Nicotinamide Adenine Dinucleotide (NAD) Augmentation As a Gerotherapeutic Approach To Prevent and Treat Age-related Diseases

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Professor of Medicine, Harvard Medical School
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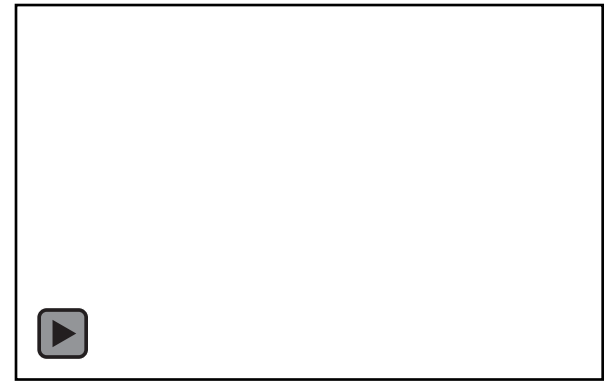
Co-Director, The Center for Transgender Health
Director, Boston Claude D. Pepper Older Americans Independence Center



BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

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Dr. Shalender Bhasin is a Professor of Medicine at the Harvard Medical School, and Director of the Research Program for Men's Health and Aging at the Brigham and Women's Hospital in Boston, Mass. He is the co-Director of the Brigham Center for Transgender Health. He is also the Director of the Boston Claude D. Pepper Aging Research Center at the Harvard Medical School.

Dr. Bhasin is one of the foremost experts in men's health and aging. He has published more than 400 original research papers in top tier journals and has conducted some of the most important randomized trials of testosterone in men and women. His lab has characterized the mechanisms of testosterone's action and the role of steroid 5-alpha reductase in adults. He led the Endocrine Society's expert panel that developed the guidelines for testosterone treatment of hypogonadal men since 2005. His lab has investigated the mechanisms of muscle loss with aging. He chaired an expert panel that developed the evidence-based definition of sarcopenia and has conducted many randomized trials of function promoting therapies. He has been investigating the role of NAD in aging biology and the potential applications of NAD augmentation to treat age-related diseases. Has received research grants for investigator-initiated studies: NIA, NCMRR, PCORI, Abbvie, Metro International Biotech, and FPT.

Dr. Bhasin has been the recipient of numerous research, teaching, and mentorship awards throughout his career. He received the Endocrine Society's Outstanding Clinical Investigator Award, and the American College of Endocrinology's Frontiers in Science Award.

Disclosures

- Dr. Bhasin discloses he is the recipient of research grants from NIA, AbbVie, Metro International Biotech (MIB) and FPT. He is also a consultant with Novartis. All relevant financial relationships have been resolved.
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Disclosures

- Research grants for investigator-initiated studies:
  NIA, NCMRR, PCORI, Abbvie, Metro International Biotech, and FPT
- Equity interest: FPT and Xyone Therapeutics
- Not speaking to represent:
  - ABIM Endocrinology Board
  - Endocrine Society

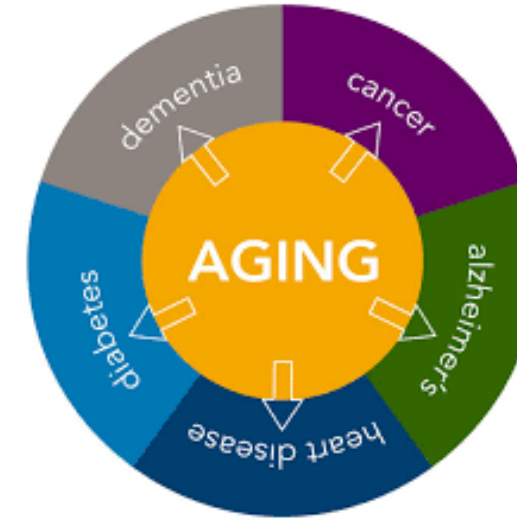
Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Describe the conceptual framework of the geroscience approach.
2. Explain the pillars or mechanisms of aging.
3. Summarize the rationale and applications of nicotinamide adenine dinucleotide (NAD) augmentation as a gerotherapeutic approach to prevent or treat age-related diseases.

The Geroscience Hypothesis

- Aging physiology and mechanisms play a major role in many — if not all — chronic diseases of old age.
- The "geroscience hypothesis" posits that age-related diseases can be prevented or delayed by targeting common mechanisms of aging.



Source: AFAR

(Kennedy et al., 2014)
(Kaeberlein, 2017)

Nine Biological Pillars of Aging As Potential Therapeutic Targets

Nine Pillars

Interventions

- Pharmacological Targets
  - NAD boosters
  - Senolytics
  - mTOR inhibitors
  - Metformin
  - Anti-inflammatory agents, including Mas receptor activators
- Stem cell therapies
- Physical exercise interventions and exercise mimetics
- Nutritional Interventions
  - Caloric restriction
  - Time restricted feeding

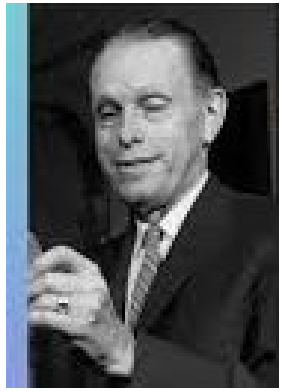
(López-Otín et al., 2013)

Pellagra and the Discovery of Niacin

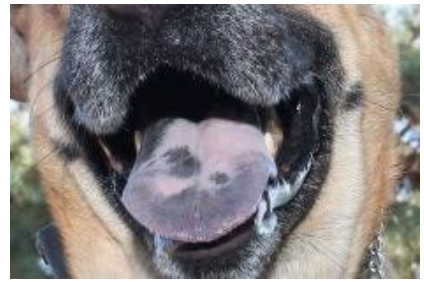
- Generalized NAD deficiency causes pellagra, a potentially fatal condition.
- Joseph Goldberger's experiments in prisoners identified pellagra as a nutritional deficiency.
- Conrad Elvehjem experimentally induced pellagra (Black-Tongue Disease) in a dog model and identified nicotinic acid as the "anti-black tongue factor" or the Pellagra Preventive Factor.
- Widespread vitamin supplementation eliminated pellagra in the US.

A patient with pellagra in Canton Mental Asylum

Joseph Goldberger's



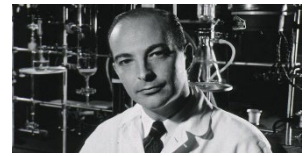
Conrad Elvehjem



https://cmeindia.in/history-today-in-medicine-prof-conrad-elvehjem/
https://www.dogster.com/lifestyle/why-are-there-dogs-with-spotted-tongues
https://www.alamy.com/stock-photo/pellagra.html?sortBy=relevant
https://history.nih.gov/pages/viewpage.action?pageId=8883184

The Illustrious History of NAD's Discovery

- 1906 - Arthur Harden and William J. Young: a heat stable factor in the fermentation reaction.
- 1929 – Hans Von Euler-Chelpin wins the Nobel Prize for for identifying NAD+ as the co-factor in the heat stable fraction of yeast cells.
- 1936 - Otto Heinrich Warburg: During fermentation reaction, NAD^+ accepts a hydride and is converted to NADH (nicotinamide adenine dinucleotide (NAD) + hydrogen (H)); hydride reactions - now referred to as redox reactions involving exchange of a hydrogen atom and accompanying electrons.
- 1948 - Arthur Kornberg purified the enzyme (nicotinamide mononucleotide adenylyl transferase, NMNAT) in the NAD+ biosynthetic pathway.
- 1958 - Jack Preiss and Philip Handler characterized the biochemical pathway for the conversion of nicotinic acid to NAD^+.
- 2000 – Guarente and Imai discover sirtuins as enzymes that use NAD+ as a co-factor and break it down.
- 2004 – Charles Brenner discovers the enzymes that convert nicotinamide riboside (NR) to NAD.
- **2005 – present Guarente, Imai, Brenner, Sinclair –elucidate role of sirtuin-NAD pathway in aging biology**

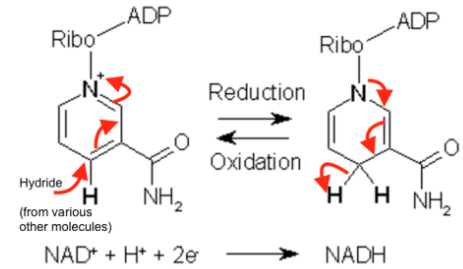


https://hub.jhu.edu/2021/06/04/ravenous-otto-warburg-sam-apple/
https://www.britannica.com/biography/Arthur-Kornberg
https://www.ahlresearch.org/leonard-guarente-phd
https://twitter.com/davidasinclair

