



EXPLORING HEALTH WITH NMN

A look into the latest scientific
evidence of NMN's critical roles
in health and aging.

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Contact Longity

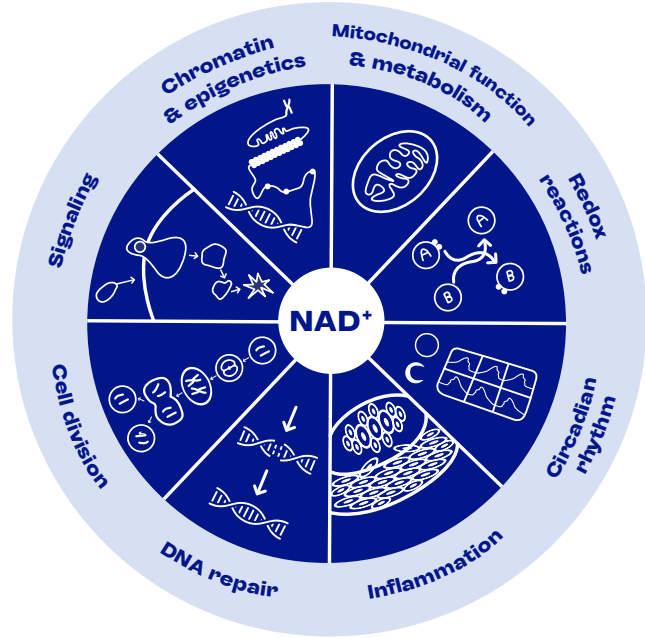
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References

THE CRUCIAL ROLE OF NAD⁺

300+

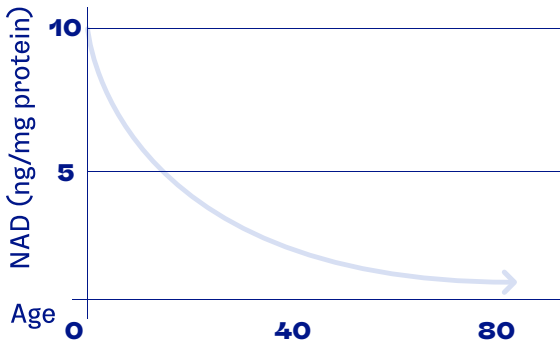
enzymes relying on NAD⁺ for their activity.



NAD⁺ has an impact on:

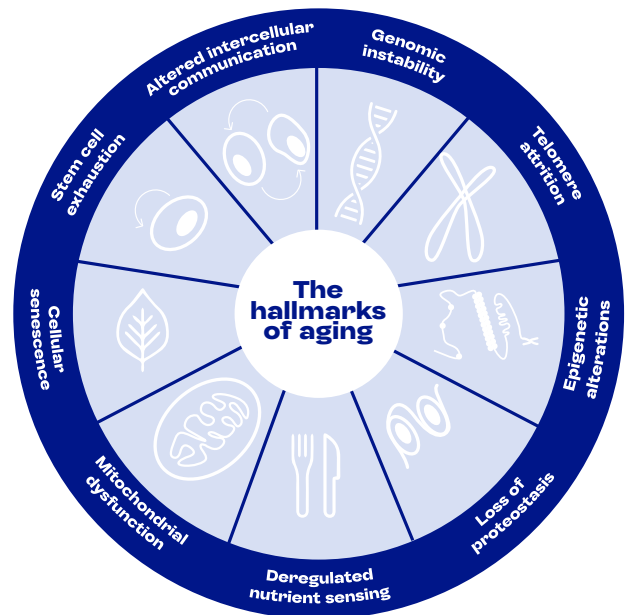
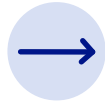
- Cellular Health
- Metabolism Health
- Immunity
- Cognitive Health
- Physical Health

Consequences of NAD⁺ depletion



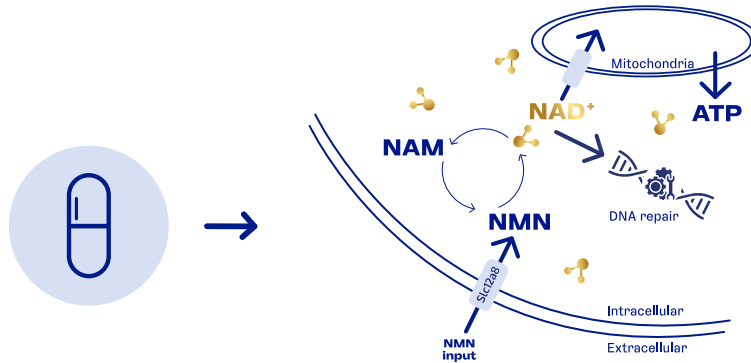
NAD⁺ level decline

An age-dependent decline in NAD⁺ levels, which ranges from 10% to 65%, depending on different organs and age¹⁵.



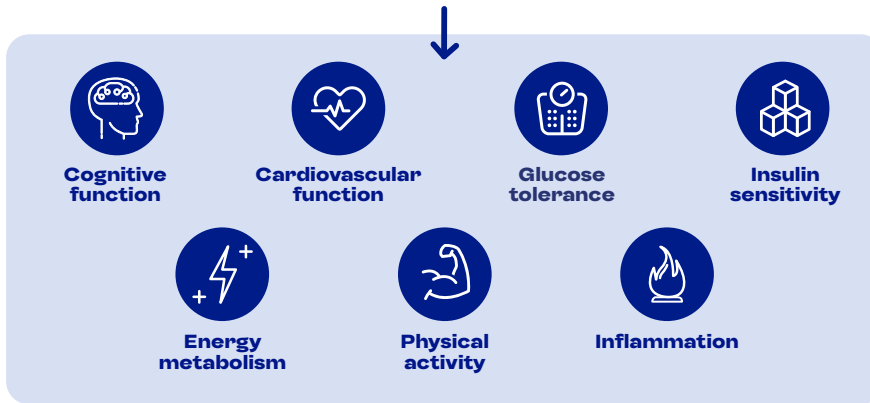
NMN SUPPLEMENTATION TO BOOST NAD⁺

NMN stands for nicotinamide mononucleotide. Numerous clinical and preclinical trials have highlighted NMN as a promising way to counter age-associated diseases and support the foundations of your health.



