind, placebo-controlled human study 113 participants received NR in conjunction with pterostilbene (NRPT). The group receiving NRPT at a daily dosage of 250mg experienced a significant 40% elevation in NAD+ levels compared to baseline. The group receiving NR of a daily dose of 500mg experienced a 90% increase of NAD+ levels after 4 weeks compared to placebo and baseline (12).

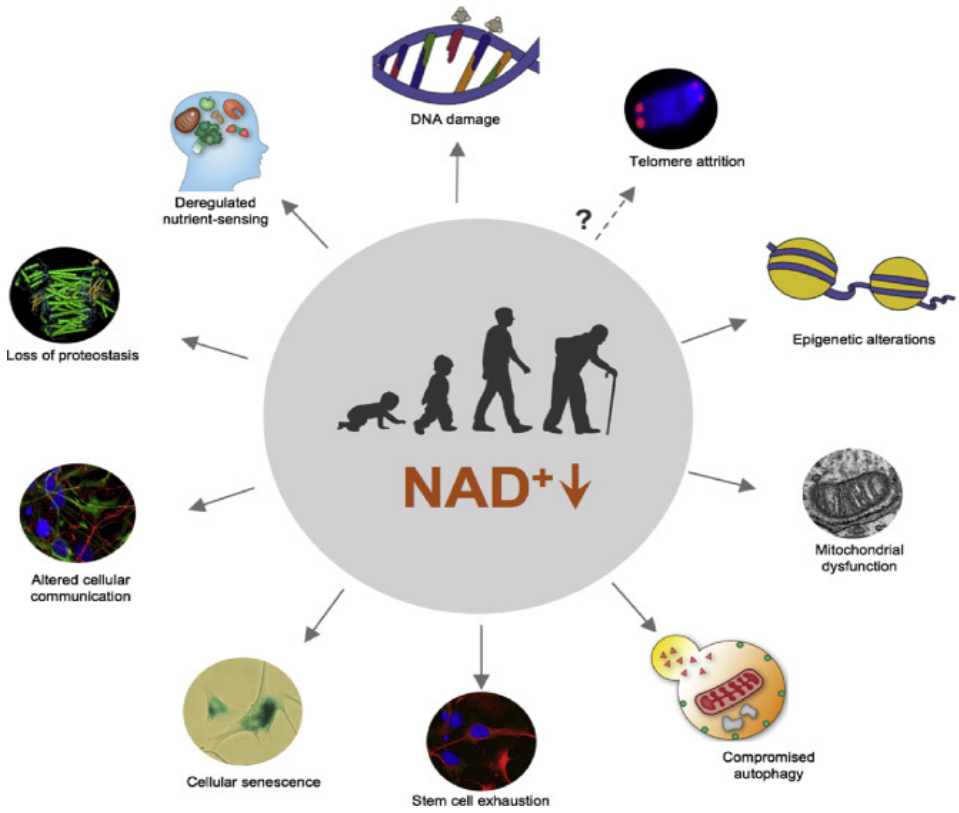


NRPT increases NAD+ levels (12)

NR Research

Ageing

A decline in NAD+ levels is linked to aging-associated diseases. Emerging evidence suggests that boosting NAD+ levels may slow or even reverse aspects of aging and delay the progression of age-related factors such as cognitive decline, glucose and lipid metabolism disorders, atherosclerosis, sarcopenia, frailty and cardiovascular diseases. New findings indicate that increasing NAD+ levels from supplementing with precursors such as NR may slow or reverse progression of these age-related diseases (13).



NAD+ decline at the core of the hallmarks of ageing (13)

NR and reduced inflammation

Chronic inflammation, mitochondrial dysfunction and increased cell senescence are some of the key features of aging, leading to the onset of age-related disorders such as cardiovascular diseases, osteoporosis, and diabetes mellitus (14).