An Expansive Role of NAD^+ in All Living Organisms

Redox reactions: – NAD+/ NADH provide reducing equivalents

NAD^+ reduction to NADH and subsequent oxidation of NADH to NAD^+ during complex I reactions critical for ATP production



Nicotinamide adenine dinucleotide phosphate (NADP)/ NADPH in biosynthetic reactions: Fatty acids, steroid hormones, and nucleic acids

Protecting against oxidative stress:

Provide reducing equivalents to antioxidants such as glutathione and thioredoxin

Otto Warburg

Hans Krebs

As a co-substrate for signaling enzymes in DNA repair and innate immunity: Sirtuins, PARP1-2, CD38 and, and SARM1

(Rajman et al., 2018)
(Yoshino et al., 2018)
(Verdin, 2015)

https://www.differencebetween.com/difference-between-nad-nadh-and-nadph/
https://www.nobelprize.org/prizes/medicine/1931/warburg/biographical/
https://www.nobelprize.org/prizes/medicine/1953/krebs/facts/

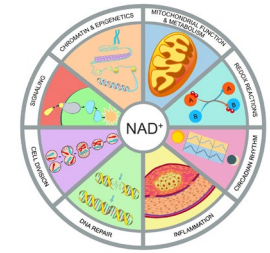
Recognition of the Role of NAD+ in Aging Biology and and Regulation of Healthspan

Beneficial effects of caloric restriction in extending lifespan and healthspan are mediated via sirtuins

NAD^+ serves as a substrate in sirtuin catalyzed deacetylation reactions resulting in silencing of proteins.

A molecular framework of NAD-dependent histone deacetylation as a pivotal pathway linking genomic silencing, metabolic regulation and ageing.

NAD plays an important role in nearly all pillars of aging: DNA repair, inflammation and innate immunity, metabolism, mitochondrial function, cellular signaling, and senescence.



(Imai et al., 2000)
(Rajman et al., 2018)
(Yoshino et al., 2018)

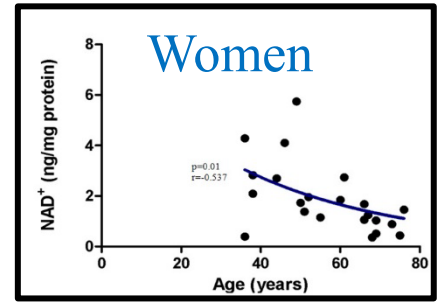
https://thelifehub.com/how-nad-works-to-biohack-energy/

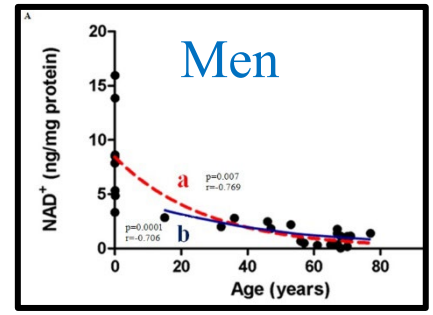
NAD Augmentation as a Gerotherapeutic Strategy to Prevent and Treat Age-Related Conditions

NAD levels decline with aging and age-related diseases and NAD depletion contributes to age-related diseases.

NAD levels and metabolome can be augmented therapeutically.

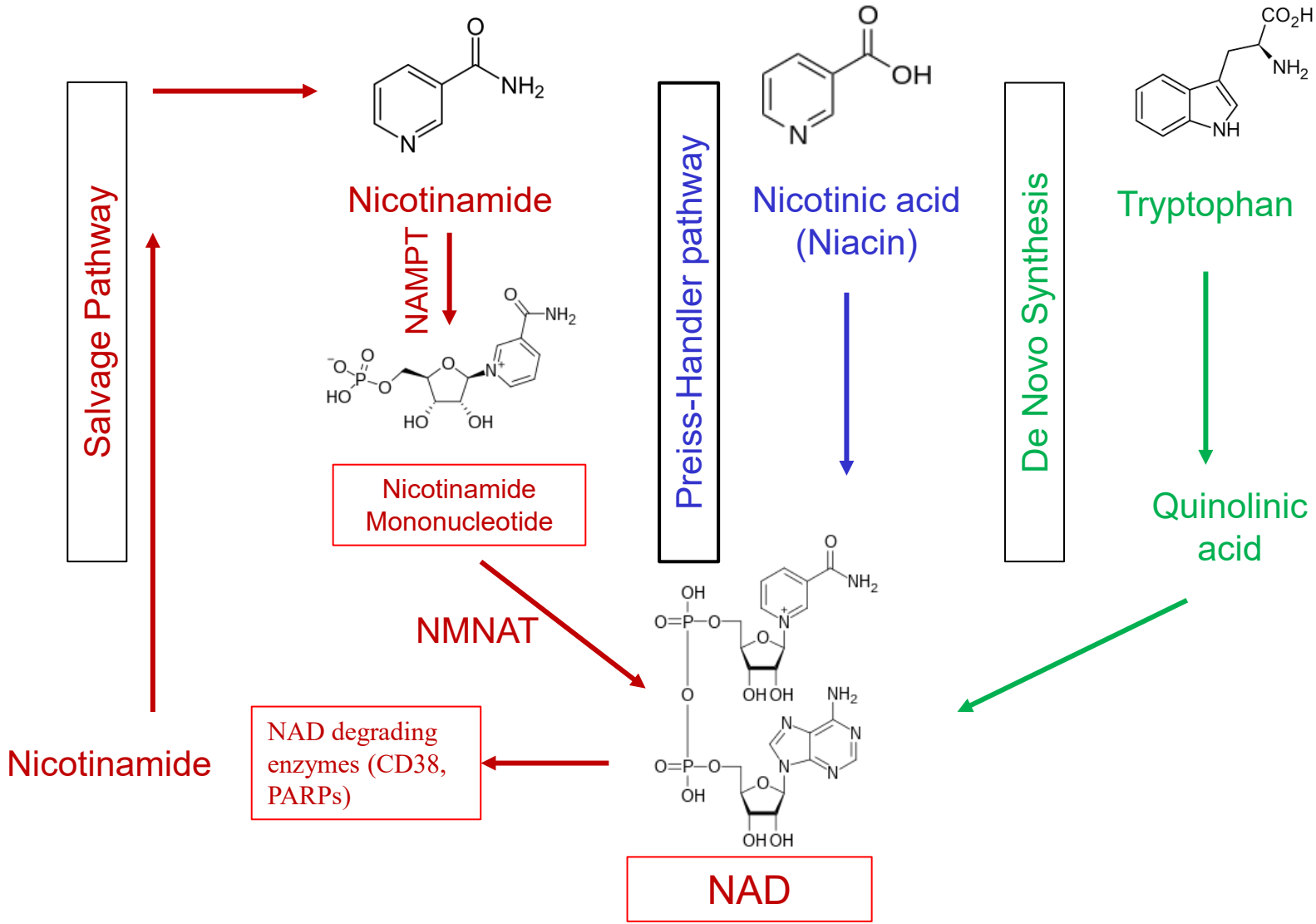
Augmenting NAD levels will prevent or reverse aging and age-related diseases.



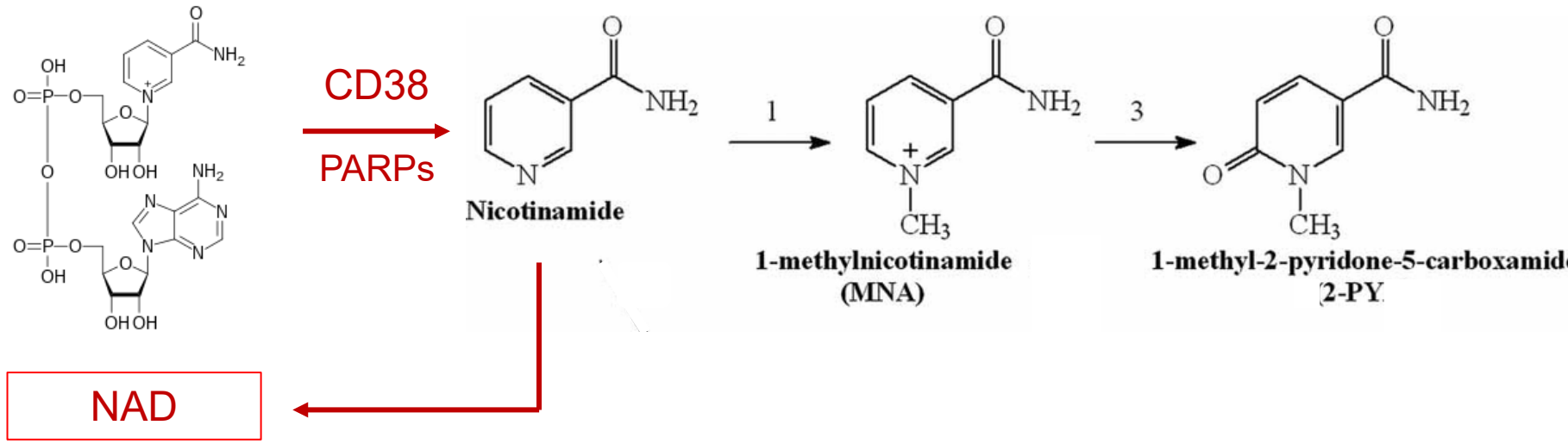


(Zhou et al., 2016)
(Massudi et al., 2012)
(Camacho-Pereira et al., 2016)