Dietary supplementation with a direct NAD⁺ precursor: NMN.

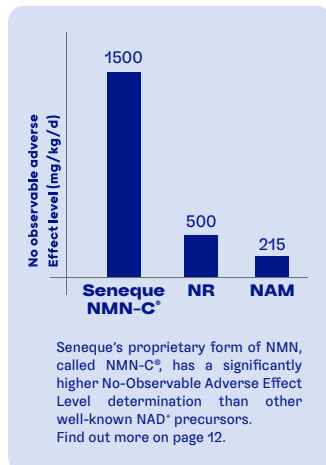
To maintain the pool of cellular NAD⁺, we use a biosynthetic route called the 'salvage pathway' that transform NMN into NAD⁺.



NOT ALL NAD⁺ BOOSTERS ARE CREATED EQUAL

A unique form of NMN, called NMN-C[®], has been developed by Seneque Laboratories.

HIGHEST TOLERANCE



HIGH QUALITY



NMN-C[®] is Self-GRAS in accordance with stringent US FDA regulatory guidelines. It is manufactured in cGMP-certified facilities in Europe. Every NMN-C[®] batch is tested for purity, and impurities.

SAFE AND TESTED



With 11 clinical trials underway, NMN-C[®] clinical trials are the most extensive in-human NMN research program to date. Less than 3% of supplements meet pharmaceutical grade standards.

Over the past century, mankind has made great leaps in eliminating diseases and understanding how to keep people alive.

Now, supplementation with a naturally occurring molecule called NMN presents a highly promising strategy to supporting health well into our later years.

Key takeaways

- Declining levels of NAD⁺ have been correlated with the body's reduced capacity to perform many processes and functions fundamental to healthy aging.
- Replenishing NAD⁺ with NMN has shown to be a promising therapeutic strategy to counter age-associated diseases.
- Clinical and preclinical studies have demonstrated that NMN has beneficial pharmacological activity on multiple critical elements of health: chiefly, energy metabolism and physical activity, glucose tolerance and insulin sensitivity, cardiovascular and cognitive functions, and inflammation.
- NMN supplementation presents a significant opportunity to address the increasing personal, social and economic burdens attributable to the cost and morbidity of age-related diseases.

Introduction

Between the beginning of the twentieth century and 1980 global life expectancy more than doubled. Although this rapid acceleration has slowed in developed countries, global life expectancy still increased by more than 6 years between 2000 and 2019¹.

The World Health Organization estimates that the number of people above 60 years of age will be 1.2 billion by 2025 and two billion by 2050². If people are experiencing these extra years in good health, their ability to do the things they value will deliver benefits to individuals, communities and economies. But if these added years are dominated by declines in physical and mental capacities, the implications for people and society may be much more negative.

Unfortunately, healthspan – the period of life spent in good health free from the chronic diseases and disabilities of aging – has not kept pace with increases in longevity. Optimal longevity (to live long, but well) can only be achieved if people remain active, productive and physically and cognitively fit as they grow older [see Fig. 1].

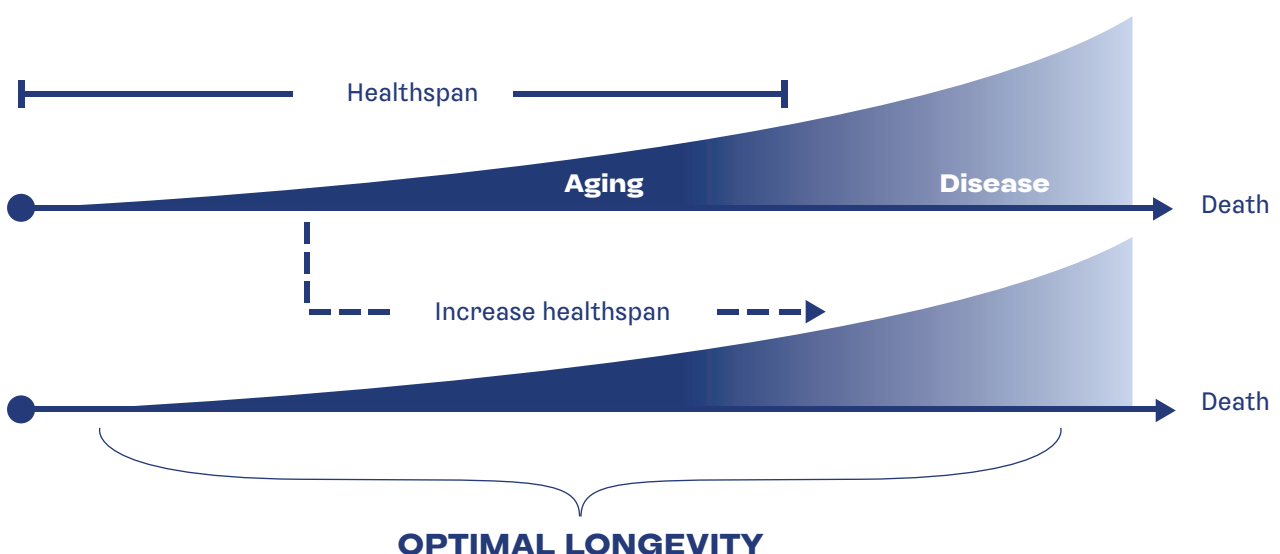


Fig 1. Extension of healthspan

Healthspan is a period of healthy aging with a modestly increasing chronic disease burden, followed by a period of age-related clinical disease. To achieve optimal longevity (living long, but primarily in wellness), healthspan must be significantly extended.

