REVERSING BIOLOGICAL AGE WITH A NEXT GENERATION NAD+ SUPPLEMENT: A HUMAN CLINICAL STUDY

DR NICHOLA CONLON

CEO, NUCHIDO LABORATORIES

NUCHIDO TIME®

DR NICHOLA CONLON
CEO and Lead Scientist
Nuchido Laboratories

- **Specialist in science of ageing**
- **8 years in drug development**
- **Developing drugs that slow cellular ageing**

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NUCHIDO
LABORATORIES

“At Nuchido we translate the latest science in the field of ageing research into consumer products for everyone”

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“BIOLOGICAL AGING”

The rate at which your cells are aging on the inside

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CHRONOLOGICAL AGE:

Number of years since birth

BIOLOGICAL AGE:

Decline in cellular processes that result in aging

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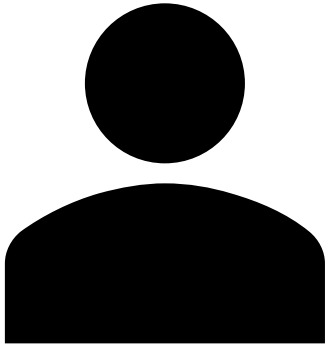
CHRONOLOGICAL AGE: 40

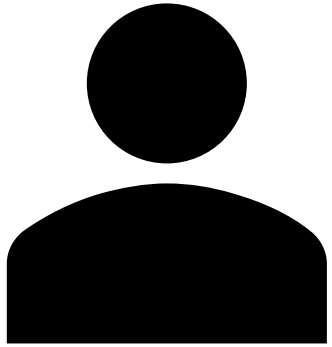
BIOLOGICAL AGE: 50



AGEING FASTER

CHRONOLOGICAL AGE: 50

BIOLOGICAL AGE: 40



AGEING SLOWER

The difference between your chronological and biological age is a good measure of how well you are ageing

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1

AGING IS NOT FIXED

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2

IT'S POSSIBLE TO MEASURE AGING

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WHAT IS CAUSING CELLULAR AGING?

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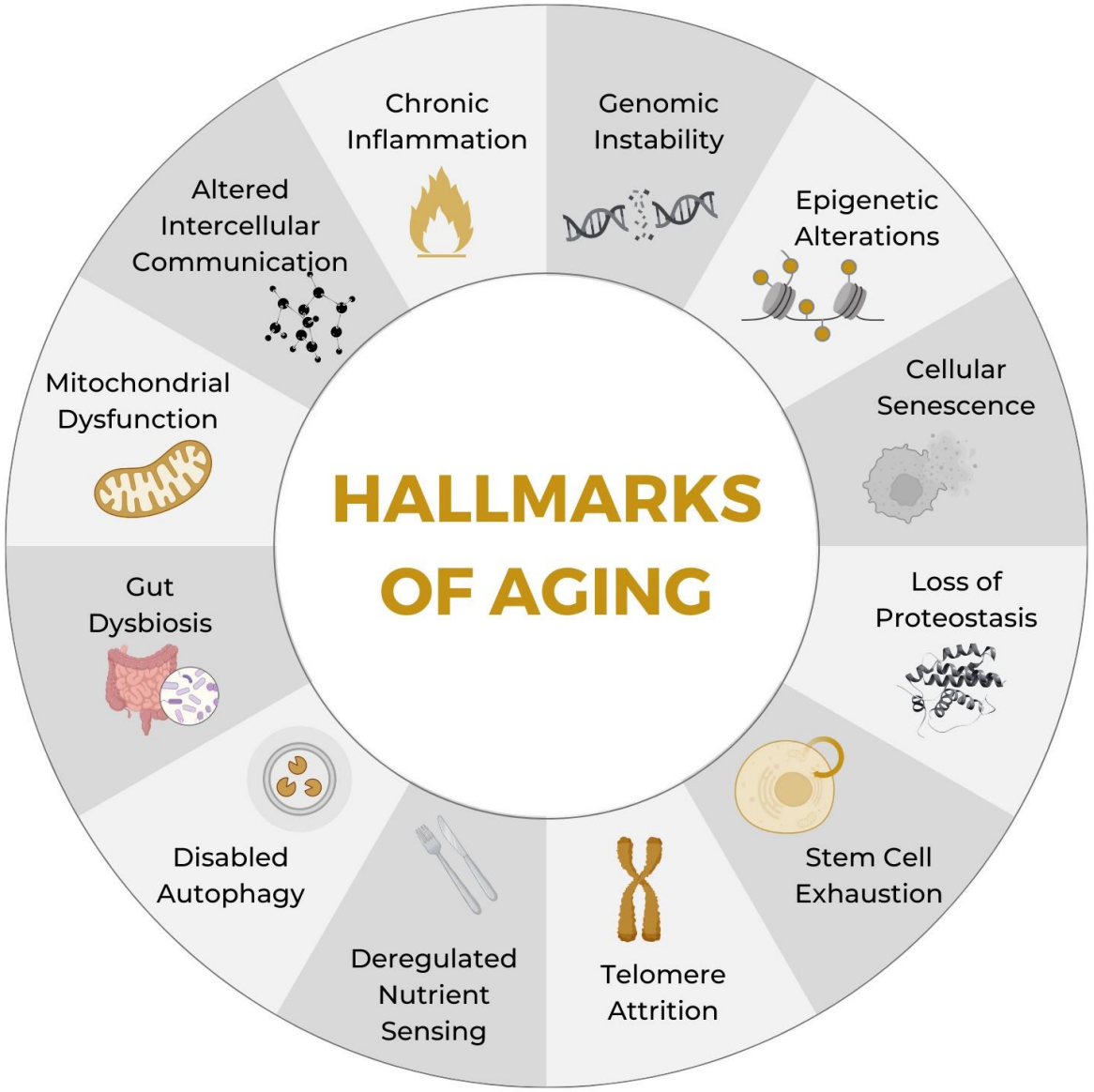

12 key cellular processes that cause the aging process

HOW DO YOU TARGET THE HALLMARKS OF AGING IN PRACTICE?

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NAD+

(Nicotinamide Adenine Dinucleotide)

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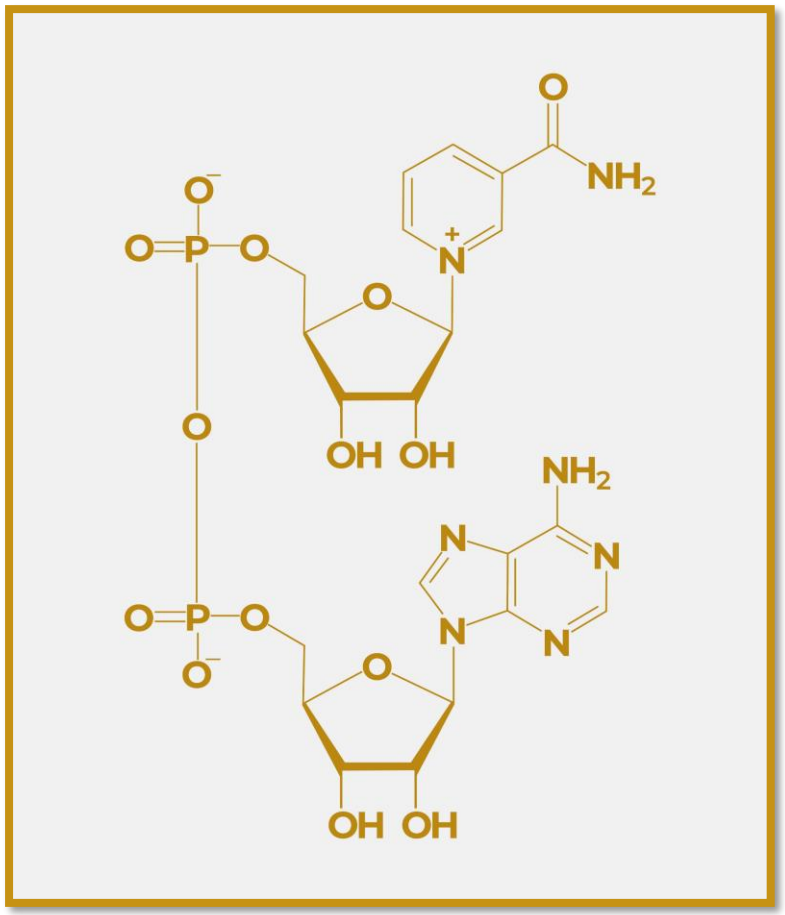
WHAT IS NAD+



NAD+ is critical for:

+ Cellular energy production
+ Cellular maintenance and repair
+ High NAD+ = high energy & repair
+ Low NAD+ = low energy & repair