Three Major Pathways for NAD Biosynthesis



Major Pathways of NAD Metabolism



Strategies to Increase NAD+ Levels

- Administration of precursors, such as NMN, NR, or NAM
- Inhibit degradation by PARPs and CD38
- Genetic modification or chemical regulators of enzymes involved in synthesis and degradation

Promise

- NAD boosters in clinical trials
- CD38 and PARP inhibitors approved for cancer therapy

HYPE: Media Frenzy about NAD Boosters

NAD Boosters:
The Fountain of Youth

https://www.evitamins.com/za/a/what-is-vitamin-b-complex-what-does-it-do-39

Major Findings of Preclinical Studies

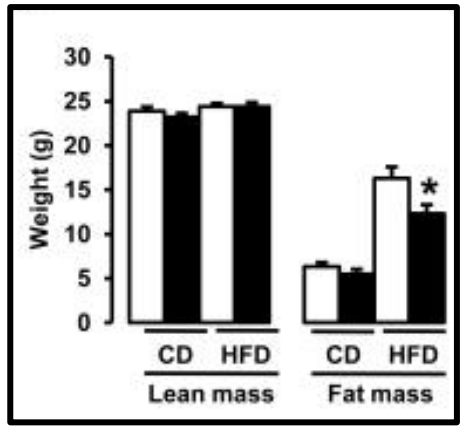
Physiologic system/ disorder	Observed Effect
Healthspan and lifespan	Improves healthspan but not lifespan in wild type mice
Metabolism and metabolic disorders	Improves insulin sensitivity/glucose tolerance, and insulin secretion; reduces weight gain and liver fat accumulation
Muscle performance, endurance, and physical function	Increases mitochondrial function, endurance and running distance in older mice
Cardiovascular effects	Reduces aortic atherogenesis progression and improves plaque stability; Protects against ischemic myocardial injury; improves heart failure in mice with reduced and preserved ejection fraction
Kidney disease	Attenuates acute kidney injury due to cis-platinum or ischemia/; Prevents development of diabetes kidney disease in db/db mice
Degenerative Neurological and Aging Conditions	Slows progression in Alzheimer's disease models; congenital mitochondrial myopathy; and in mice with premature aging syndromes
Other Conditions	Improves liver regeneration after partial hepatectomy

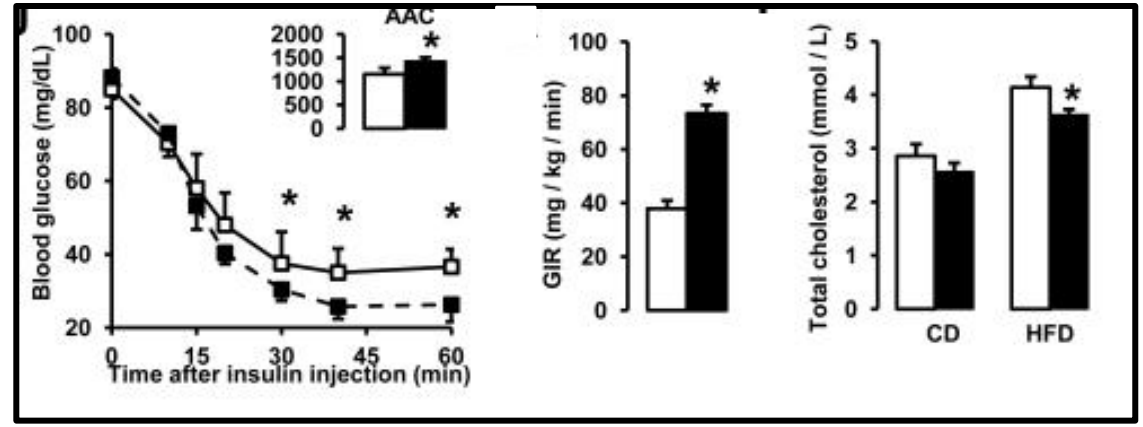
Nicotinamide Riboside Attenuates Fat Mass Gain and Improves Insulin Sensitivity in Mice fed High fat Diet

Lean and Fat Mass

Insulin Sensitivity

Insulin Tolerance Test Hyperinsulinemic Clamp



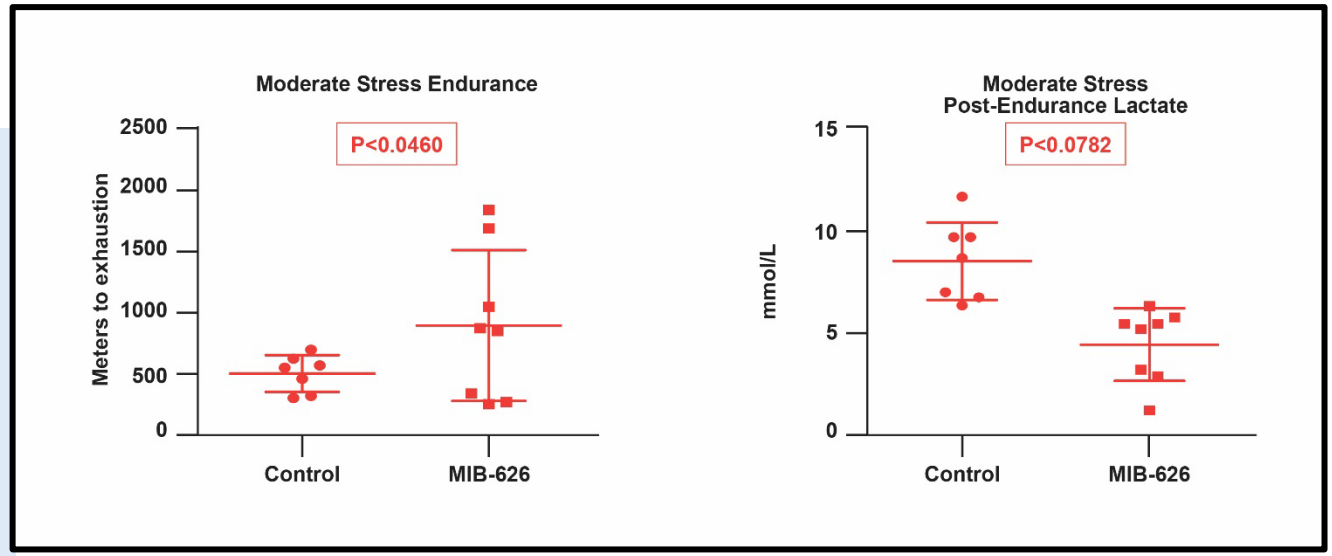


(Canto et al., 2012)

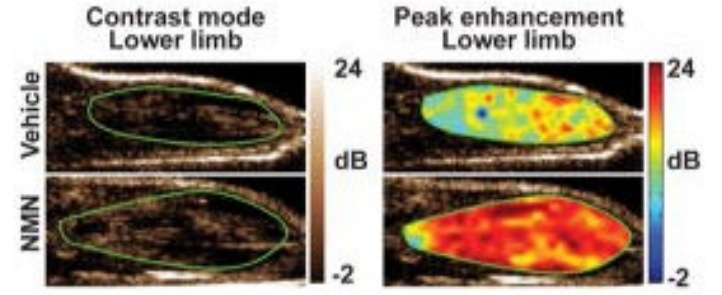
Aged Mice Dosed with MIB-626 Run Longer than Young Mice

Study Design

- 500 mg/kg of MIB-626 once-daily in mice for 3 weeks.
- Endurance benefit without elevating serum lactate.