Rapidly aging societies across the world are seeing an increasing healthcare burden attributable to both the cost and morbidity of age-related diseases⁴. Long-term treatment and medical surveillance also incur a significant emotional cost⁵. Patients with chronic conditions often must adjust their aspirations, lifestyle, and employment.

The toll that these psychological, social, and cultural dimensions of illness can take is not only distressing for the individual, but can also be linked to additional adverse health outcomes^{6,7,8}. Clearly, remaining in good health for as long as possible is desirable from multiple personal, social and economic perspectives.

The aging phenotype

Aging is described as a progressive functional decline and an increased vulnerability to diseases. The body is constantly subjected to environmental and internal stimuli that can potentially lead to damage at genomic, cellular and tissue levels. It is this time-dependent accumulation of cellular damage that causes the aging phenotype.

To help categorize the aging process, nine hallmarks of aging have been identified and grouped into three main categories which are sequentially related⁹:

THE HALLMARKS OF AGING

CAUSE OF CELLULAR DAMAGE

- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Loss of proteostasis

CELLULAR REPOSSES TO DAMAGE

- Deregulated nutrient sensing
- Altered mitochondrial function
- Cellular senescence

PHENOTYPE INDUCED BY CELLULAR DAMAGE AND RESPONSE

- Stem cell exhaustion
- Altered intercellular communication

The amelioration of each 'hallmark' can delay the normal aging process and, hence, increase healthy lifespan¹⁰.

A decline in levels of nicotinamide adenine dinucleotide (NAD⁺: a natural cellular cofactor) has been correlated with many hallmarks of aging [see Fig. 2]. Replenishing NAD⁺ with nicotinamide mononucleotide (NMN: an NAD⁺ intermediate) has been shown in a growing number of clinical and preclinical studies to be a promising therapeutic strategy to counter age-associated diseases¹¹.



NAD⁺: A natural solution

NAD⁺ is a coenzyme found in all living cells. It is a mediator of key cellular and metabolic functions, with more than 300 enzymes relying on NAD⁺ for their activity¹². NAD⁺ serves as a critical coenzyme for reduction-oxidation (redox) reactions, carrying electrons from one reaction to another, making it central to energy production in the mitochondria.

In addition to energy metabolism and redox state cell maintenance, NAD⁺ plays a critical role as the cofactor of NAD⁺-consuming enzymes such as poly (adenosine diphosphate-ribose) polymerases (PARPs) and sirtuins^{13,14}. These enzymes have a key role in cellular homeostasis and longevity by controlling DNA repair, genomic stability, epigenetic regulation, chromatin remodeling and gene expression¹¹. These processes and functions are fundamental to healthy aging.

Preclinical studies have firmly established that there is an age-dependent decline in NAD⁺ levels, which ranges from 10% to 65%, depending on different organs and age¹⁵. NAD⁺ decline has been associated with the development and progression of age-related pathologies such as atherosclerosis, arthritis, hypertension, cognitive and memory decline, and diabetes¹¹.

Altered NAD⁺ homeostasis has also been linked to multiple diseases affecting different organs including the brain and nervous system, liver, heart and kidney, such as type 2 diabetes, obesity, heart failure, Alzheimer's disease and cerebral ischemia¹⁶. Countering this decline by modulating NAD⁺ usage or production can prolong both healthspan and lifespan¹⁷.