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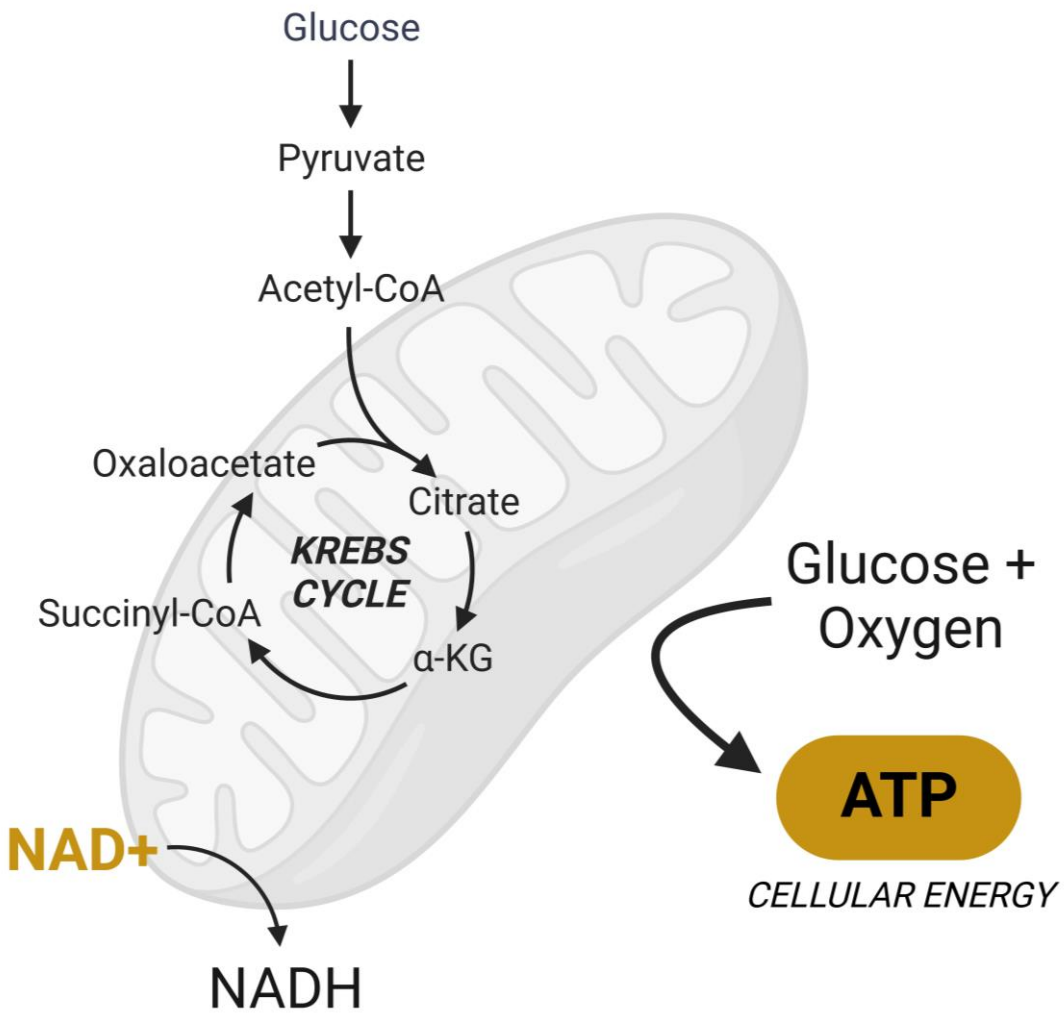
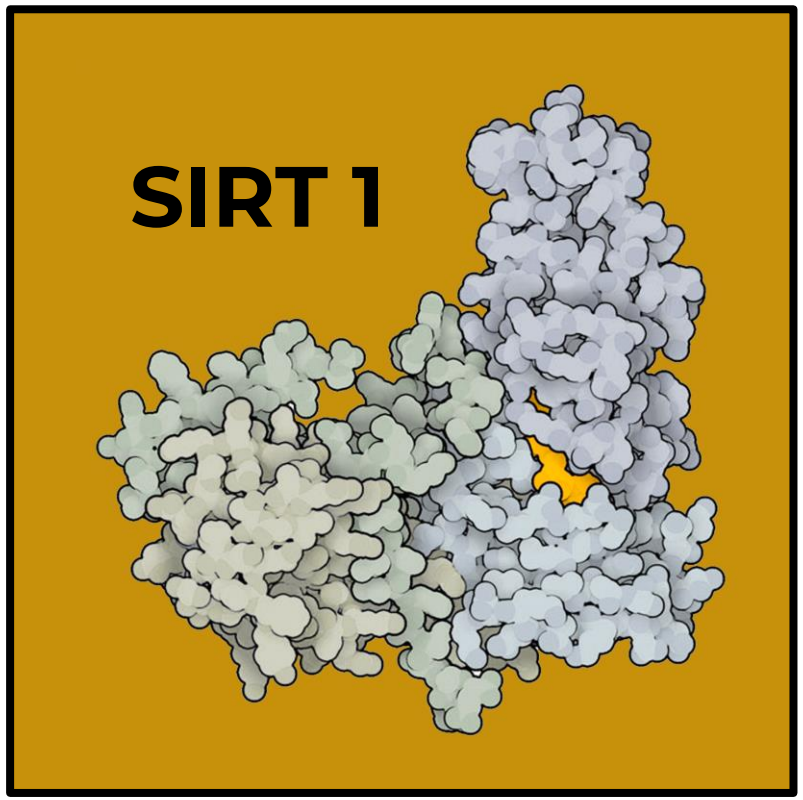
NAD+ AND ENERGY PRODUCTION



NAD+ is critical for the production of ATP by the Krebs cycle

SIRTUINS AND NAD+



Imai & Guarente 2014 (PMID: 24786309)

- Many of the beneficial effects of NAD+ are due to its interaction with the sirtuins
- The sirtuins are a family of 'longevity proteins' (SIRT1-7)
- They switch on many pathways associated with cellular health
- Sirtuins need NAD+ to function

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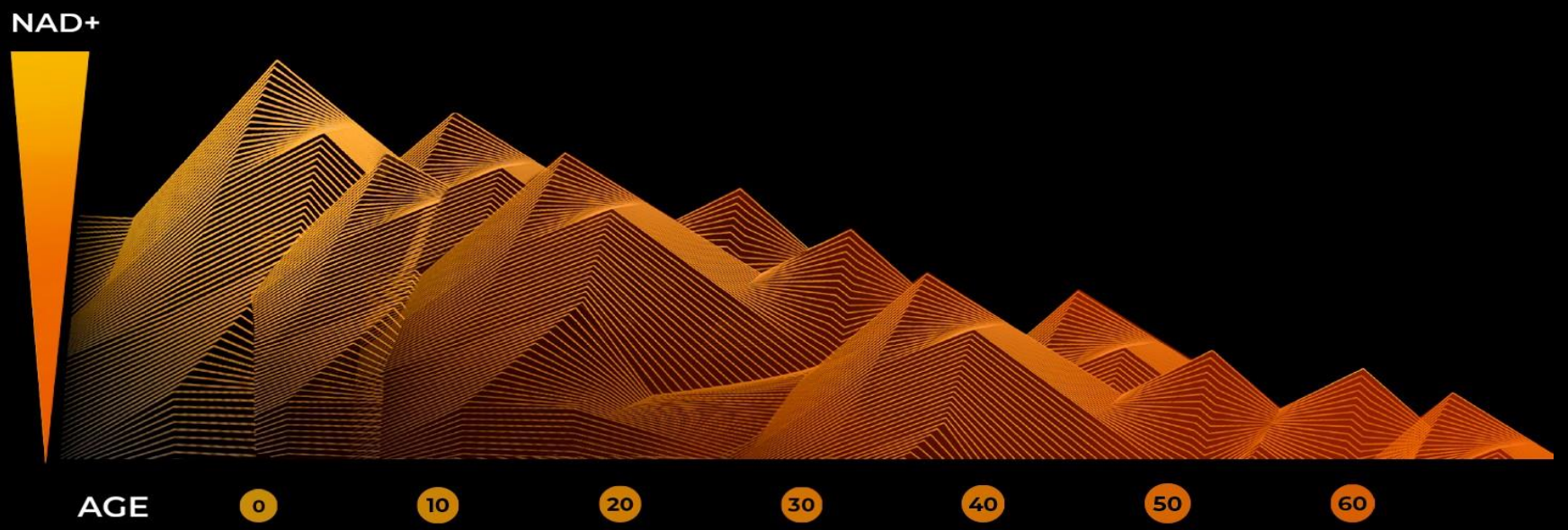
NAD+ DECLINES WITH AGE



The amount of NAD+ in your body drops
by approximately 50% every 20 years

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NAD+ DECLINE IN DISEASE

NEURODEGENERATIVE DISEASES

E.g. Alzheimer's disease, Parkinson's disease, Axonal degeneration, Amyotrophic lateral sclerosis

CARDIOVASCULAR DISEASES

E.g. heart failure, Ischemia

CONGENITAL MALFORMATIONS

GENETIC DISORDERS

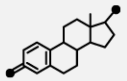
E.g. Ataxia telangiectasia, Cockayne syndrome (CS)

METABOLIC DISORDERS

E.g. Type 2 diabetes, Obesity, Metabolic syndrome, Overnutrition

MUSCLE DISORDERS

E.g. Sarcopenia, Duchenne muscular dystrophy



LOSS OF FEMALE FERTILITY

KIDNEY DISEASE

E.g. Acute Kidney Injury

LIVER DISEASE

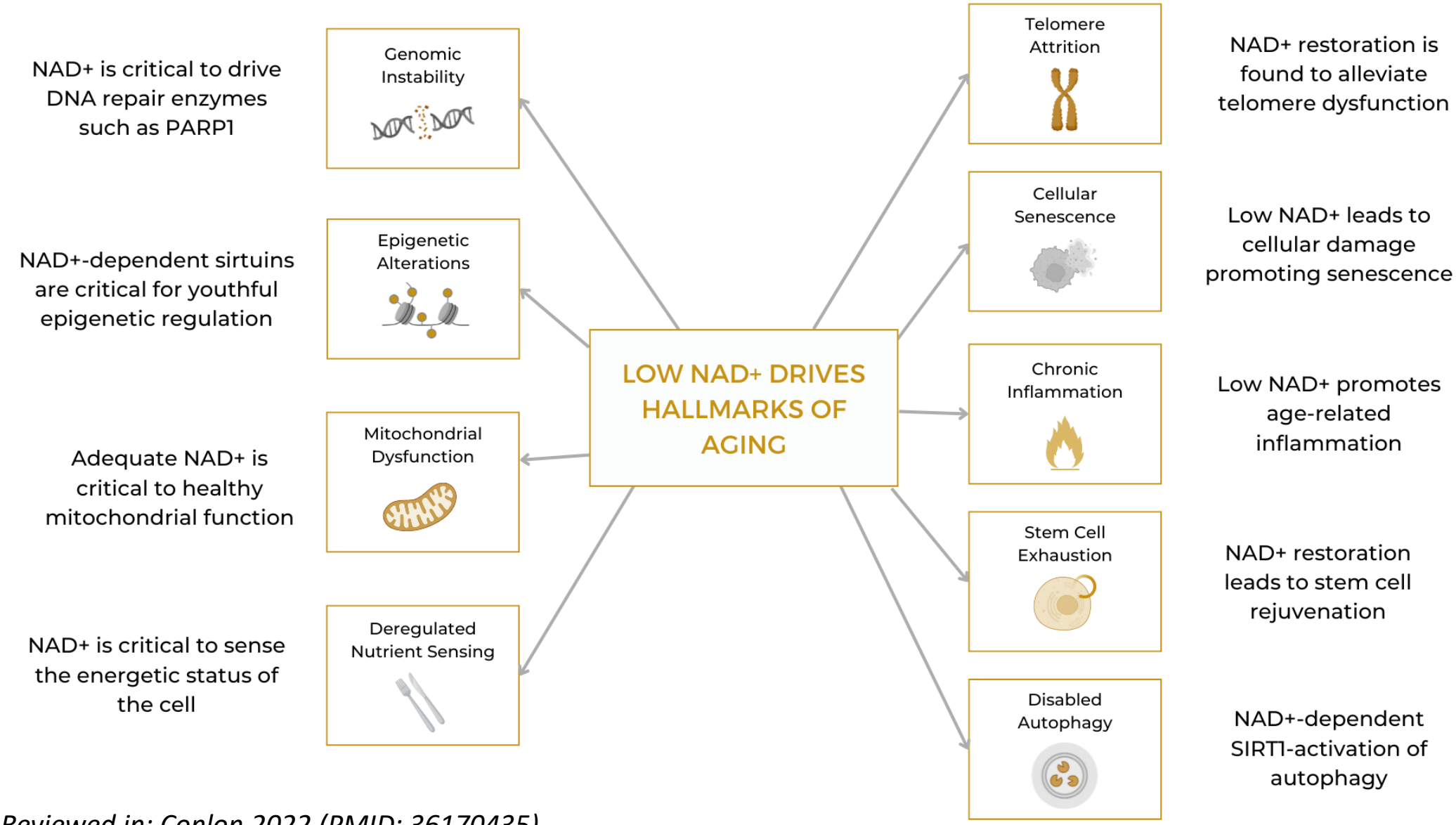
E.g. Non-alcoholic fatty liver disease (NAFLD), Liver hepatotoxicity, Alcohol injury