NMN Improved Blood Flow

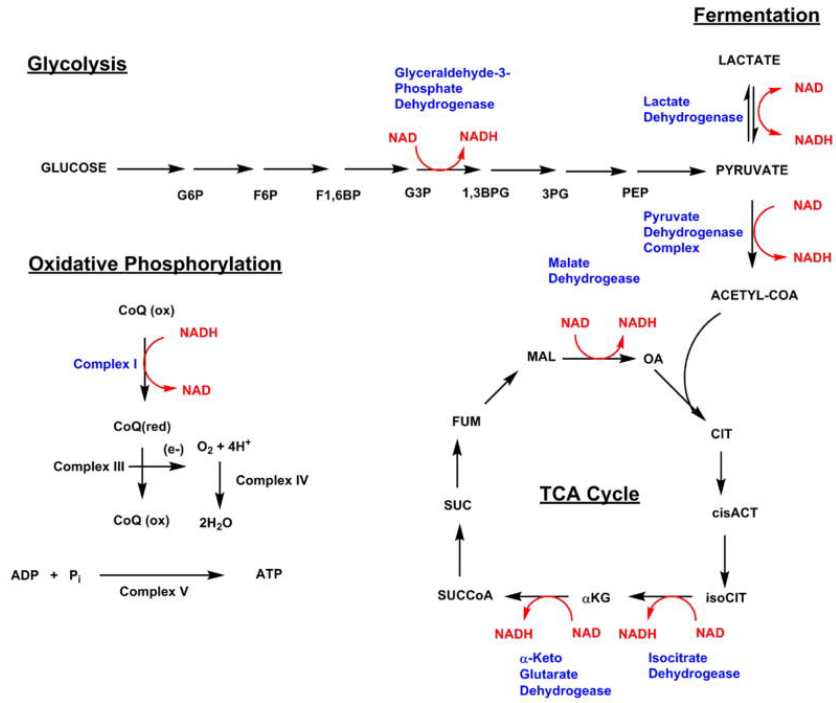


(Das A et al., 2018)

Critical Role of NAD in Muscle Energy Production

NAD Reduction

NAD Oxidation



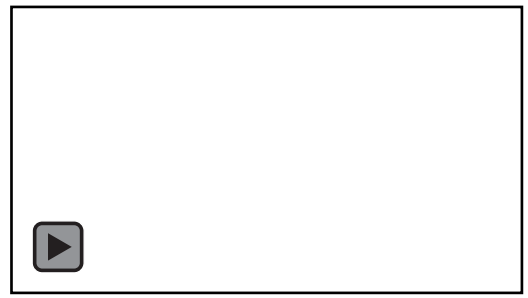
Otto Warburg

Hans Krebs

NAD^+ reduction to NADH occurs during glycolysis, pyruvate dehydrogenase, and TCA cycle, Subsequent NADH oxidation to NAD^+ in cytoplasm by lactate dehydrogenase and in mitochondria by action of Complex I is critical for ATP production.

Challenges in Clinical Trials of Sirtuin – NAD Activators

Challenge	Strategy
Variable quality of over the counter (OTC) products	Good Clinical Practice (GCP) grade formulation that has undergone tox studies
Issues with pre-analytical stability of NMN, NAD and their metabolites in human blood and tissues	Developed sample collection processes to ensure preclinical stability
Suboptimal assays for NAD	Validated LC-MS/MS assays 7T MRS for NAD/ NADH measurement in the muscle at rest and during exercise
Clinical pharmacology in humans incompletely understood	Controlled PK/PD and stable isotope studies in CRC setting Early phase studies have shown that 1 and 2 g NMN SAFELY increases blood NAD and its metabolome in healthy adults

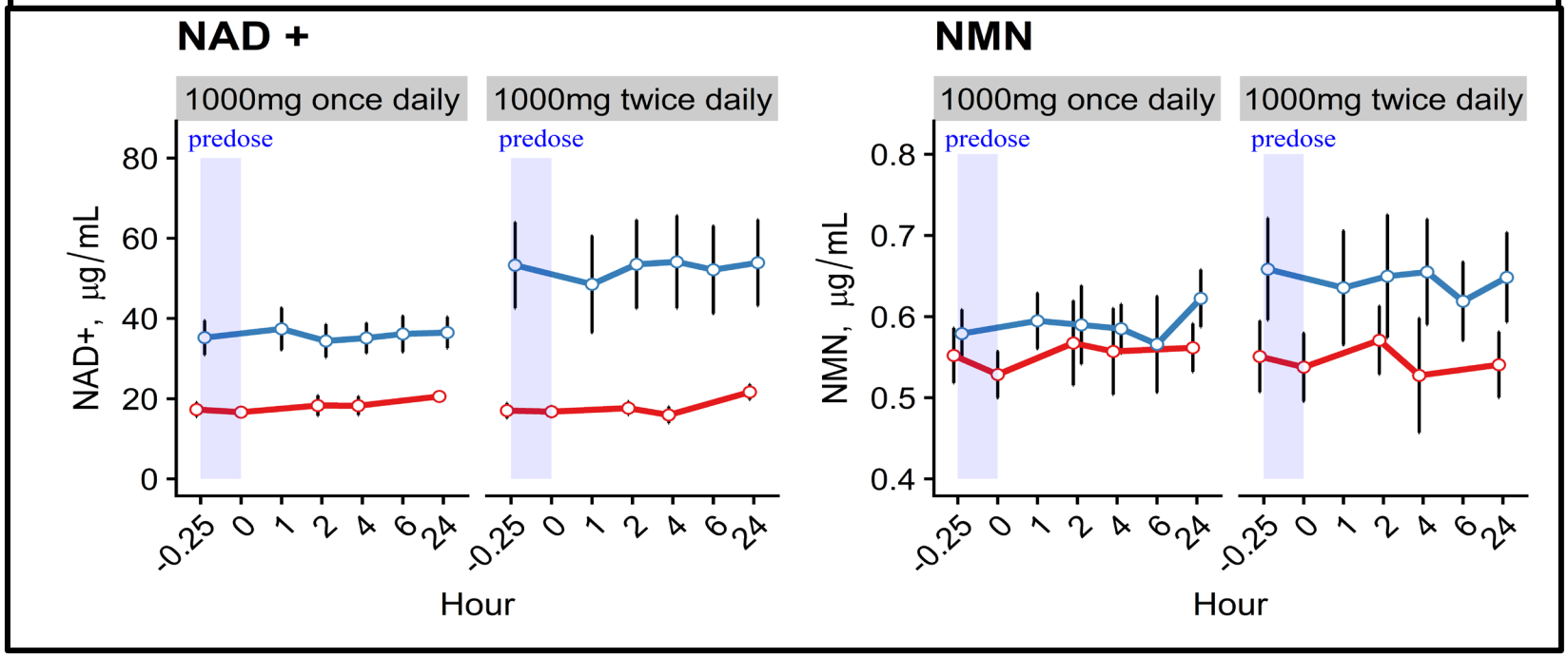


http://pnl.bwh.harvard.edu/wp-content/uploads/2013/08/LinnProfile.jpg

Findings of Early Phase Pharmacokinetic and Pharmacodynamic Human Studies

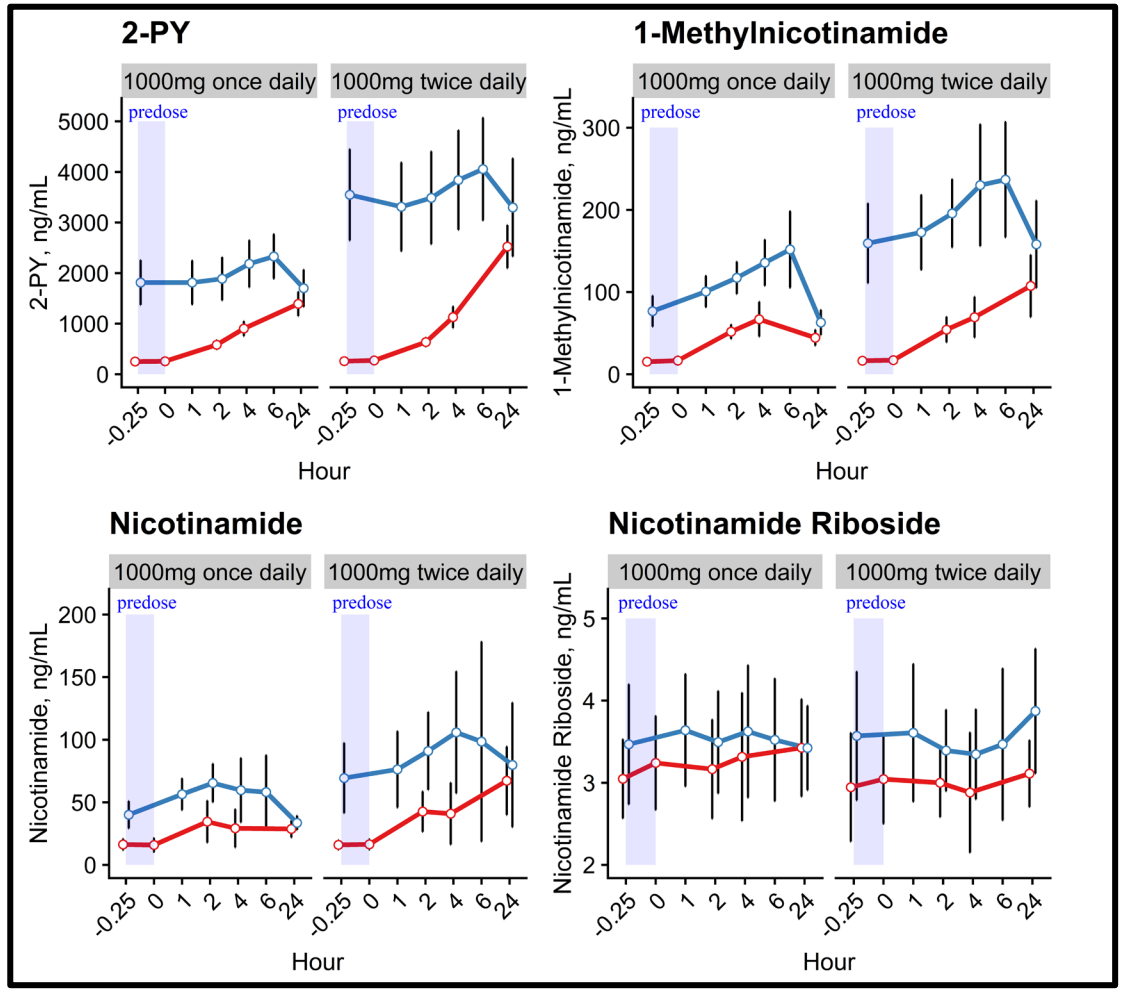
- Doses of up to 2 g of NAD precursors, NMN and NR, are safe and raise NAD+ levels and in some tissues.