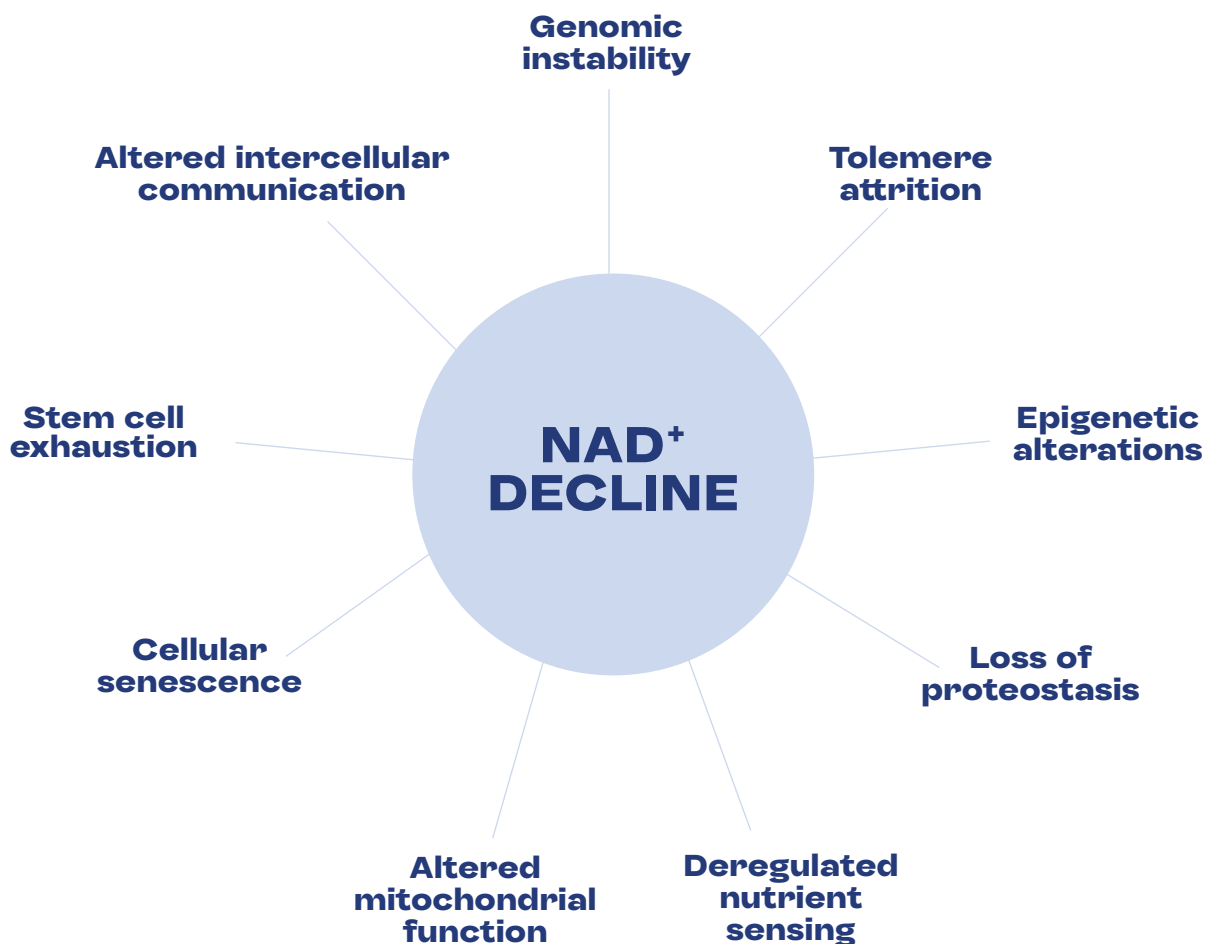


Fig 2. NAD⁺ decline and the hallmarks of aging

To help describe the progressive functional decline and increased vulnerability to diseases that comes with the aging process, aging has been categorized into nine 'hallmarks'. Declining NAD⁺ levels are correlated with the manifestation of many hallmarks of aging. Adapted from Aman et al¹⁸.

NMN supplementation to boost NAD⁺

Mammalian cells mostly rely on intracellular generation of NAD⁺ to fuel NAD⁺ levels¹⁵. One of the key pharmacological approaches to enhancing NAD⁺ biosynthesis is via dietary supplementation with a direct NAD⁺ precursor: NMN.

To maintain the pool of cellular NAD⁺, mammals largely use a biosynthetic route called the 'salvage pathway' [see Fig. 3]. In this pathway, nicotinamide (NAM), a byproduct generated by the activities of NAD⁺-consuming enzymes, is converted to NMN by the rate-limiting enzyme NAMPT (nicotinamide phosphoribosyltransferase). NMN can also be generated from another NAD⁺ precursor, nicotinamide riboside (NR), by NR kinases (NRKs). During the last step of the salvage pathway, NMN is converted to NAD⁺ by NMN adenylyltransferases (NMNATs).

NMN is naturally found in small amounts in fruits and vegetables such as avocados, broccoli, cabbage, edamame, and cucumbers¹⁴. Unfortunately for aging individuals, these food sources do not contain high enough amounts of NMN to increase the intracellular levels of NAD⁺ and counteract a wide range of pathologies associated to NAD⁺ decline.

Boosting NAD⁺ levels via NMN supplementation has shown significant beneficial effects in a wide array of pathophysiological conditions important for an aging population¹⁷ [see Fig. 4]. In numerous studies, systemic supplementation with NMN has been demonstrated to increase NAD⁺ biosynthesis and to improve age-related adipose tissue inflammation, insulin insensitivity, glucose intolerance, mitochondrial dysfunction, and more¹⁹.