NOISE INJURY

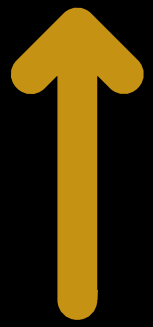
CATARACT

Reviewed in: Rajman et al. 2018 (PMID: 29514064)

NAD+ TARGETS THE HALLMARKS OF AGING



Reviewed in: Conlon 2022 (PMID: 36170435)



NAD+

Can you increase NAD+ levels?

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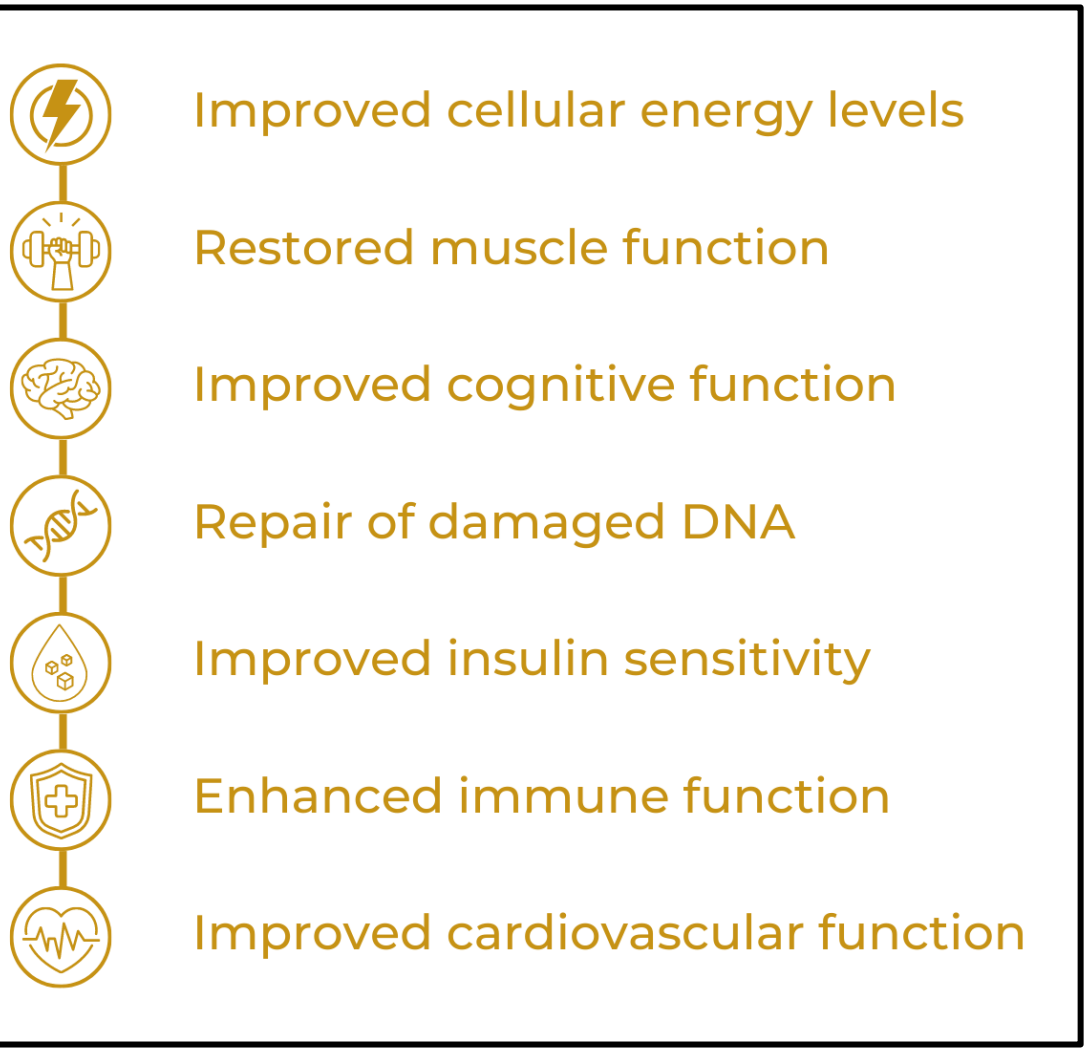
NAD+ BENEFITS

NAD+ restoration leads to improved all round cellular health and HEALTHSPAN



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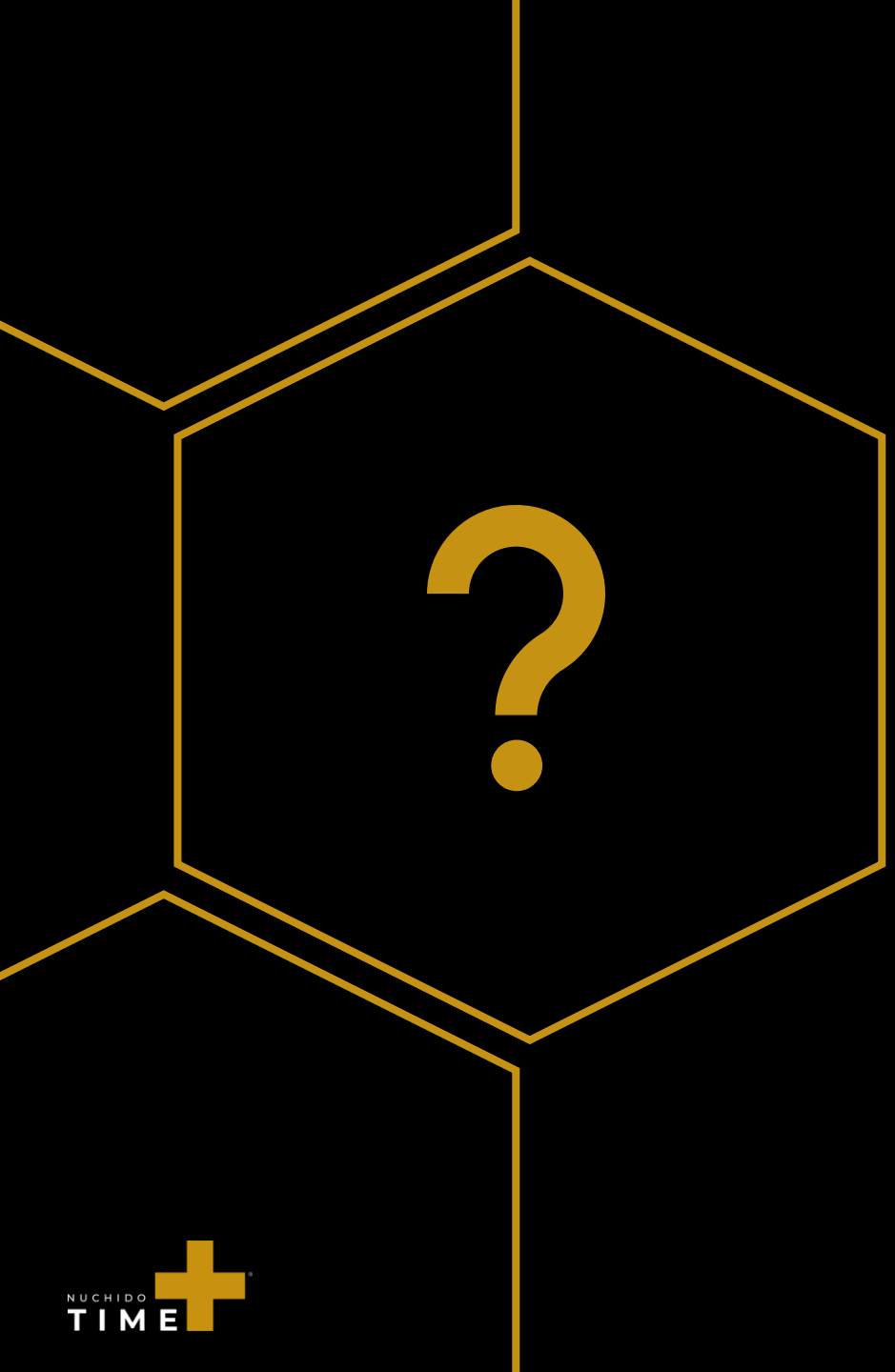

HOW DO YOU BOOST NAD+?

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HOW TO BOOST NAD+

‘Pure’ NAD+ :

Capsules, topicals,

IV infusions, injections ???