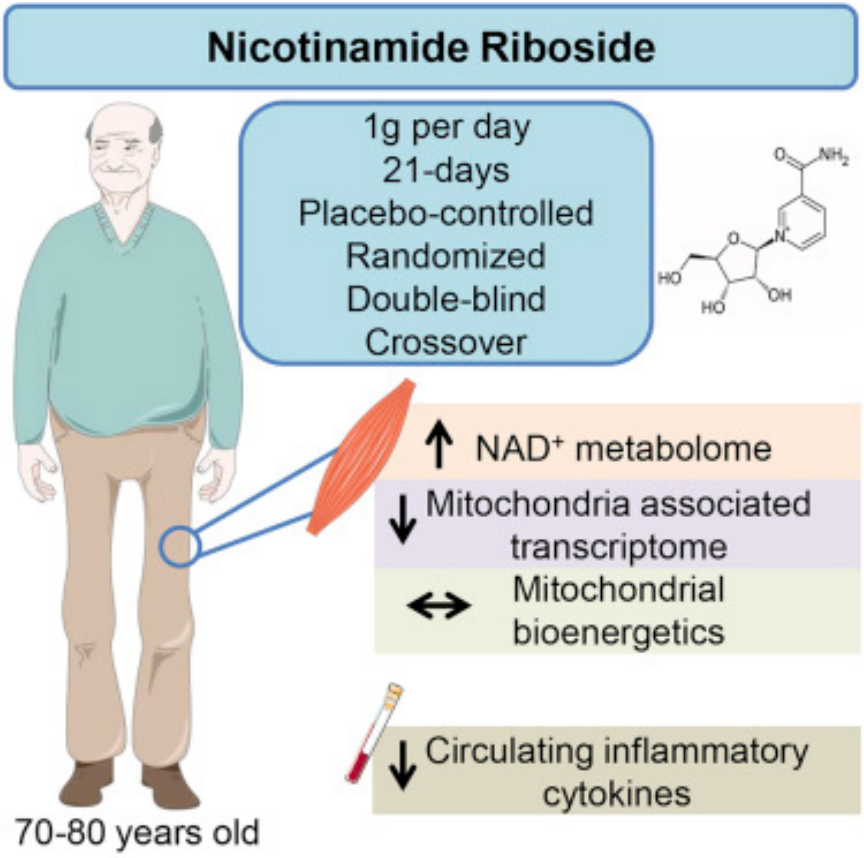
2. NR: Reduction in inflammation and elevated muscle NAD+ levels-In vivo human trial

A placebo-controlled, randomised, double-blind, crossover study, aimed to investigate the effects of oral nicotinamide riboside (NR) supplementation on NAD+ levels in skeletal muscle and its potential impact on muscle mitochondrial energy metabolism in elderly participants.

Over a 21-day period, twelve elderly men were administered a daily 1g NR supplement and results showed:

- elevation in muscle NAD+ levels
- reduction in circulating inflammatory cytokines
- reduction in IL-6, IL-5, IL-2 and tumour necrosis factor alpha (TNF-α).

These findings suggest that oral NR is accessible to aging human muscle and has anti-inflammatory effects (15).



Nicotinamide Riboside Augments the Aged Human Skeletal Muscle NAD+ Metabolome and Induces Transcriptomic and Anti-inflammatory Signatures (15)

NR and reduced cellular senescence

Senescence is increasingly recognised as a key contributor to the aging process. Cellular senescence is a biological process in which cells enter a state of stable growth arrest, ceasing to divide and function normally. This can be triggered by various factors such as DNA damage, telomere dysfunction, and oncogene activation. Senescent cells also exhibit a senescence-associated secretory phenotype (SASP), releasing inflammatory molecules that can affect neighbouring cells and its prolonged presence can contribute to aging, age-related diseases, and impaired tissue regeneration (16)

1. An in vivo mouse model

A clinical study investigated the impact of boosting intracellular NAD+ levels with nicotinamide riboside (NR) on senescence and mitochondrial dysfunction in ataxia telangiectasia (A-T).

- The research demonstrated that boosting intracellular NAD+ levels with nicotinamide riboside (NR) can prevent senescence and senescence-associated secretory phenotype (SASP), suppress neurodegeneration and neuroinflammation, and improve motor function in Atm−/− mice (14).

NR and reduced mitochondrial dysfunction

The research on Nicotinamide Riboside (NR) and its effects on mitochondria has yielded valuable insights. Below are some key findings from the provided search results.

1. Mitochondrial Myopathy in Mice

A study significantly postponed the advancement of the disease in both its early and late stages.

- It achieved this by strongly promoting the generation of new mitochondria in skeletal muscle and brown adipose tissue, thus averting abnormalities in mitochondrial structure and mtDNA deletion formation.
- The findings suggest that NR has a protective function in mitochondrial disease. Approaches that enhance NAD+ levels hold promise as a treatment strategy for mitochondrial myopathy (17).

2. NR and Muscle Mitochondrial Biogenesis in Humans

A study on obesity indicators using Body Mass Index (BMI)between monozygotic (genetically identical) twin pairs with very different BMI's.