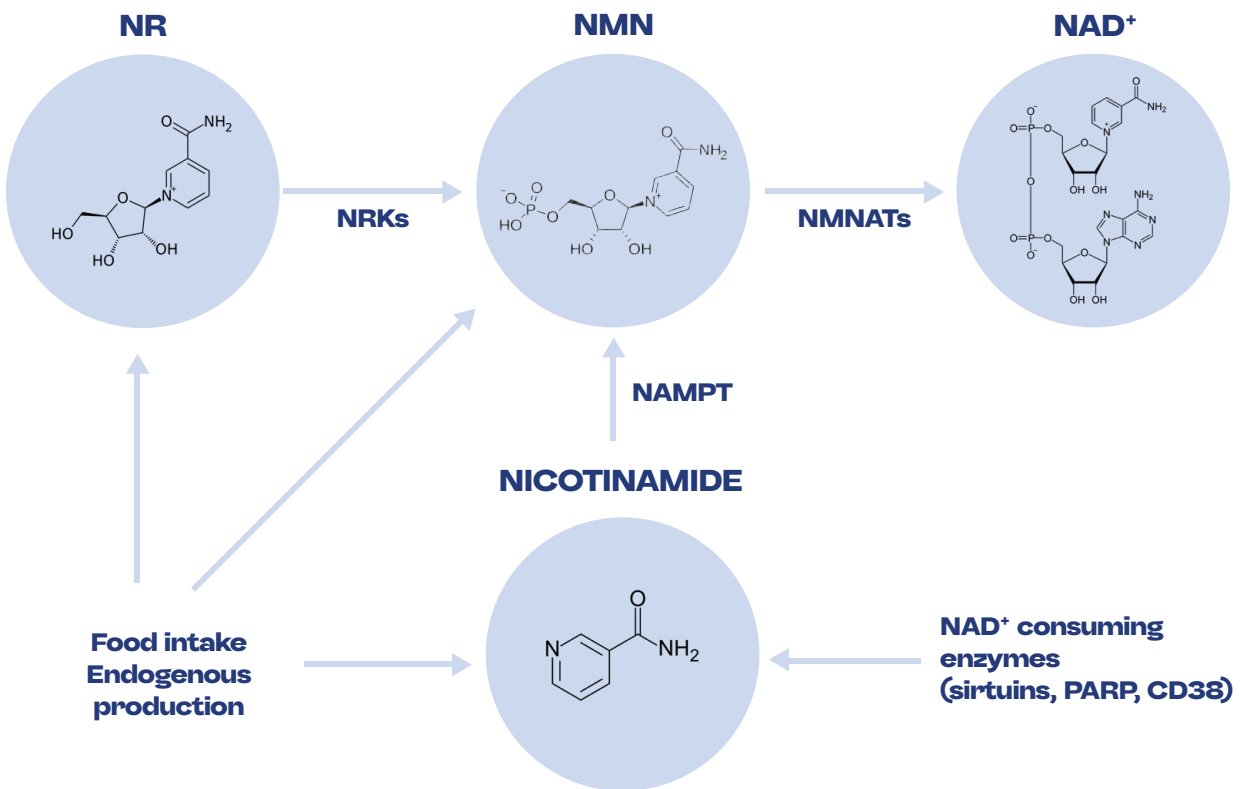


Fig 3. NAD⁺ intermediates in the salvage pathway

Mammals largely use a biosynthetic route called the 'salvage pathway' to create NAD⁺. In this pathway, NMN is the final step in NAD⁺ synthesis. Adapted from Yoshino et al. (2018)¹⁵.



The crucial roles of NMN

Several clinical and preclinical studies have demonstrated that NMN has beneficial pharmacological activity on multiple critical elements of health, including energy metabolism and physical activity, glucose tolerance and insulin sensitivity, cardiovascular and cognitive functions, and inflammation^{16,20} [see Fig. 4].

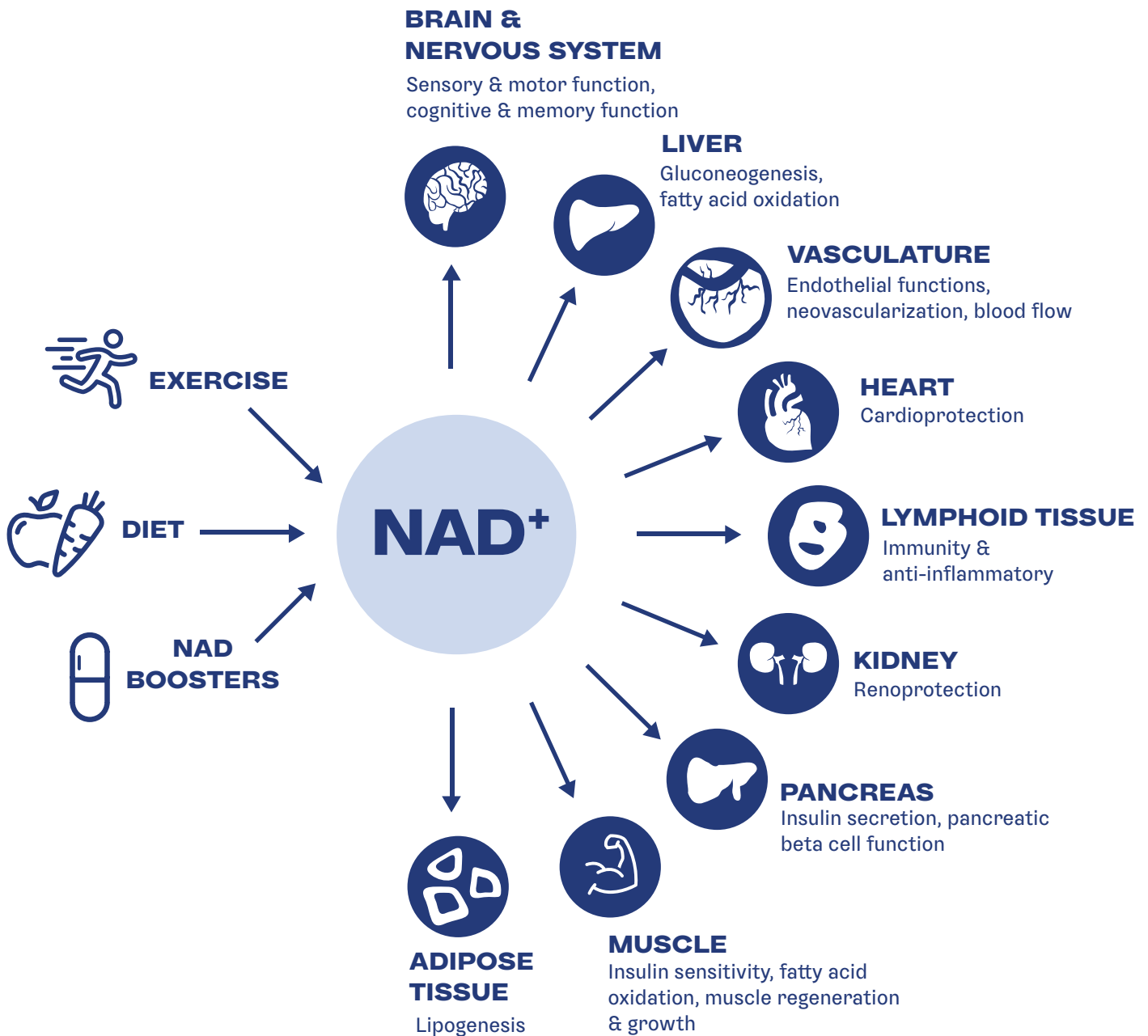


Fig 4. Physiological effects of NAD⁺-boosting molecules

By raising NAD⁺, NAD⁺ boosters can have profound effects on the health and survival of mammals.