Low efficacy 👎

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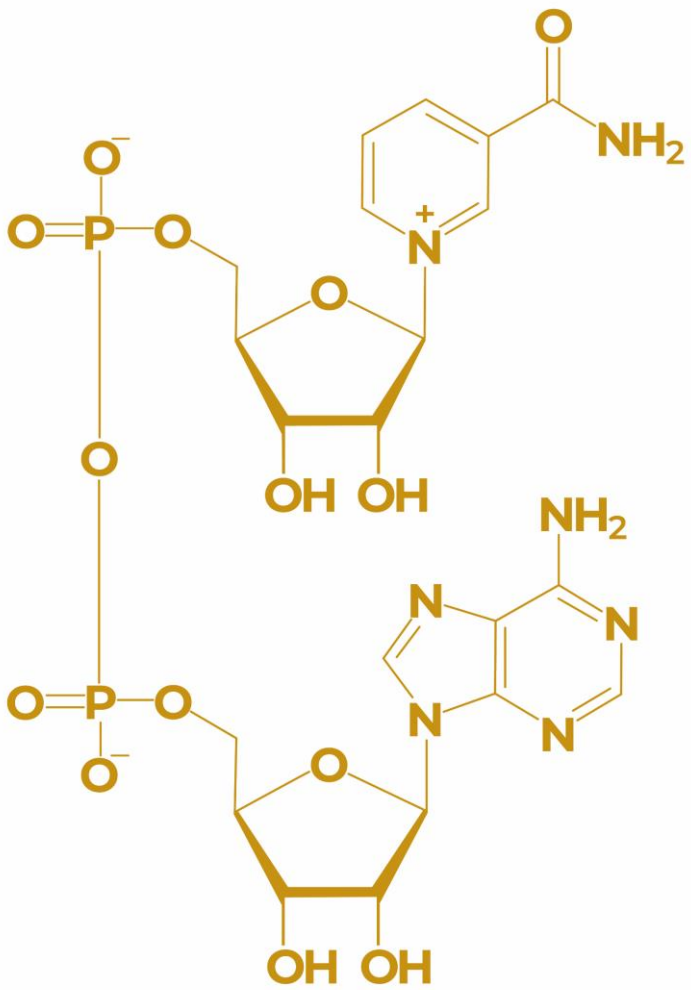
HOW TO BOOST NAD+

- NAD+ is an <u>unstable molecule</u> - it doesn't survive well outside of the body
- NAD+ is a <u>large molecule</u> - it struggles to enter the cells where it is needed
- It cannot freely diffuse across the membrane of many cells



Bruzzone et al. 2001 (PMID: 11099492)

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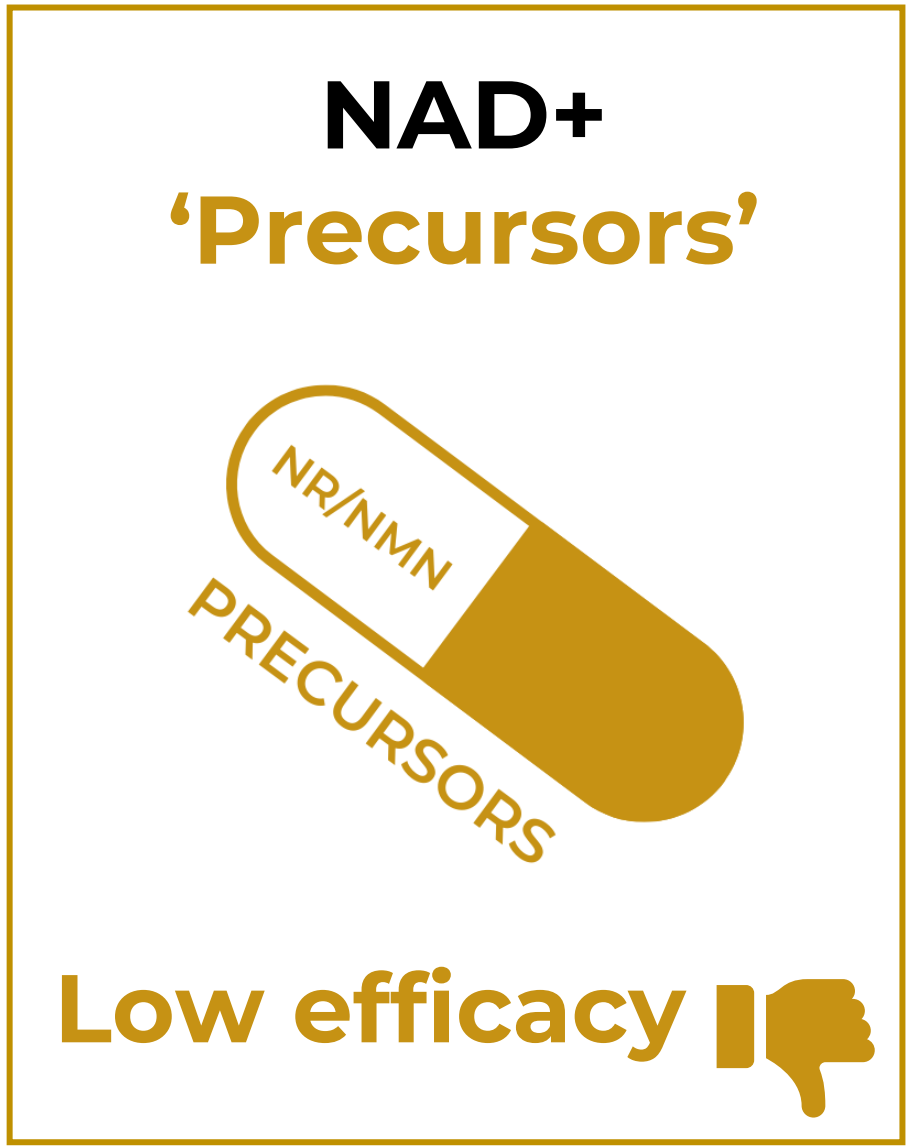
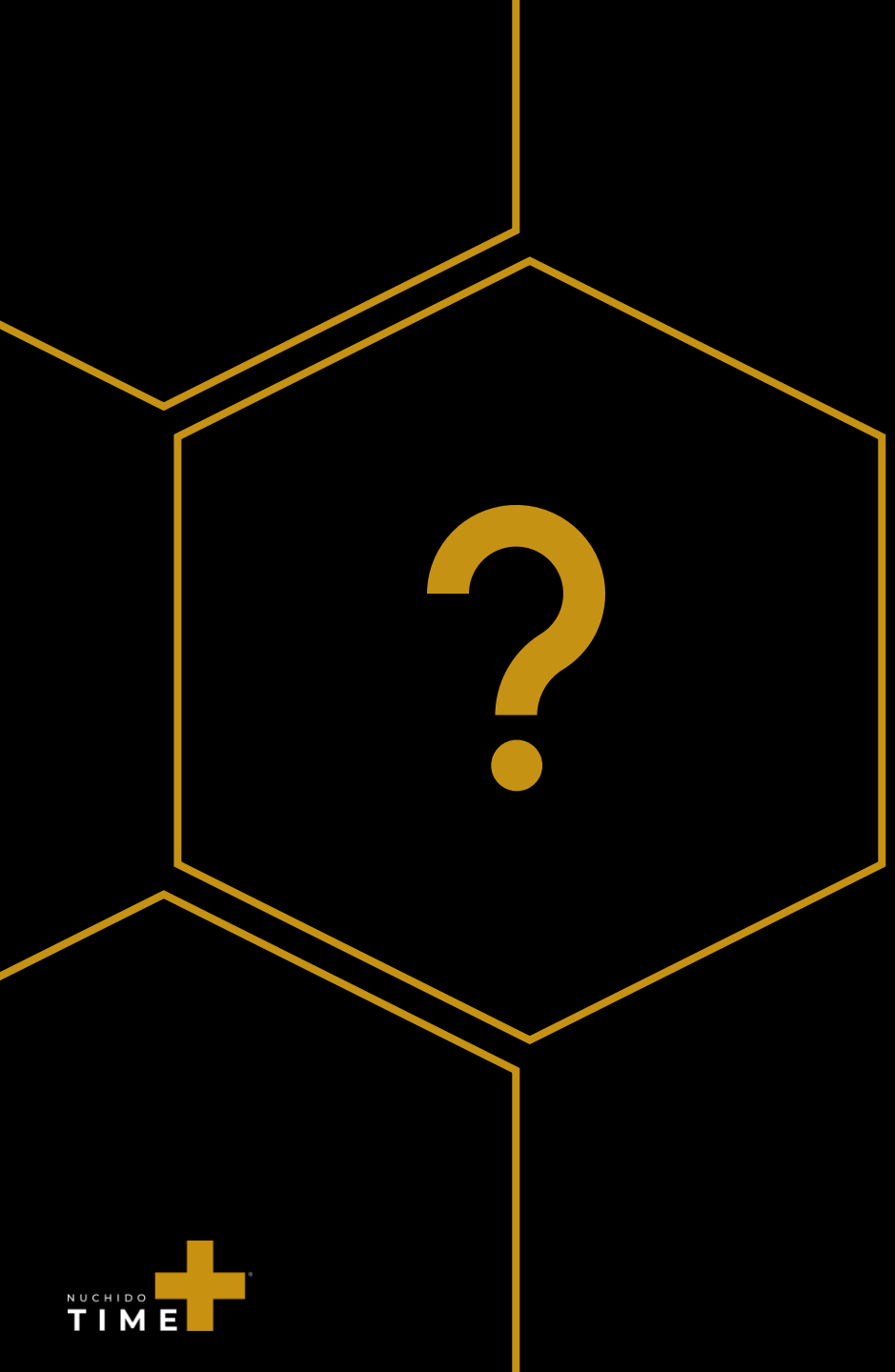
HOW TO BOOST NAD+

- Precursors such as NR and NMN are raw materials that the body uses to make NAD+
- But they do not address the root causes of NAD+ decline
- Evidence that they cause methylation problems and inadvertently drive inflammation



Trammell et al. 2016 (PMID: 27721479)
Chini et al. 2020 (PMID: 33199925)

NUCHIDO TIME



WHAT IS CAUSING NAD+ DECLINE?