- Findings revealed that long-term NR supplementation improved muscle mitochondrial biogenesis, myoblast differentiation, influenced gut microbiota and systemic NAD+ metabolism in humans, irrespective of BMI.
- Additionally, NR demonstrated the ability to regulate the epigenetic control of gene expression in both muscle and adipose tissue (18).

3. The Role of NR in Mitochondrial Biogenesis

A study is currently underway aimed to investigate if NR could increase energy production and reduce symptoms in humans with mitochondrial disease by increasing the number of mitochondria, potentially leading to improved energy production and reduced symptoms.

- These findings collectively suggest that NR holds potential for improving mitochondrial health and addressing mitochondrial disorders in both animal models and humans (19).

NR enhances metabolism

1. A mouse study

A mouse study investigated the effects of nicotinamide riboside (NR) supplementation on oxidative metabolism and obesity in mice. The study found that NR supplementation increased NAD+ levels and activated SIRT1 and SIRT3, leading to enhanced oxidative metabolism and protection against high-fat diet-induced metabolic abnormalities.

- The research demonstrated that NR could be used as a nutritional supplement to ameliorate metabolic and age-related disorders characterised by defective mitochondrial function. Additionally, the study highlighted the role of NR in reducing inflammation and oxidative stress by activating Sirtuin 1 in alcohol-stimulated macrophages (20).

2. Human clinical trial

A randomised, double-blinded, placebo-controlled, crossover intervention study with 13 participants, received 1000 mg/d of NR for 6 weeks.

- The study revealed that nicotinamide riboside (NR) supplementation increased skeletal muscle NAD+ metabolites, indicating enhanced NAD+ synthesis.
- It further demonstrated that NR supplementation led to positive changes in body composition, including a 1.33% reduction in body fat mass and a corresponding improvement in lean muscle mass. Additionally, the research revealed an increase in sleeping metabolic rate, indicating enhanced metabolic activity, even in the absence of exercise (21).