Energy metabolism and physical activity

Research indicates that NMN can increase catabolism of fats²¹ and suppress age-associated body weight gain¹⁴. NMN treatment in obese mouse models significantly reduced liver fat mass and triglyceride content and increased citrate synthase activity. Its supplementation has also been shown to help reduce the effects of maternal obesity and reverse some of the negative consequences of high fat diet consumption²².

Long-term administration of NMN has been shown to significantly reduce age-associated body weight gain in mice by decreasing fat mass and increasing lean mass¹⁴. After 12 months of NMN administration, the average percent body weight reduction for a subject group of mice receiving NMN normalized to a control group was 9%¹⁴.

This highlights NMN as an effective therapeutic approach for maintaining body weight and reversing metabolic dysfunctions caused by obesity.

In the long-term administration study mentioned above, energy expenditure, as well as oxygen consumption, showed significant increases in groups receiving NMN. Respiratory quotient (a value that indicates which macronutrients [fats, carbohydrates, or proteins] are being metabolized) significantly reduced, suggesting that NMN-administered groups switched their main energy source from glucose to fatty acids.

Interestingly, mice treated with NMN for 12 months were able to maintain oxygen consumption and energy expenditure close to that observed at six months in subjects without NMN (correlating in human terms to approximately 24 years' difference).

Additionally, NMN supplementation has been shown to promote higher physical activity. An evaluation of whole-body movements and vertical activity showed that NMN can stimulate locomotor movement in aged mice¹⁴.

These results strongly suggest that NMN has significant preventive effects against age-associated energy metabolism impairment and supports higher physical activity in aged mice¹⁴.

Glucose tolerance and insulin sensitivity

Age-related decline in pancreatic β cell function is one of the higher risk factors for developing type 2 diabetes^{23,24}. Long-term NMN administration has been shown to ameliorate age-associated de-

creased insulin sensitivity in aged mice¹⁴. Furthermore, in diabetic mouse models, NMN administration for 11 days was sufficient to improve glucose tolerance by affecting either insulin sensitivity or insulin secretion²⁵.

Remarkably, a recent (2021) human clinical trial proved that oral administration of 250 mg NMN for 10 weeks in postmenopausal obese or overweight women with prediabetes has a robust effect on muscle insulin signaling. Insulin-stimulated genes involved in skeletal muscle remodeling and regeneration were increased. Muscle insulin sensitivity was also affected by improving insulin-stimulated glucose disposal rate²⁶.

Moreover, the clinical trial showed oral NMN administration was able to significantly increase basal NAD⁺ levels in peripheral blood mononuclear cells and in metabolites derived from NAD⁺ turnover in skeletal muscle. From an in-human tolerance perspective, no adverse events and no abnormalities in standard blood tests were reported²⁶.

These results position NMN as an effective approach for ameliorating age-associated decline in insulin sensitivity.

Cardiovascular functions

Cardiovascular disease is the leading cause of mortality worldwide and aging is a direct risk factor for the disease¹⁶. Vascular endothelial dysfunction and large elastic artery stiffness are two predictors of cardiovascular disease. NMN treatment has been shown to improve heart health by reversing age-associated endothelial dysfunction and by normalizing aortic stiffness²⁷. NMN administration has also been demonstrated to improve blood flow by increasing capillary density²⁸, which in turn supports proper and efficient function of the lungs, heart and muscles.

Studies have shown that disturbances in myocardial NAD⁺ levels are linked to metabolic remodeling and mitochondrial dysfunction in the failing heart. Maintaining homeostatic NAD⁺ levels protects from heart failure, ischemia-reperfusion injury, arrhythmia and hypertension²⁹. Therefore, NAD⁺-boosting interventions could be a promising strategy to improve mitochondrial and cardiac functions³⁰.

NMN administration has been shown to reverse the decrease of NAD⁺ content during myocardial ischemia in mouse models, protecting the heart from ischemia/reperfusion injury in both ischemic and reperfusion phases³¹. These findings support earlier preclinical results that show elevated NAD⁺ levels may be linked to beneficial impacts on cardiac arrhythmias and conditions³².

The role of NAD⁺ in cardiovascular health extends beyond the heart to the extensive network of arteries, capillaries, and veins that make up the vascular system. Studies have shown that increasing NAD⁺ can support the vascular system by optimizing healthy blood flow²⁷. A clinical trial also found that boosting NAD⁺ improved different indicators of cardiovascular functions, such as decreasing blood pressure and arterial stiffness – two major risk factors for cardiovascular events and disease with aging³³.

Neuroprotection and cognitive function

Increasing NAD⁺ concentrations via supplementation of NAD⁺ intermediaries such as NMN can provide therapeutic benefits in delaying the onset and slowing the progression of elements of cognitive decline^{34,35}.

NMN has been demonstrated to prevent age-induced cognitive impairment by improving cerebrovascular coupling responses, by rejuvenating the neurovascular gene expression profile^{36,37} and by reducing apoptosis in the prefrontal cortex and hippocampus of aged animals³⁸.

In a study using an in vitro model of Parkinson's disease, NMN was reported to improve energy activity and survival rate of cells³⁹. In another study, researchers demonstrated that mitochondrial respiratory function was restored with NMN treatment in a mouse model of Alzheimer's disease⁴⁰. Both these studies demonstrate the potential of NMN supplementation as a therapeutic option for neurological disorders.

It is not just in a neuroprotective capacity that NMN can benefit the brain. Research has also highlighted NMN's therapeutic potential for treatment of cerebral ischemia. Administration of NMN following ischemic insult in mouse models protects hippocampal neurons from ischemic cell death and preserves neuronal functions after global cerebral ischemia⁴¹.