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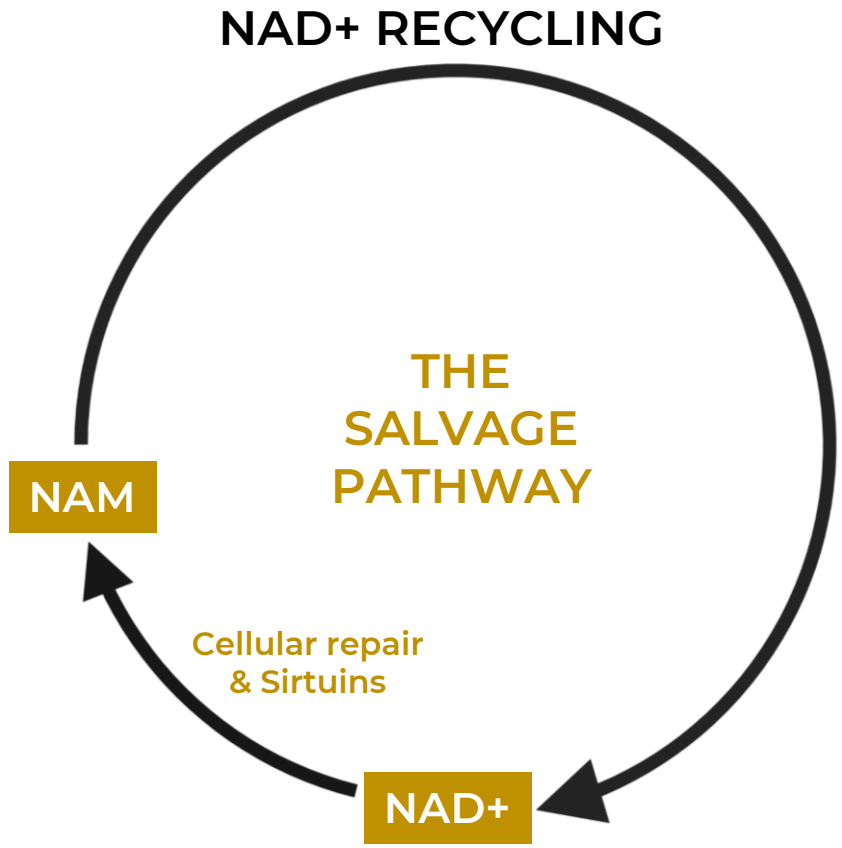
WHY DOES NAD+ DECLINE?

1. **Older cells use more NAD+**
2. **Our ability to make and recycle NAD+ declines**

NAD+ PRODUCTION : IN YOUNG CELLS

In healthy young cells, the majority of NAD+ is recycled

1. NAD+ is used for cellular repair and to power the sirtuins
2. The breakdown product is nicotinamide (NAM)
3. In healthy young cells NAM is recycled back into fresh NAD+
4. This means as NAD+ is used up, it is automatically restored

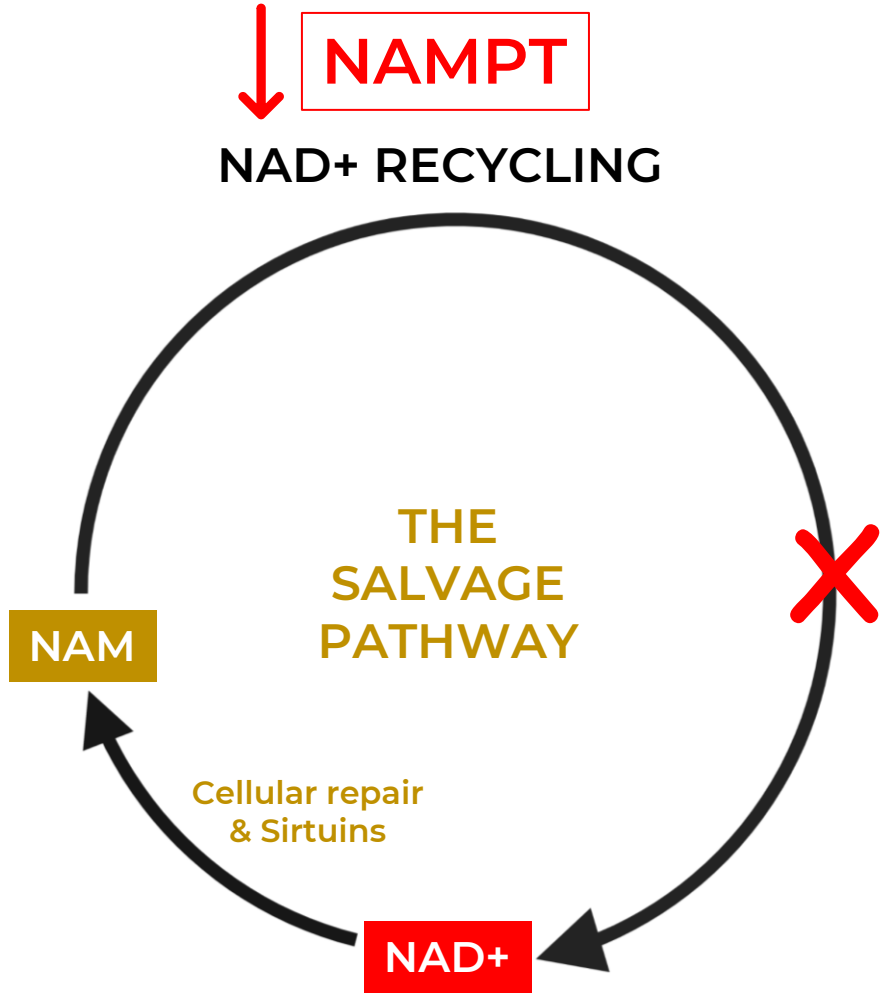


Canto et al. (PMID: 26118927)

NAD+ PRODUCTION : IN OLDER CELLS

In older cells less NAD+ is recycled

1. The key enzyme for NAD+ production and recycling is NAMPT
2. Levels of the NAMPT enzyme decrease with age
3. NAM can no longer be recycled causing NAD+ to decline

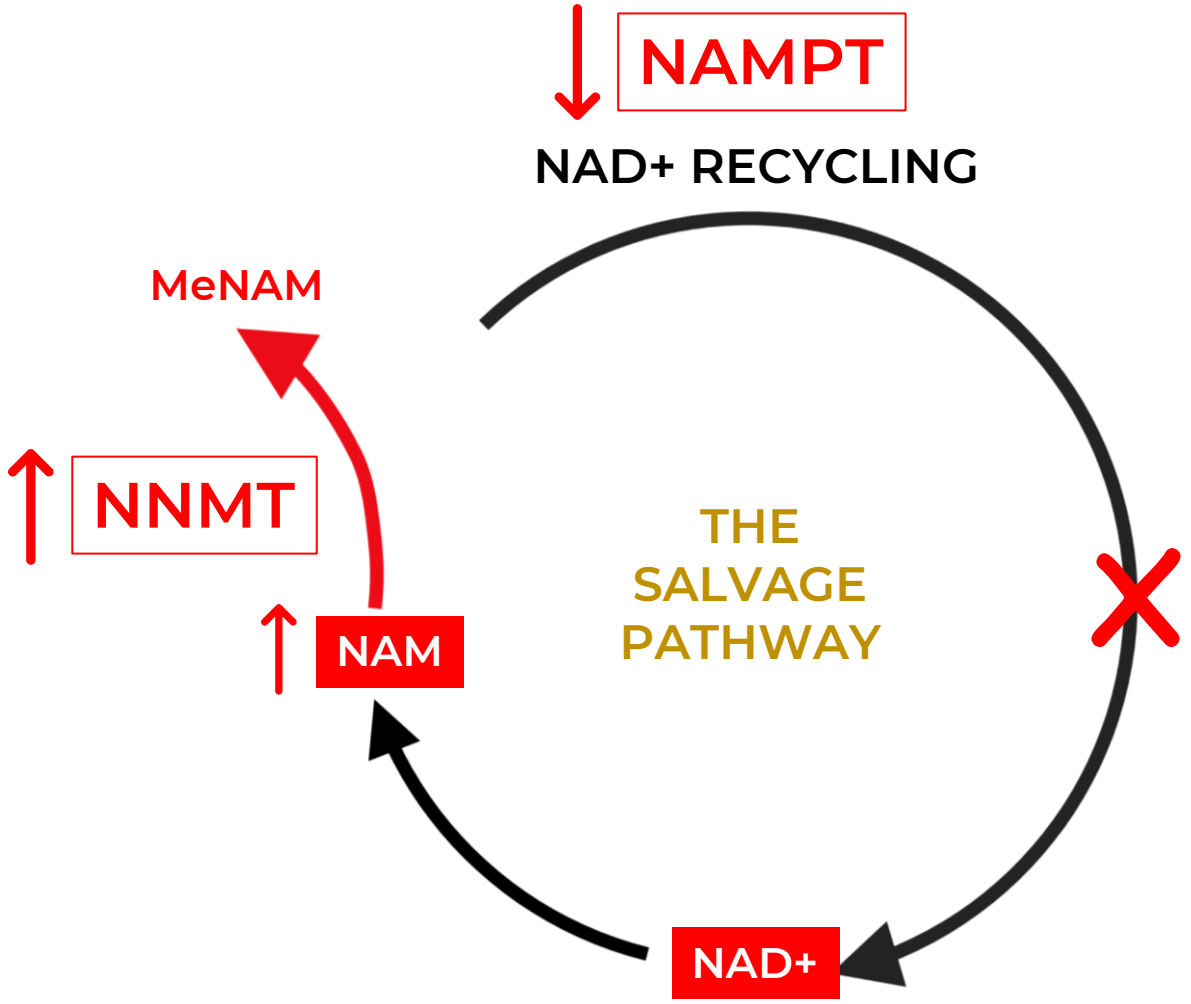


Zhou et al. 2016 (PMID: 27174364)
de Guia et al. 2019 (PMID: 31207144)

NAD+ PRODUCTION : IN OLDER CELLS

This causes methylation problems...