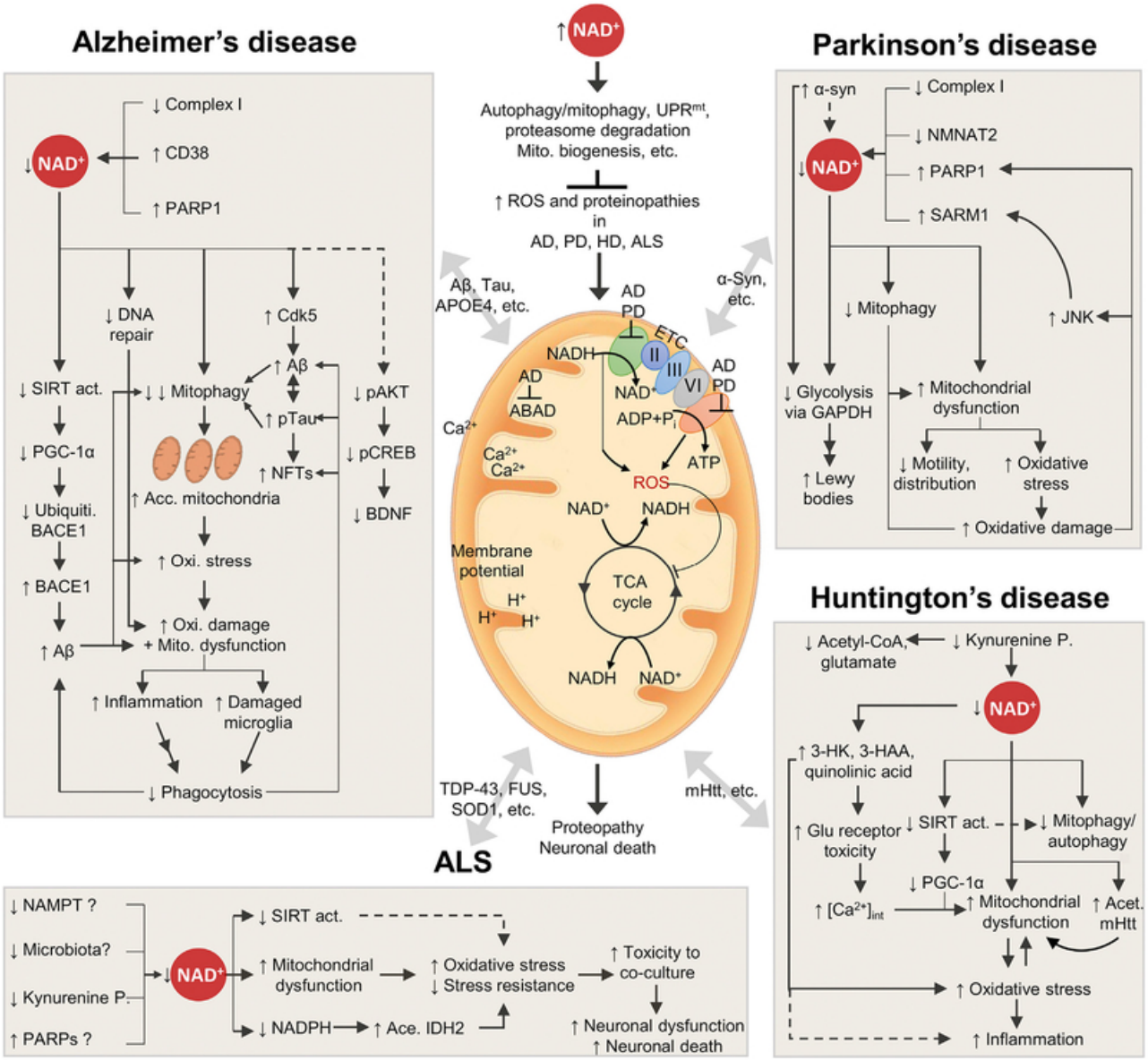
NR impacts cognition

Overall, the research suggests that NR may hold promise for supporting brain health and improving cognitive function in the context of aging and neurodegenerative diseases.

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, ALS, and in some cases, ASD, are linked to NAD+ depletion, neuroinflammation, DNA damage and oxidative stress. Nicotinamide riboside (NR) has shown to increase NAD+ levels in the brain, leading to improved cognition and reduced inflammation in serum and cerebrospinal fluid. This may help in reducing symptoms and slowing the progression of these cognitive and neuromuscular diseases (22).

The NADPARK human trial, a randomised phase I study of nicotinamide riboside (NR) supplementation in Parkinson's disease, observed a significant 90% increase in cerebral NAD+ levels in patients recently diagnosed with Parkinson's disease.

- Over a 30-day period, patients were administered either 1000mg of NR daily or a placebo. The group receiving NR treatment exhibited heightened expression of genes associated with mitochondrial energy production, as well as enhanced lysosomal and proteasomal antioxidant functions in both blood and muscle. Additionally, inflammatory cytokine levels were found to be reduced in the NR treatment group (22).



NAD+ levels and impact on neurodegenerative disorders (9)

NR and cardiovascular health

An 8-week randomised, double-blind, placebo-controlled trial with 120 healthy adults aged 60 to 80. Daily administration of 250 milligrams of NR and pterostilbene

- The study resulted in a 40 percent increase in participants' whole blood NAD+ levels compared to their baseline after just four weeks. Individuals receiving the lower dose showed reduced diastolic blood pressure and decreased levels of the liver enzyme alanine aminotransferase, indicating diminished liver damage markers (12).

References

1. Covarrubias AJ, Perrone R, Grozio A, Verdin E. NAD+ metabolism and its roles in cellular processes during ageing. Nature Reviews Molecular Cell Biology. 2020 Dec 22;22(2):119–41.

2. Mehmel M, Jovanović N, Spitz U. Nicotinamide Riboside—The Current State of Research and Therapeutic Uses. Nutrients. 2020 May 31;12(6):1616.

3. Xie N, Zhang L, Gao W, Huang C, Huber PE, Zhou X, et al. NAD+ metabolism: pathophysiologic mechanisms and therapeutic potential. Signal Transduction and Targeted Therapy [Internet]. 2020 Oct 7;5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7539288/

4. Fabiana G, Glaucia Maria Pastore. NAD+ Precursors Nicotinamide Mononucleotide (NMN) and Nicotinamide Riboside (NR): Potential Dietary Contribution to Health. Current Nutrition Reports. 2023 Jun 5;12.

5. Chini CCS, Tarragó MG, Chini EN. NAD and the aging process: Role in life, death and everything in between. Molecular and Cellular Endocrinology. 2017 Nov;455:62–74.

6. Kelly G. A Review of the Sirtuin System, its Clinical Implications, and the Potential Role of Dietary Activators like Resveratrol: Part 2. Alternative Medicine Review [Internet]. 2010 [cited 2024 Jan 9];15(4). Available from: https://altmedrev.com/wp-content/uploads/2019/02/v15-4-313.pdf

7. Zhao L, Cao J, Hu K, He X, Yun D, Tong T, et al. Sirtuins and their Biological Relevance in Aging and Age-Related Diseases. Aging and disease. 2020;11(4):927.