Blood NAD and NMN Levels during the 24 h after 1000 mg once daily or 1000 mg twice daily NMN on days 1 (red) and 14 (green).



(Pencina, Lavu, Dos Santos, Beleva, Cheng, Livingston, Bhasin, 2023)

Circulating Concentrations of NAD Metabolome After 1000 mg Once Daily or Twice Daily for 14 Days



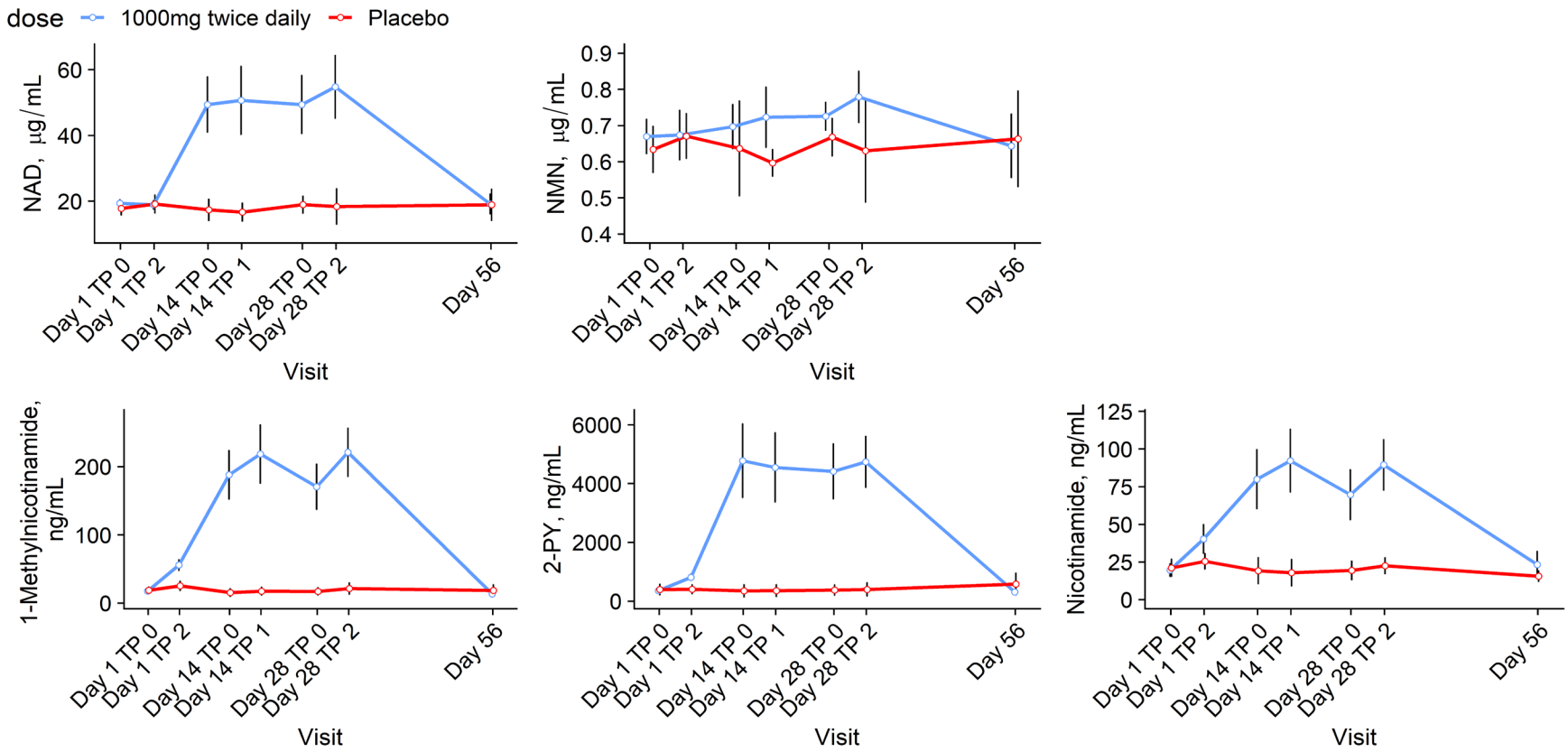
(Pencina, Lavu, Dos Santos, Beleva, Cheng, Livingston, Bhasin, 2023)

Proof of Concept/ Mechanism Study of NAD precursor Nicotinamide Mononucleotide (NMN)

- Aims:
  - Physiologic effects on NAD metabolome, metabolic markers, BP, muscle performance and physical function
- Participants: Middle-aged or older men and postmenopausal women, 45 to 80 years, with overweight or obesity
- Participant allocation: Concealed randomized allocation, stratified by sex in 2:1 ratio (NMN to placebo)
- Interventions: a micro crystalline polymorph formulation of β-Nicotinamide Mononucleotide (MIB-626) 1000-mg twice daily or matching placebo twice daily
- Intervention duration: 28 days

(Pencina et al., 2023)

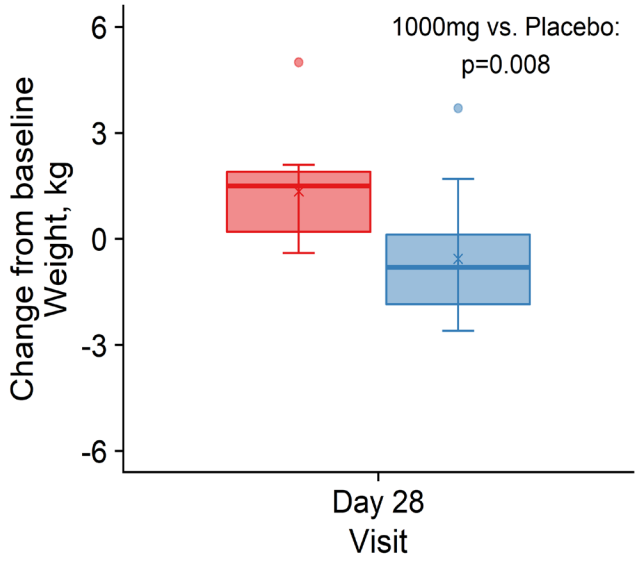
Oral Microcrystalline Tablet Formulation of NMN Safely Increases Blood NAD Levels in Middle-aged Men and Women



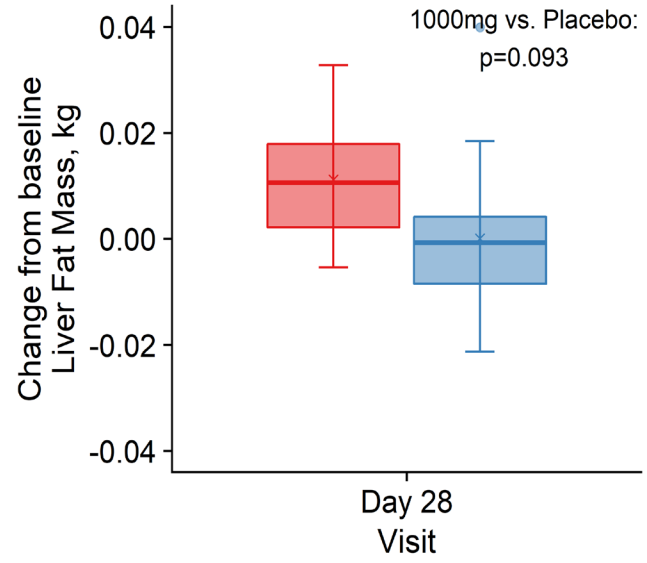
(Pencina et al., 2023)