1. Reduced NAM recycling causes excess NAM to accumulate in the cell
2. To compensate, cells overexpress another enzyme called NNMT
3. NNMT methylates NAM signaling it to be removed from the cell as MeNAM

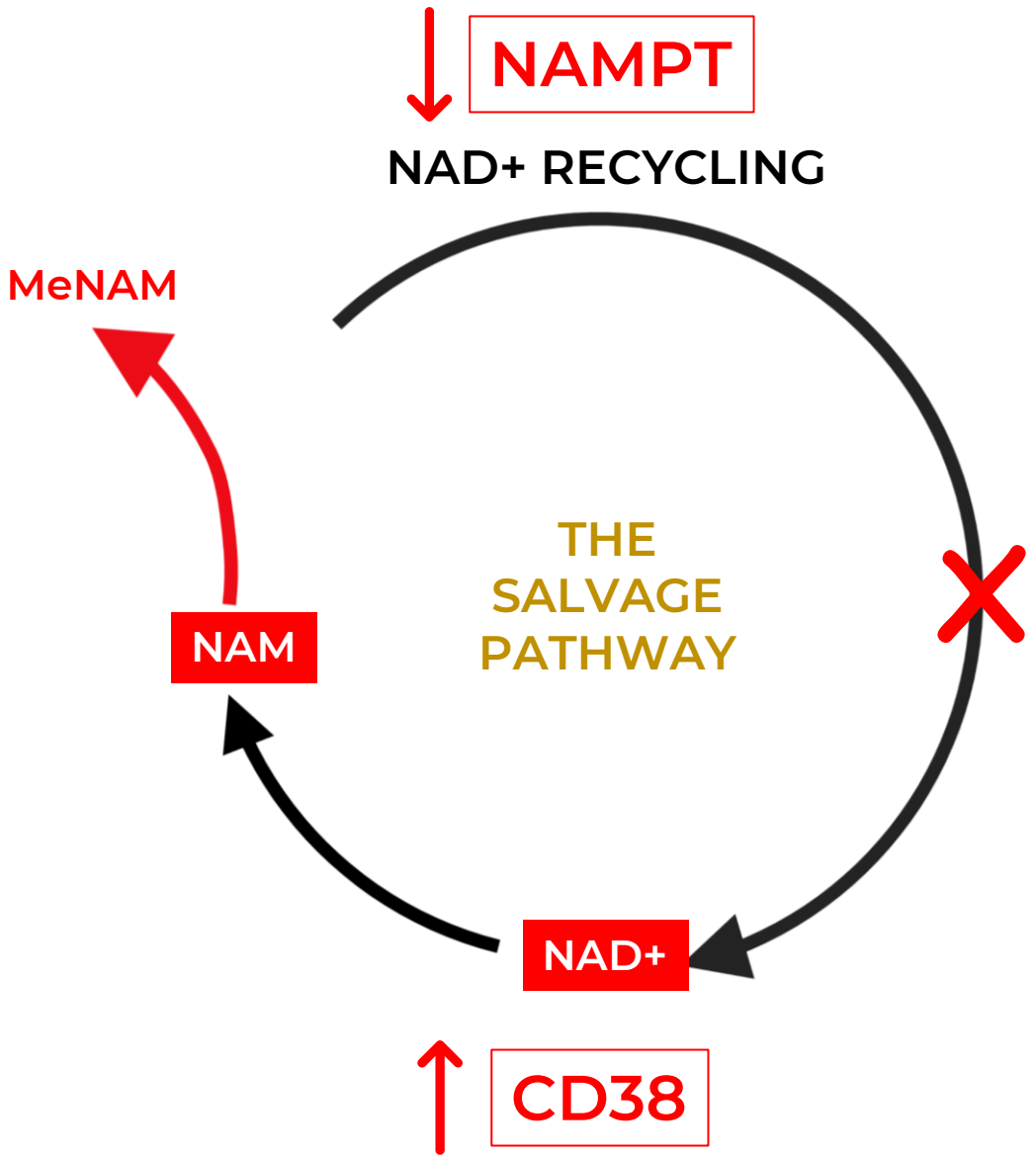


Komatso et al. 2018 (PMID: 29872122)

NAD+ PRODUCTION : IN OLDER CELLS

In older cells inflammation also wastes NAD+

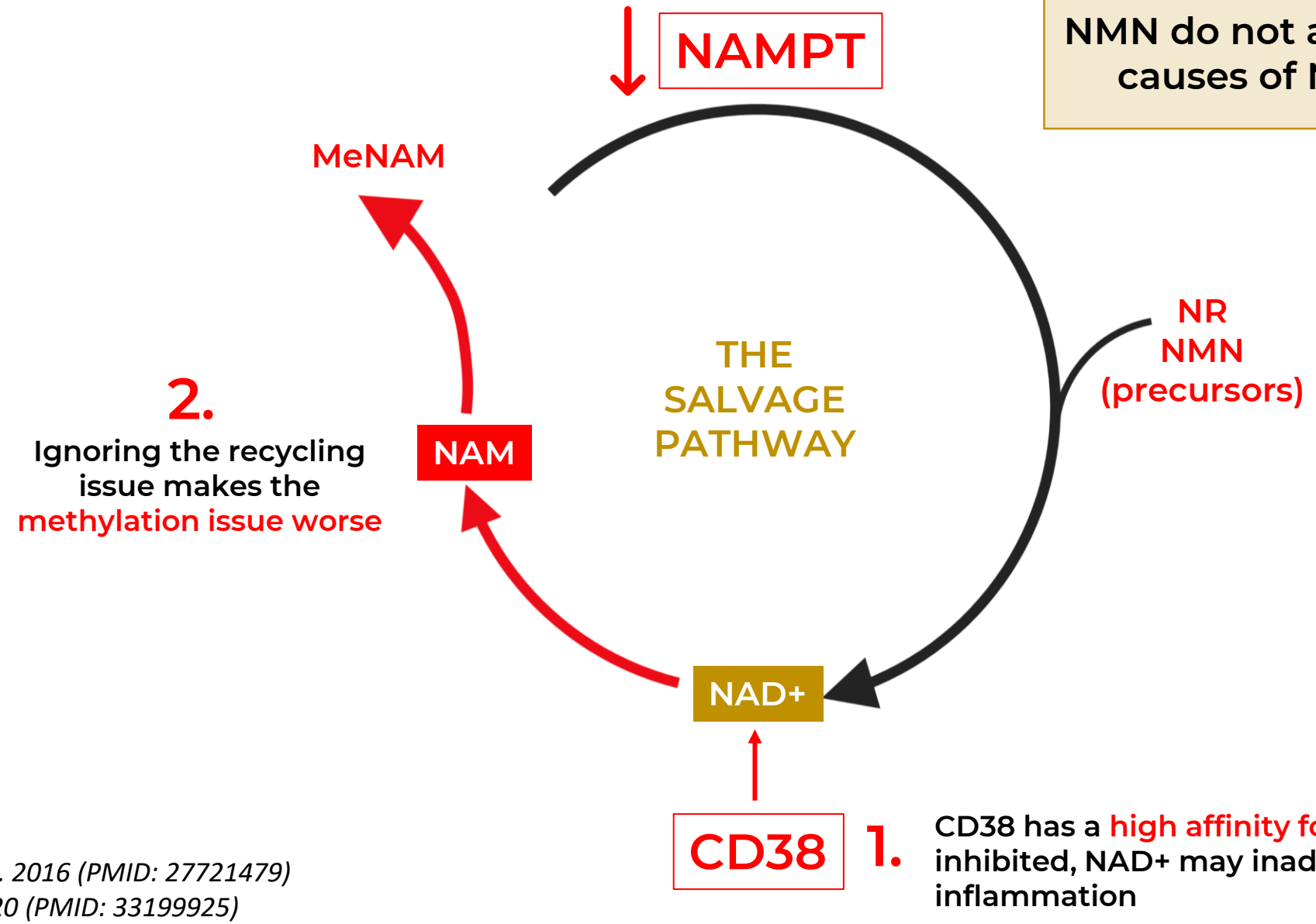
1. Inflammation increases levels of CD38
2. CD38 is an inflammatory enzyme that uses huge amounts of NAD+
3. CD38 breaks NAD+ down into nicotinamide (NAM)
4. Resulting in even more NAM methylation and excretion



Camacho-Pereira et al. 2016 (*PMID*: 27304511)

THE PROBLEM WITH NMN/NR

Precursors such as NR or NMN do not address the root causes of NAD+ decline



2. Ignoring the recycling issue makes the methylation issue worse

1. CD38 has a high affinity for NAD+ so if it's not inhibited, NAD+ may inadvertently drive inflammation

Trammell et al. 2016 (PMID: 27721479)
Chini et al. 2020 (PMID: 33199925)

THE PROBLEM WITH NMN/NR

Evidence that precursors such as NR can cause methyl-donor depletion

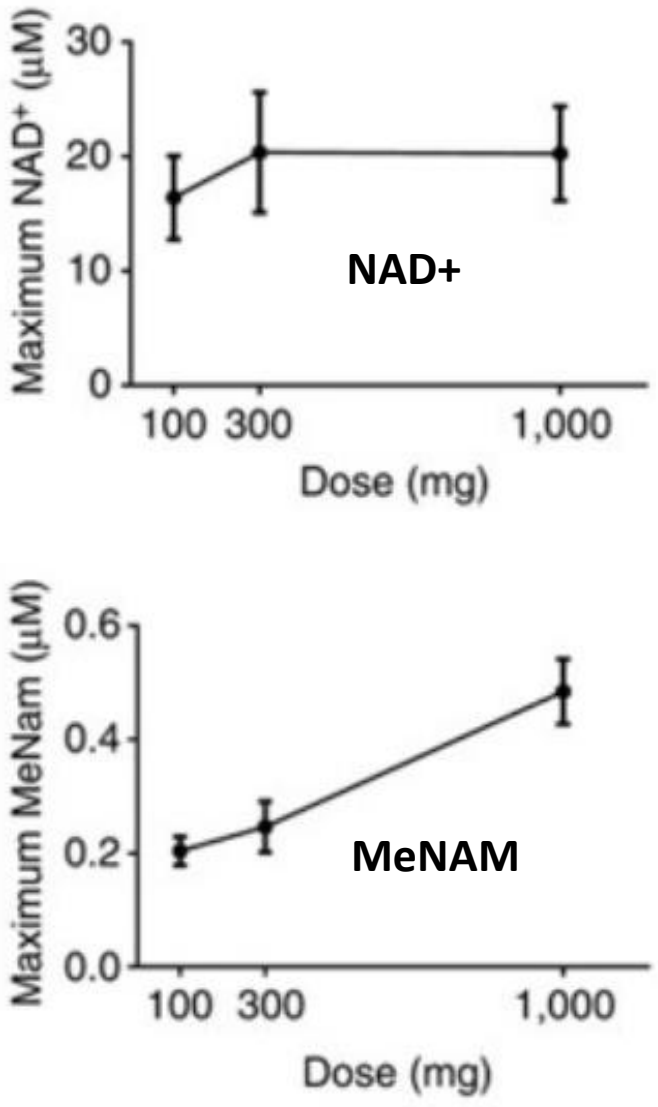
Nicotinamide riboside is uniquely and orally bioavailable in mice and humans.