Inflammation

As adults age their immune system declines. People get sick more easily, and it becomes harder to bounce back from illnesses. And because NAD⁺ declines with age, the body's ability to manage the chronic and low-grade inflammation (called inflammaging) that is a key driver for a broad range of age-related and metabolic diseases such as hypertension, diabetes, atherosclerosis, and cancer⁴¹ is lessened. Inflammaging is characterized by aberrant activation of the innate immune system, enhanced expression of pro-inflammatory cytokines (TNF α , IL-6, IL-1 β)

and activation of immune complexes⁴¹.

During aging, declining levels of NAD⁺ are associated with increased accumulation of pro-inflammatory macrophages (called M1-like macrophages) instead of anti-inflammatory macrophages (called M2-like macrophages) in metabolic tissues including liver and fat⁴².

M1-like macrophages are characterized by an increased expression of the ectoenzyme (an enzyme acting outside the cell), CD38. The enhanced CD38-dependent NADase activity on M1-like macrophages reduces tissue NAD⁺ levels⁴². This type of macrophage, in addition to senescent cells, may be a major source of pro-inflammatory cytokines in aging tissues^{42,43}. Increases in these pro-inflammatory cytokines lead to increased inflammation, tissue and DNA damage, and an acceleration in physiological age-related decline.

In vitro studies have shown that modification of NAD⁺ metabolism with NAD⁺ precursors such as NMN could regulate macrophage polarization by promoting anti-inflammatory phenotypes^{42,44}. Boosting NAD⁺ in patients with heart failure via oral administration of an NAD⁺ precursor resulted in an up to 30-fold reduction of pro-inflammatory gene expressions in peripheral blood mononuclear cells⁴⁵. In healthy aged patients, 3 weeks' supplementation with an NAD⁺ booster was sufficient to reduce the level of circulating pro-inflammatory cytokines such as TNF- α and IL-6⁴⁶.

Regulating NAD⁺ levels could be a therapeutic strategy to controlling inflammaging. It could also serve to regulate diseases driven by chronic inflammation, such as neurodegenerative diseases and some cancers, where macrophage polarization can be either tumor-promoting or tumor-inhibiting.



NMN is rapidly absorbed

One of the key properties that positions NMN as an effective NAD⁺ booster is its potential speed of absorption into the body. Seneque Chief Scientist Dr. Alessia Grozio was part of a team that in 2019 published research which highlighted a key driver of NMN's efficiency – a transporter that carries NMN directly into cells within minutes after ingestion⁴⁷.

It was demonstrated that the Slc12a8 gene encodes a protein that is a specific NMN transporter in mammals. This protein uses a sodium ion to transport NMN (but not NR or NAM) across cell membranes and facilitates direct uptake of NMN into the gut and other organs. There, it is immediately used for NAD⁺ biosynthesis and significantly increases NAD⁺ concentration in cells over the course of 60 minutes following ingestion. This indicates that NMN represents a direct entry point into the NAD⁺ synthesis pathway⁴⁷.

NMN is safe and well tolerated

No negative side effects of nicotinamide mononucleotide have been documented in humans to date, and NMN's safety as a dietary supplement has been shown in numerous regulatory studies following FDA-guidelines.

A study of NMN in humans revealed no safety concerns following single oral doses of 100, 250, and 500 mg of NMN⁴⁸. Five hours following the single oral administration of NMN, scientists found no changes in heart rate, blood pressure, blood oxygen levels, or body temperature. Laboratory analyses of blood did not show significant changes.

In 2020 Seneque undertook an OECD 408 toxicology study in Sprague-Dawley rats over a 90-day sub-chronic period of repeated oral administration of its proprietary form of NMN, called NMN-C[®], at doses of 375, 750 and 1500 mg/kg/d⁴⁹. NMN-C[®] appeared to be safe and did not promote toxic effects as seen from body weight change, food and water consumption, feed conversion efficiency, biochemical and blood parameters as well as organ toxicity and histological examinations of main organs.

This data highlights the safety of short to intermediate term (sub-chronic) oral administration of NMN and allowed a No-Observable Adverse Effect Level (NOAEL) determination of ≥ 1500 mg/kg/d for NMN-C[®]⁴⁹. When compared to NOAEL determinations for other well-known NAD⁺ precursors, NMN fares well against NR (500 mg/kg/d)⁵⁰ and NAM (215 mg/kg/d)⁴⁹.

A preclinical long-term NMN administration study showed no toxicity, serious side effects, or increased mortality rate throughout its 12-month intervention period¹⁴.

NMN is a preferred NAD⁺ precursor

NMN is considered as an NAD⁺-boosting molecule of choice for human supplementation not only due to its solubility and oral availability. Its appeal also lies in the fact that other NAD⁺ precursors present some characteristics that NMN does not (or if NMN does, it displays them to a much lesser extent) [see Fig. 5].

Several studies have shown the ability of nicotinic acid (NA) to raise NAD⁺ levels. However, its use is limited due to uncomfortable side effects such as flushing and itching of skin caused by prostaglandin release⁵¹. NMN does not cause this flushing effect.

Another precursor, NAM, does not efficiently increase NAD⁺ in cells because to generate NMN it must use nicotinamide phosphoribosyltransferase (NAMPT). NAMPT is a rate-limiting enzyme in the salvage pathway, meaning that NAMPT has a plateau of activity that cannot be overcome even if more NAM is provided.

Furthermore, NAM is also a byproduct of NAD⁺ catabolism. At millimolar (high) concentrations it has been shown to act as a feedback inhibitor for NAD⁺-dependent enzymes, such as PARPs and sirtuins (which are important for longevity)^{52,53} and to increase methylated NAM. High levels of methylated NAM have been associated with the pathogenesis of type 2 diabetes, Parkinson's disease and cardiac diseases⁵⁴.