Changes in Body Weight, Liver Fat and Intra-abdominal Fat

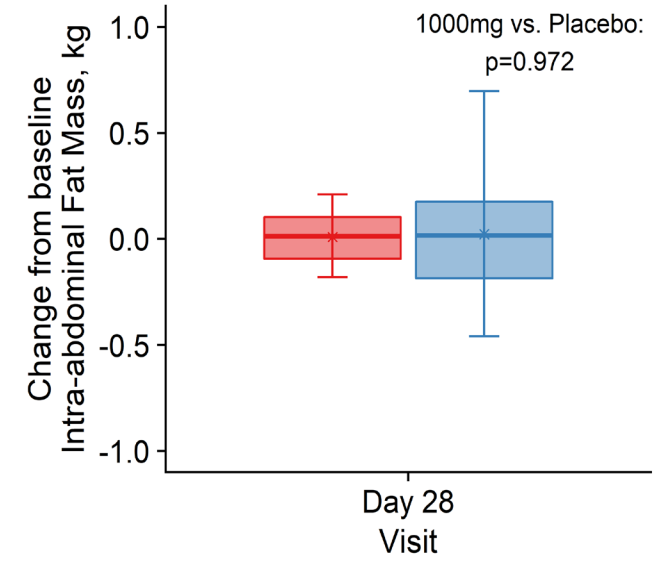
Body Weight



Liver Fat



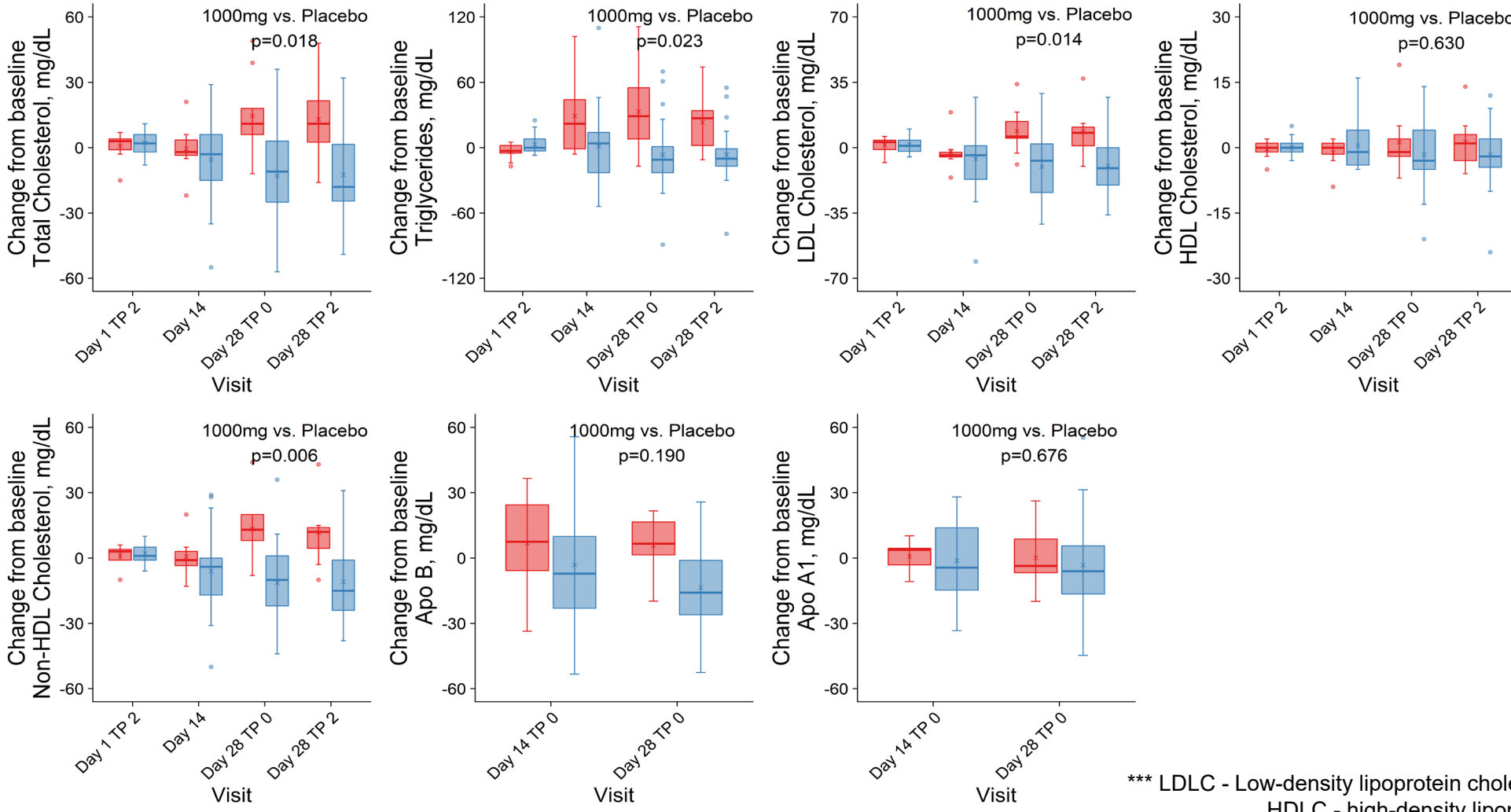
Intra-abdominal Fat



A greater reduction in body weight in NMN vs placebo arms; between group difference = 1.9 kg

(Pencina et al., 2023)

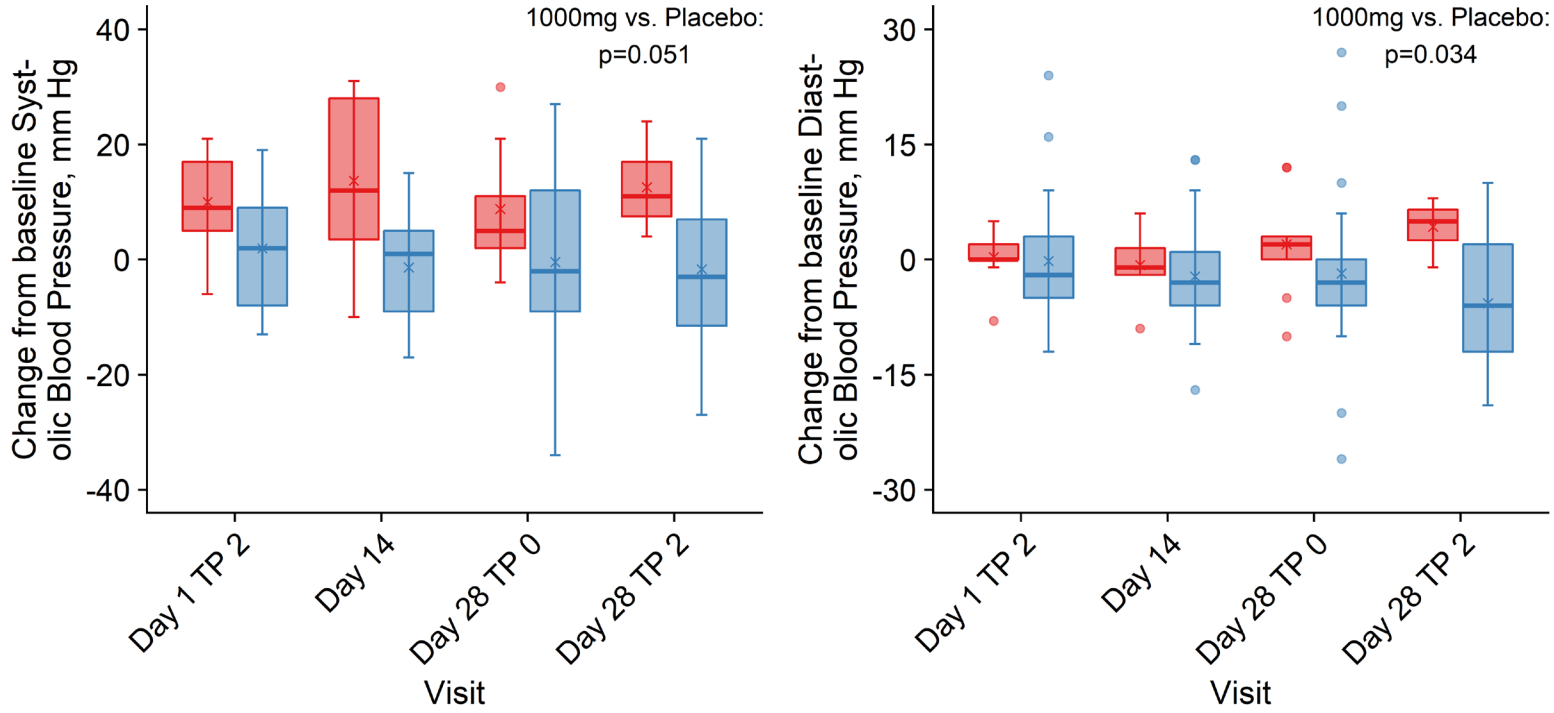
NMN Administration Associated with Decrease in Total Cholesterol, LDLC, non-HDLC, and TG but not HDLC