Trammell SA, Schmidt MS, Weidemann BJ, Redpath P, Jaksch F, Dellinger RW, Li Z, Abel ED, Migaud ME, Brenner C.

Nat Commun. 2016 Oct 10;7:12948. doi: 10.1038/ncomms12948.

PMID: 27721479 Free PMC article.

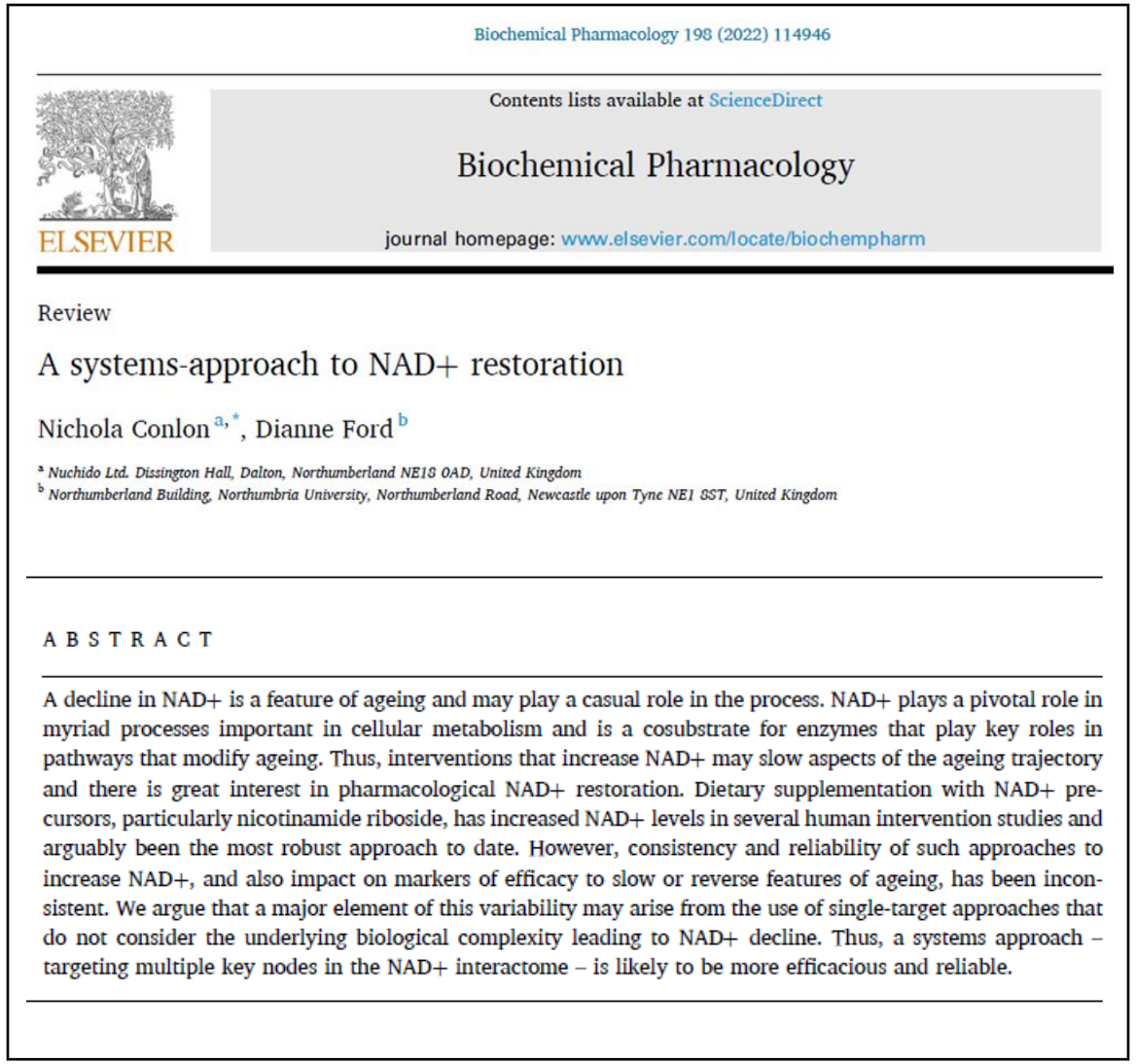
Fig. 8



A SYSTEMS APPROACH TO NAD+ RESTORATION

The latest research shows that NR and NMN precursors are not the most effective way to boost NAD+

Instead, the root causes of NAD+ decline must be addressed using a multitarget systems approach



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journal homepage: www.elsevier.com/locate/biochempharm

Review

A systems-approach to NAD+ restoration

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ABSTRACT

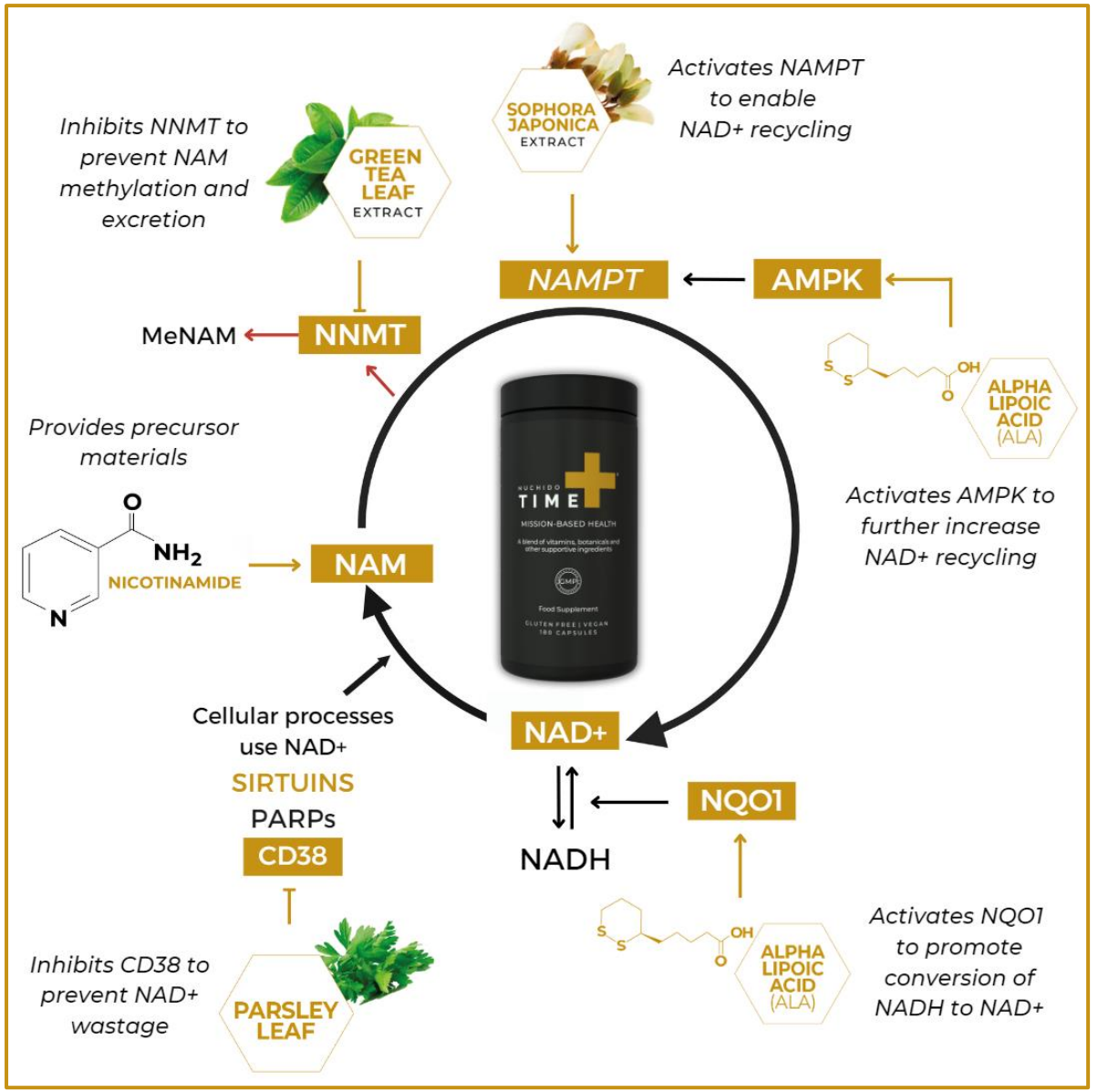
A decline in NAD+ is a feature of ageing and may play a casual role in the process. NAD+ plays a pivotal role in myriad processes important in cellular metabolism and is a cosubstrate for enzymes that play key roles in pathways that modify ageing. Thus, interventions that increase NAD+ may slow aspects of the ageing trajectory and there is great interest in pharmacological NAD+ restoration. Dietary supplementation with NAD+ precursors, particularly nicotinamide riboside, has increased NAD+ levels in several human intervention studies and arguably been the most robust approach to date. However, consistency and reliability of such approaches to increase NAD+, and also impact on markers of efficacy to slow or reverse features of ageing, has been inconsistent. We argue that a major element of this variability may arise from the use of single-target approaches that do not consider the underlying biological complexity leading to NAD+ decline. Thus, a systems approach – targeting multiple key nodes in the NAD+ interactome – is likely to be more efficacious and reliable.