Another precursor commonly marketed to consumers as an NAD⁺ booster, NR, is unstable in solutions and body fluids (blood plasma) and is degraded into NAM^{55,56}.



	Seneque NMN-C[®] (Nicotinamide Mononucleotide)	NR (Nicotinamide Riboside)	NAM (Vitamin B3/Nicotinamide)
Increase intracellular NAD⁺	Efficient	Efficient	Inefficient
Clinically tested	✓	✓	✓
Verified safe through GRAS or SELF-GRAS	✓	✓	✓
Tolerance level (NOAEL-mg/kg/day in rats*)	1500	500	215
Direct NAD⁺ precursors	✓	No	No
Stable in blood plasma	✓	No	Yes
Demonstrated transporter into cells	✓	No	No

*Lowest level of both genders

Fig 5. Aspects of molecules in the NAD⁺ salvage pathway

The appeal of Seneque's proprietary form of NMN, called NMN-C[®], lies in the fact that it has characteristics and a testing profile that other molecules in the salvage pathway of NAD⁺ synthesis do not.

Ongoing clinical discovery

Many preclinical and a growing number of clinical studies have demonstrated NMN's promising properties regarding NAD⁺ biosynthesis and its associated health impacts. Additional research investigating the bioavailability and effects of NMN in human subjects will be of high interest to the scientific and healthcare fields. These goals are well on the path to being achieved, with Seneque undertaking an extensive program of clinical trials using NMN [see Fig. 6].

These clinical trials will assess the effect of NMN on different conditions including immune health, cognitive performance, lipid and glucose metabolism, fatigue management and more. This research program is being performed in collaboration with some of the world's leading NAD⁺ and NMN scientists, including the Chair of Seneque's Scientific Advisory Board and President of the Buck Institute for Research on Aging, Dr. Eric Verdin, and Seneque Chief Scientist Dr. Alessia Grozio.

Findings from these studies will expand the body of knowledge on NMN's benefits in multiple cellular processes and age-associated pathophysiological

conditions. At the same time, they will enable continued implementation of evidence-based consumer solutions that can support the health needs of the global community.



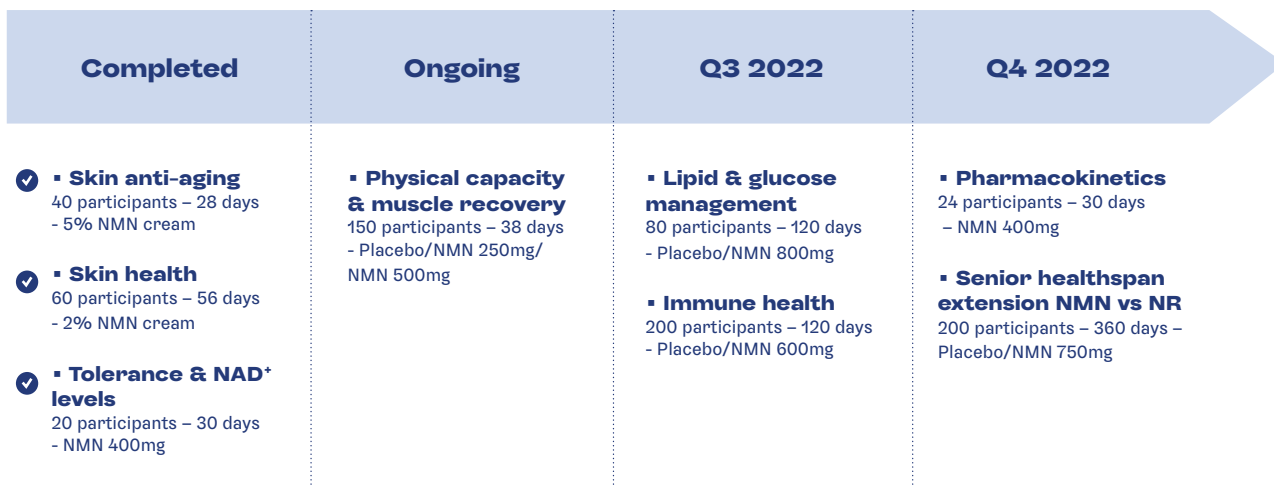


Fig 6. Seneque's pipeline of clinical trials

Seneque's clinical research is being performed in collaboration with some of the world's leading NAD⁺ and NMN scientists, including the Chair of Seneque's Scientific Advisory Board and President of the Buck Institute for Research on Aging, Dr. Eric Verdin, and Seneque Chief Scientist Dr. Alessia Grozio.

Where can NMN deliver results?

It is now accepted that NAD⁺ depletion plays a critical role in several pathophysiological conditions, including neurodegenerative, metabolic and progeroid disorders.


Several clinical and pre-clinical studies have demonstrated that NMN is a high-potential active ingredient, able to improve energy metabolism and physical activity, glucose tolerance and insulin sensitivity, cardiovascular and cognitive functions, inflammation, and many other critical conditions related to aging and diet.

For these reasons, in combination with an adequate diet and exercise, NMN supplementation can be considered a promising strategy to boost intracellular NAD⁺ levels and, hence, to support healthspan.

Seneque is addressing the NAD⁺ needs of consumers with a proprietary form of NMN, called NMN-C°. NMN-C° is verified safe and is demonstrated to be well tolerated. It carries self-GRAS (Generally Recognized as Safe) status in accordance with stringent US FDA regulatory guidelines, and is produced in CGMP-certified facilities in Europe.

NMN supplementation presents a significant opportunity to address the increasing personal, social and economic burdens attributable to the cost and morbidity of age-related diseases in rapidly aging societies across the world.





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to learn more about
how we can help you,
your patients or your
clients live in better
health, for longer.**

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