(Pencina et al., 2023)

*** LDLC - Low-density lipoprotein cholesterol
HDLC - high-density lipoprotein
TG - triglycerides

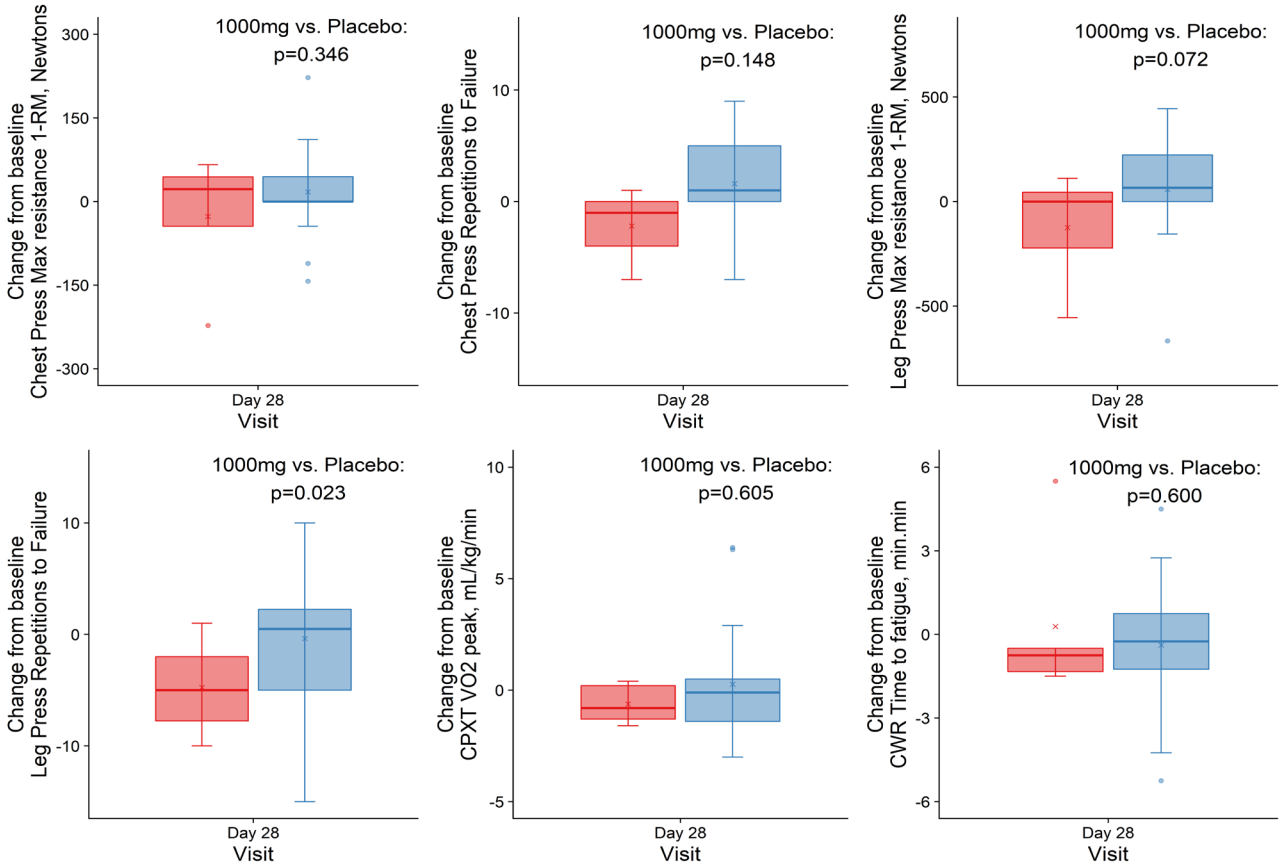
Changes in Systolic and Diastolic Blood Pressure



A greater reduction in diastolic pressure in NMN vs placebo arms

(Pencina et al., 2023)

Muscle Performance and Aerobic Capacity

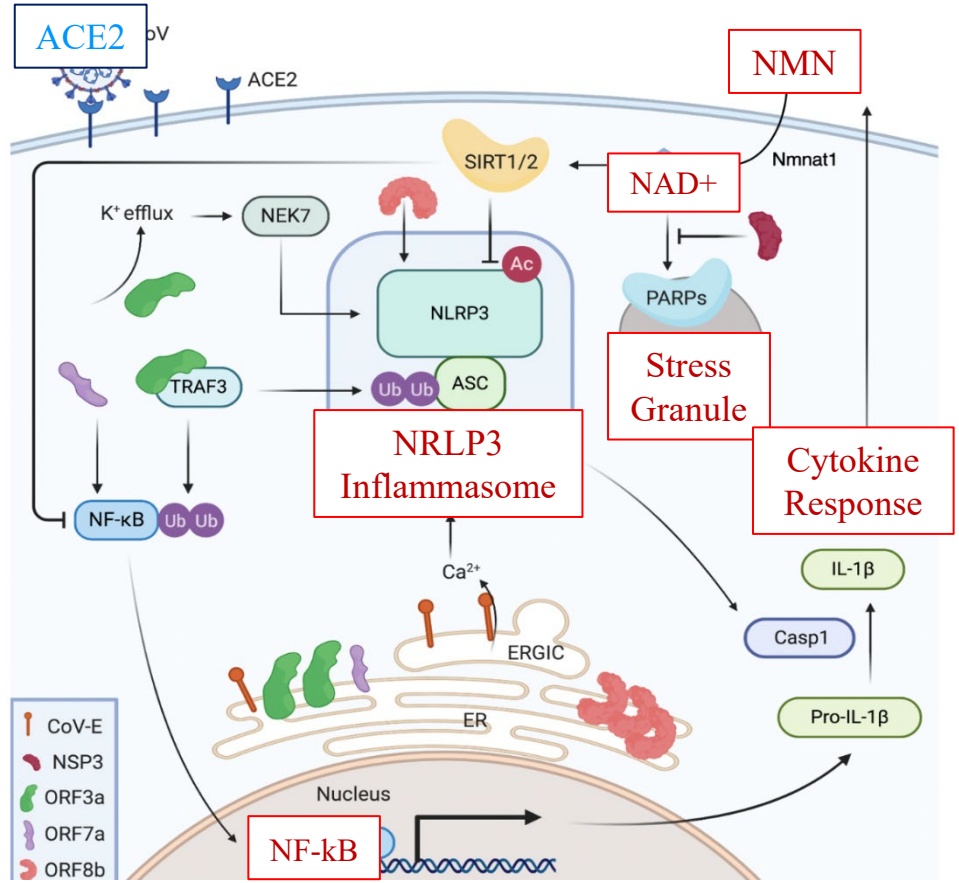


A greater improvement in muscle fatigability in NMN vs placebo arms

(Pencina et al., 2023)

NAD is an Important Player in Regulating Body's Anti-viral Response to Infections Such as SARS-CoV-2

SARS-CoV-2

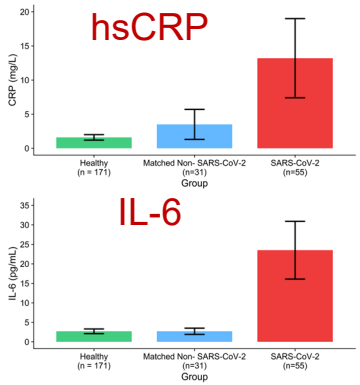


- NAD is a key regulator of NRLP3 inflammasome, stress granule formation, and NF-kB-mediated cytokine response to virus.
- NAD depletion is a conserved response to infections in plants and animals.

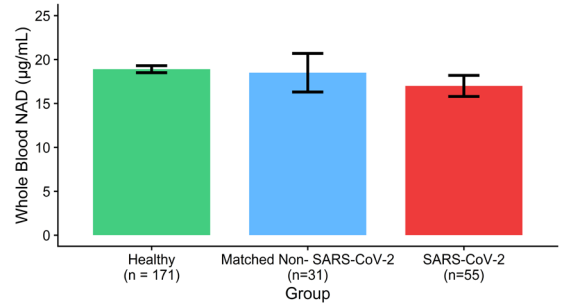
Uncontrolled Trials in Patients Hospitalized with SARS-CoV-2:
Reduced length of stay, lower levels of inflammatory markers, lower rates of acute kidney injury.