8. Guo S, Zhang S, Zhuang Y, Xie F, Wang R, Kong X, et al. Muscle PARP1 inhibition extends lifespan through AMPKα PARylation and activation in Drosophila. Proceedings of the National Academy of Sciences of the United States of America [Internet]. 2023 Mar 28 [cited 2024 Jan 9];120(13):e2213857120. Available from: https://pubmed.ncbi.nlm.nih.gov/36947517/

9. Lautrup S, Sinclair DA, Mattson MP, Fang EF. NAD+ in Brain Aging and Neurodegenerative Disorders. Cell Metabolism [Internet]. 2019 Oct;30(4):630–55. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1550413119305029

10. She J, Sheng R, Qin ZH. Pharmacology and Potential Implications of Nicotinamide Adenine Dinucleotide Precursors. Aging and Disease [Internet]. 2021 Dec 1;12(8):1879–97. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8612620/

11. Martens CR, Denman BA, Mazzo MR, Armstrong ML, Reisdorph N, McQueen MB, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. Nature Communications. 2018 Mar 29;9(1).

12. Dellinger RW, Santos SR, Morris M, Evans M, Alminana D, Guarente L, et al. Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD+ levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. npj Aging and Mechanisms of Disease. 2017 Nov 24;3(1).

13. Aman Y, Qiu Y, Tao J, Fang EF. Therapeutic potential of boosting NAD+ in aging and age-related diseases. Translational Medicine of Aging [Internet]. 2018 Jan 1;2:30–7. Available from: https://www.sciencedirect.com/science/article/pii/S2468501118300063

14. Yang B, Dan X, Hou Y, Lee J, Wechter N, Krishnamurthy S, et al. NAD + supplementation prevents STING-induced senescence in ataxia telangiectasia by improving mitophagy. Aging Cell. 2021 Mar 18;20.

15. Elhassan YS, Kluckova K, Fletcher RS, Schmidt MS, Garten A, Doig CL, et al. Nicotinamide Riboside Augments the Aged Human Skeletal Muscle NAD+ Metabolome and Induces Transcriptomic and Anti-inflammatory Signatures. Cell Reports [Internet]. 2019 Aug 13 [cited 2022 Apr 26];28(7):1717-1728.e6. Available from: https://pubmed.ncbi.nlm.nih.gov/31412242/
16. Korolchuk VI, Miwa S, Carroll B, von Zglinicki T. Mitochondria in Cell Senescence: Is Mitophagy the Weakest Link? EBioMedicine. 2017 Jul;21:7–13.

17. Khan NA, Auranen M, Paetau I, Pirinen E, Euro L, Forsström S, et al. Effective treatment of mitochondrial myopathy by nicotinamide riboside, a vitamin B3. EMBO molecular medicine [Internet]. 2014 Jun 1;6(6):721–31. Available from: https://pubmed.ncbi.nlm.nih.gov/24711540/

18. Lapatto HA K., Kuusela M, Heikkinen A, Muniandy M, van der Kolk BW, Gopalakrishnan S, et al. Nicotinamide riboside improves muscle mitochondrial biogenesis, satellite cell differentiation, and gut microbiota in a twin study. Science Advances. 2023 Jan 11;9(2).

19. The role of Nicotinamide Riboside in mitochondrial biogenesis (NR) [Internet]. www-neurosciences.medschl.cam.ac.uk. [cited 2024 Jan 9]. Available from: https://www-neurosciences.medschl.cam.ac.uk/mitocamb/our-research-2/research-studies/treatment-studies/the-role-of-nicotinamide-riboside-in-mitochondrial-biogenesis-nr/

20. Cantó C, Houtkooper Riekelt H, Pirinen E, Youn Dou Y, Oosterveer Maaike H, Cen Y, et al. The NAD+ Precursor Nicotinamide Riboside Enhances Oxidative Metabolism and Protects against High-Fat Diet-Induced Obesity. Cell Metabolism. 2012 Jun;15(6):838–47.

21. Remie CME, Roumans KHM, Moonen MPB, Connell NJ, Havekes B, Mevenkamp J, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. The American Journal of Clinical Nutrition. 2020 Apr 22;112(2):413–26.

22. Brakedal B, Dölle C, Riemer F, Ma Y, Nido GS, Skeie GO, et al. The NADPARK study: A randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. Cell Metabolism. 2022 Mar;34(3):396-407.e6.