Increased NAD Flux in in SARS-CoV-2 Infection: Enzymes Involved in NAD Degradation as well as Synthesis are Upregulated

Marked Increase in Infl. Markers



Only a modest decrease in Steady State NAD levels

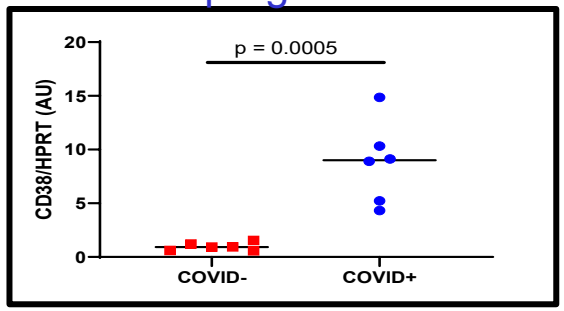


RNAseq analysis reveals marked dysregulation of NAD-dependent pathways:

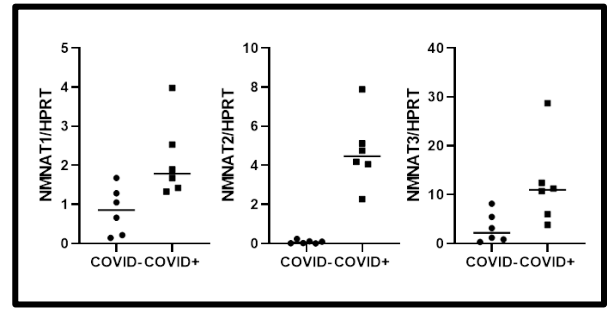
- Inflammation and immunity
- Mitochondrial function and bioenergetics
- Metabolic regulation
- Enzymes in redox reactions
- Enzymes involved in NAD synthesis and degradation

But NAD Flux is Markedly Increased

NAD Consuming Enzyme CD38 is Upregulated

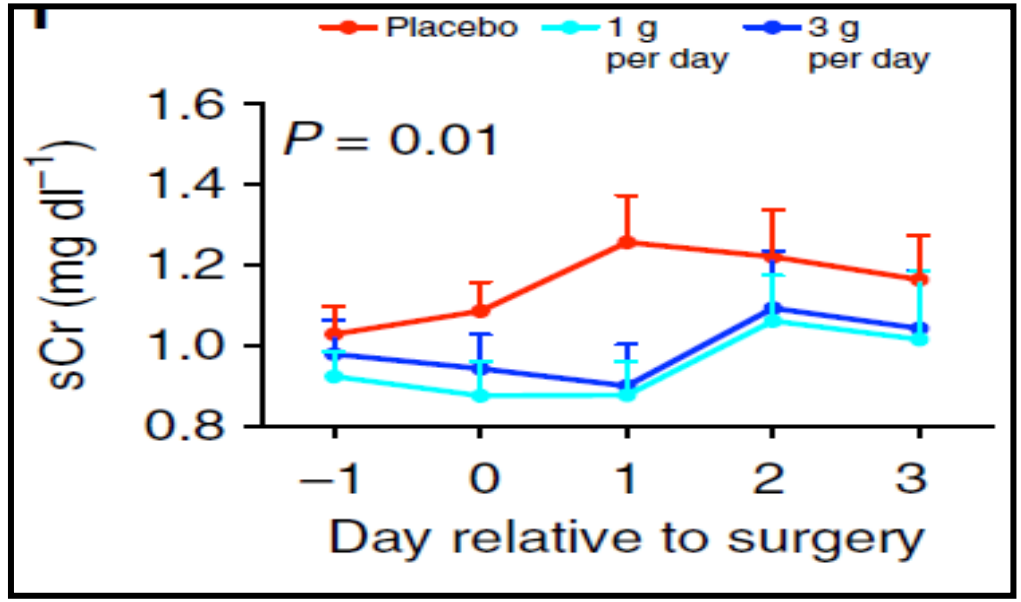


NAD Synthesizing Enzymes: NMNAT Isoforms are Upregulated



(Pencina, Valderrabano, Wipper and Bhasin unpublished)

Effect of NAD Augmentation in Acute Kidney Injury



Following cardiac surgery, serum creatinine increased significantly less in the NAM groups compared to placebo.

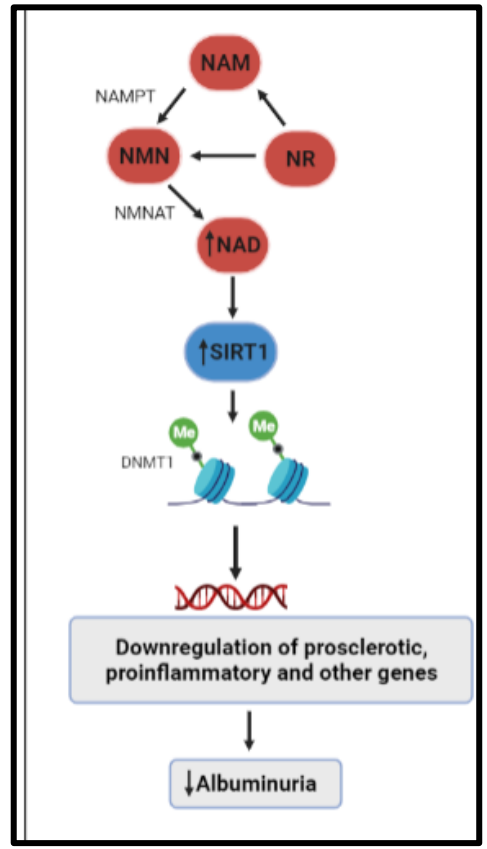
(Poyan Mehr, 2018)

NAD Augmentation in Diabetes Kidney Disease (DKD)

- NMN increases Sirt1 expression in the kidneys of db/db mice, attenuates the increase in Urine Albumin-to-Creatinine Ratio (UACR), and provides protection against DKD without change in HbA1c.
- NMN treatment also provides a survival benefit in db/db mice.

Ongoing RCT of NAD Augmentation in DKD:
To determine the efficacy of 6 months of NMN treatment vs placebo in reducing UACR in older adults with T2DM and UACR 100 – 2000 mg/mg creatinine

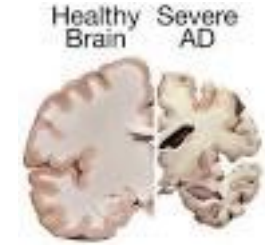
Putative mechanisms of NAD Augmentation



(Hasegawa et al., 2013)
(Yasuda et al., 2021)
(Hyndman & Griffin, 2021)

NAD Augmentation in Alzheimer's Disease (AD)

- AD is a heterogeneous disease with several incompletely understood mechanisms underlying β-amyloid and tau deposition, and neuronal death.
- Disease modifying trials to date have focused mostly on one mechanism — production and deposition of Aβ.
- In preclinical models, βNMN targets multiple contributors to pathology of AD: improves mitochondrial function and insulin sensitivity, inhibits Aβ accumulation, reduces neuro-inflammation, exerts neuronal protective effects, and promotes neuronal regeneration.



https://www.psychologytoday.com/us/blog/explorations-the-mind/202210/neurodegenerative-diseases-novel-treatments

A proof-of-mechanism trial to determine whether NMN penetrates across the blood brain barrier, increases brain NAD levels, and improves blood and cerebrospinal fluid (CSF) biomarkers of AD.
NIA Grant. 1R01AG071074
Principal Investigators: Bhasin S, Marshall G

(Donmez et al., 2010)
(Xie et al., 2019)
(Hou et al., 2018)
(Wang et al., 2016)

Summary of results of early phase data in human diseases and conditions

Potential beneficial effects

- Attenuating acute kidney injury:
  - In adults undergoing elective cardiac surgery
  - In patients infected with SARS-Co-V-2
- Lowering blood pressure in people with hypertension
- Attenuating the severity of SARS-CoV-2 infection
- Attenuation of metabolic changes in brain and inflammation in Parkinson's disease

No effects on:

- Body composition
- Glucose, whole body insulin sensitivity, A1c

Inconsistent Effects on:

- Muscle performance and aerobic capacity

(Poyan Mehr et al., 2018)

Synthesis and Conclusions: Key Takeaways

- NAD+ plays an important role in the biology of aging and pathobiology of many age-related diseases.
- Preclinical data on the efficacy of NAD augmentation in improving health span and many age-related diseases in model organisms are promising.
- The initial early phase trials:
  - NAD precursors are safe and increase NAD levels in blood and some tissues.
  - Promising results in lowering blood pressure and lipids, attenuating inflammatory response, in attenuating acute kidney injury, Parkinson's Disease (PD), and severity of COVID-19.
- The early studies have not been sufficiently large and or long to permit strong inferences about their efficacy in disease states.
- Rigorously designed, adequately powered trials are being planned and their results could be transformative in shaping our therapeutic approach to age-related diseases.

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