Conlon & Ford 2022 (PMID: 35134387)

NUCHIDO TIME+ FORMULATION

Nuchido TIME+ has been specifically designed to:

- Fix the root causes of NAD+ decline
- Switch back on natural NAD+ production and recycling (NAMPT)
- Inhibit inflammatory processes that waste NAD+ (CD38)
- Promote recycling of nicotinamide (NAM) rather than methylation and excretion



NUCHIDO TIME®

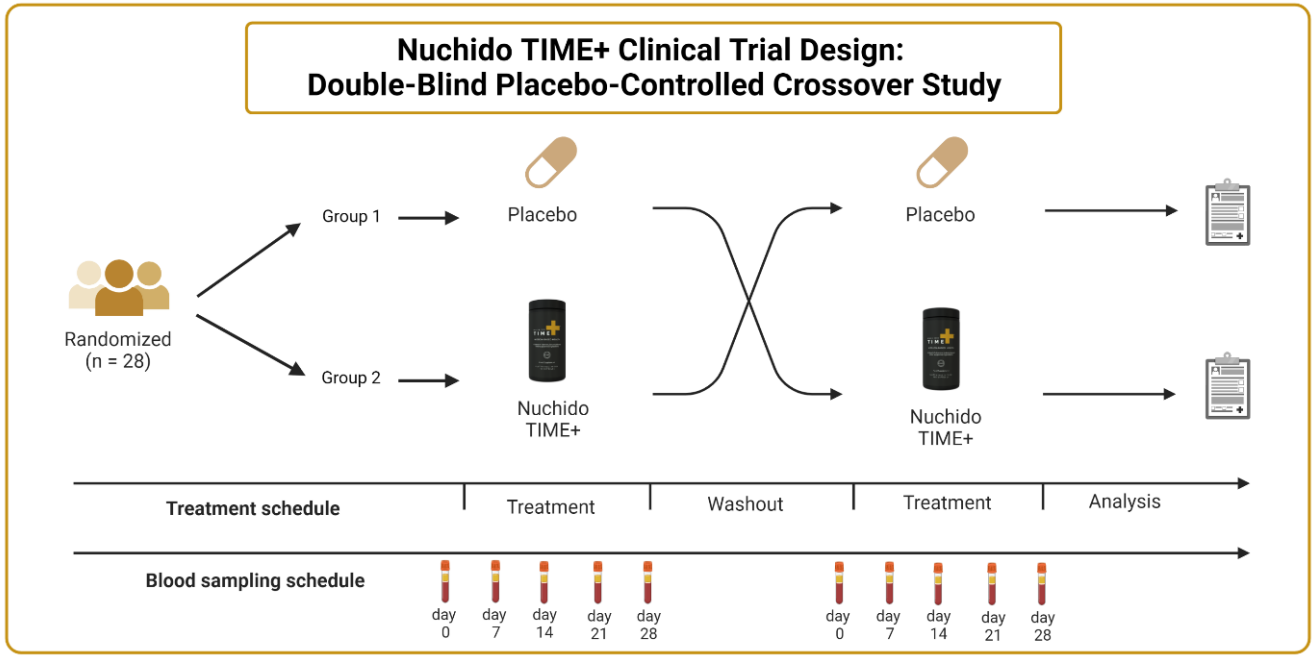
CLINICAL TRIAL

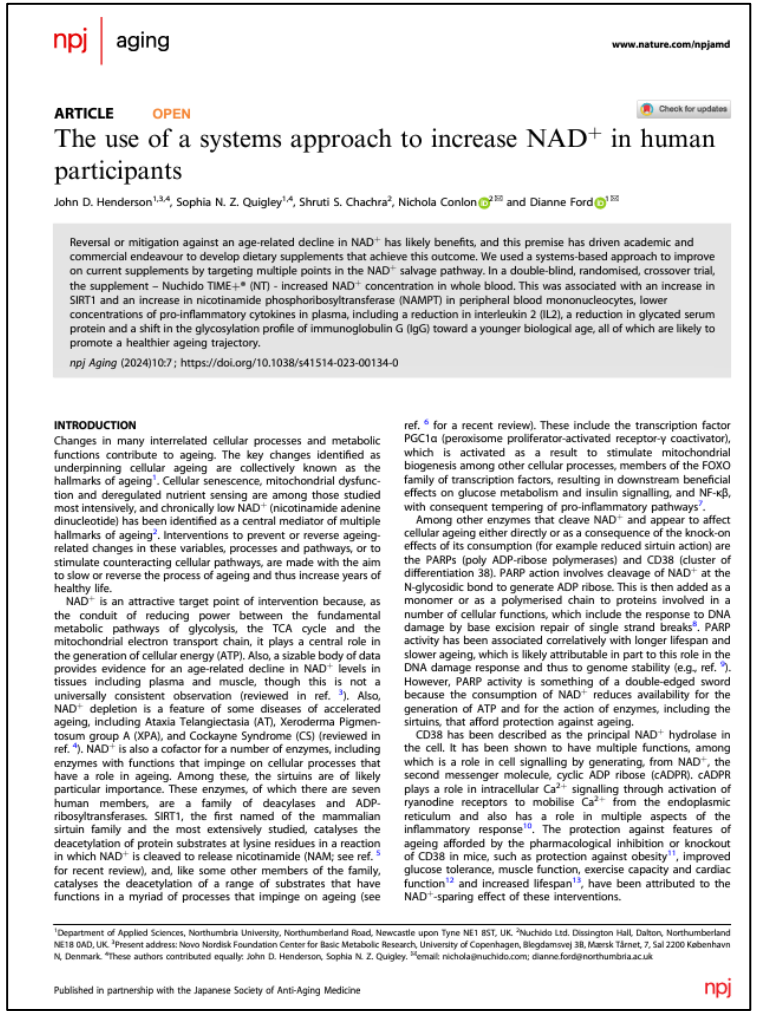
CLINICAL TRIAL

Clinical trial to assess the efficacy of Nuchido TIME+ dietary supplement in human participants

Study design: Randomised, double-blinded, placebo-controlled, crossover design.

Participants: 20-80 years, male and female (n=28)





npj | aging

www.nature.com/npjamd

ARTICLE OPEN

Check for updates

The use of a systems approach to increase NAD^+ in human participants

John D. Henderson[1,3,4], Sophia N. Z. Quigley[1,4], Shruti S. Chachra[2], Nichola Conlon[2]✉ and Dianne Ford[1]✉

Reversal or mitigation against an age-related decline in NAD^+ has likely benefits, and this premise has driven academic and commercial endeavour to develop dietary supplements that achieve this outcome. We used a systems-based approach to improve on current supplements by targeting multiple points in the NAD^+ salvage pathway. In a double-blind, randomised, crossover trial, the supplement – Nuchido TIME+® (NT) - increased NAD^+ concentration in whole blood. This was associated with an increase in SIRT1 and an increase in nicotinamide phosphoribosyltransferase (NAMPT) in peripheral blood mononucleocytes, lower concentrations of pro-inflammatory cytokines in plasma, including a reduction in interleukin 2 (IL2), a reduction in glycated serum protein and a shift in the glycosylation profile of immunoglobulin G (IgG) toward a younger biological age, all of which are likely to promote a healthier ageing trajectory.

npj Aging (2024)10:7 ; https://doi.org/10.1038/s41514-023-00134-0

INTRODUCTION

Changes in many interrelated cellular processes and metabolic functions contribute to ageing. The key changes identified as underpinning cellular ageing are collectively known as the hallmarks of ageing[1]. Cellular senescence, mitochondrial dysfunction and deregulated nutrient sensing are among those studied most intensively, and chronically low NAD^+ (nicotinamide adenine dinucleotide) has been identified as a central mediator of multiple hallmarks of ageing[2]. Interventions to prevent or reverse ageing-related changes in these variables, processes and pathways, or to stimulate counteracting cellular pathways, are made with the aim to slow or reverse the process of ageing and thus increase years of healthy life.

NAD^+ is an attractive target point of intervention because, as the conduit of reducing power between the fundamental metabolic pathways of glycolysis, the TCA cycle and the mitochondrial electron transport chain, it plays a central role in the generation of cellular energy (ATP). Also, a sizable body of data provides evidence for an age-related decline in NAD^+ levels in tissues including plasma and muscle, though this is not a universally consistent observation (reviewed in ref. [3]). Also, NAD^+ depletion is a feature of some diseases of accelerated ageing, including Ataxia Telangiectasia (AT), Xeroderma Pigmentosum group A (XPA), and Cockayne Syndrome (CS) (reviewed in ref. [4]). NAD^+ is also a cofactor for a number of enzymes, including enzymes with functions that impinge on cellular processes that have a role in ageing. Among these, the sirtuins are of likely particular importance. These enzymes, of which there are seven human members, are a family of deacylases and ADP-ribosyltransferases. SIRT1, the first named of the mammalian sirtuin family and the most extensively studied, catalyses the deacetylation of protein substrates at lysine residues in a reaction in which NAD^+ is cleaved to release nicotinamide (NAM; see ref. [5] for recent review), and, like some other members of the family, catalyses the deacetylation of a range of substrates that have functions in a myriad of processes that impinge on ageing (see ref. [6] for a recent review). These include the transcription factor PGC1α (peroxisome proliferator-activated receptor-γ coactivator), which is activated as a result to stimulate mitochondrial biogenesis among other cellular processes, members of the FOXO family of transcription factors, resulting in downstream beneficial effects on glucose metabolism and insulin signalling, and NF-κβ, with consequent tempering of pro-inflammatory pathways[7].

Among other enzymes that cleave NAD^+ and appear to affect cellular ageing either directly or as a consequence of the knock-on effects of its consumption (for example reduced sirtuin action) are the PARPs (poly ADP-ribose polymerases) and CD38 (cluster of differentiation 38). PARP action involves cleavage of NAD^+ at the N-glycosidic bond to generate ADP ribose. This is then added as a monomer or as a polymerised chain to proteins involved in a number of cellular functions, which include the response to DNA damage by base excision repair of single strand breaks[8]. PARP activity has been associated correlatively with longer lifespan and slower ageing, which is likely attributable in part to this role in the DNA damage response and thus to genome stability (e.g., ref. [9]). However, PARP activity is something of a double-edged sword because the consumption of NAD^+ reduces availability for the generation of ATP and for the action of enzymes, including the sirtuins, that afford protection against ageing.

CD38 has been described as the principal NAD^+ hydrolase in the cell. It has been shown to have multiple functions, among which is a role in cell signalling by generating, from NAD^+, the second messenger molecule, cyclic ADP ribose (cADPR). cADPR plays a role in intracellular Ca^{2+} signalling through activation of ryanodine receptors to mobilise Ca^{2+} from the endoplasmic reticulum and also has a role in multiple aspects of the inflammatory response[10]. The protection against features of ageing afforded by the pharmacological inhibition or knockout of CD38 in mice, such as protection against obesity[11], improved glucose tolerance, muscle function, exercise capacity and cardiac function[12] and increased lifespan[13], have been attributed to the NAD^+-sparing effect of these interventions.

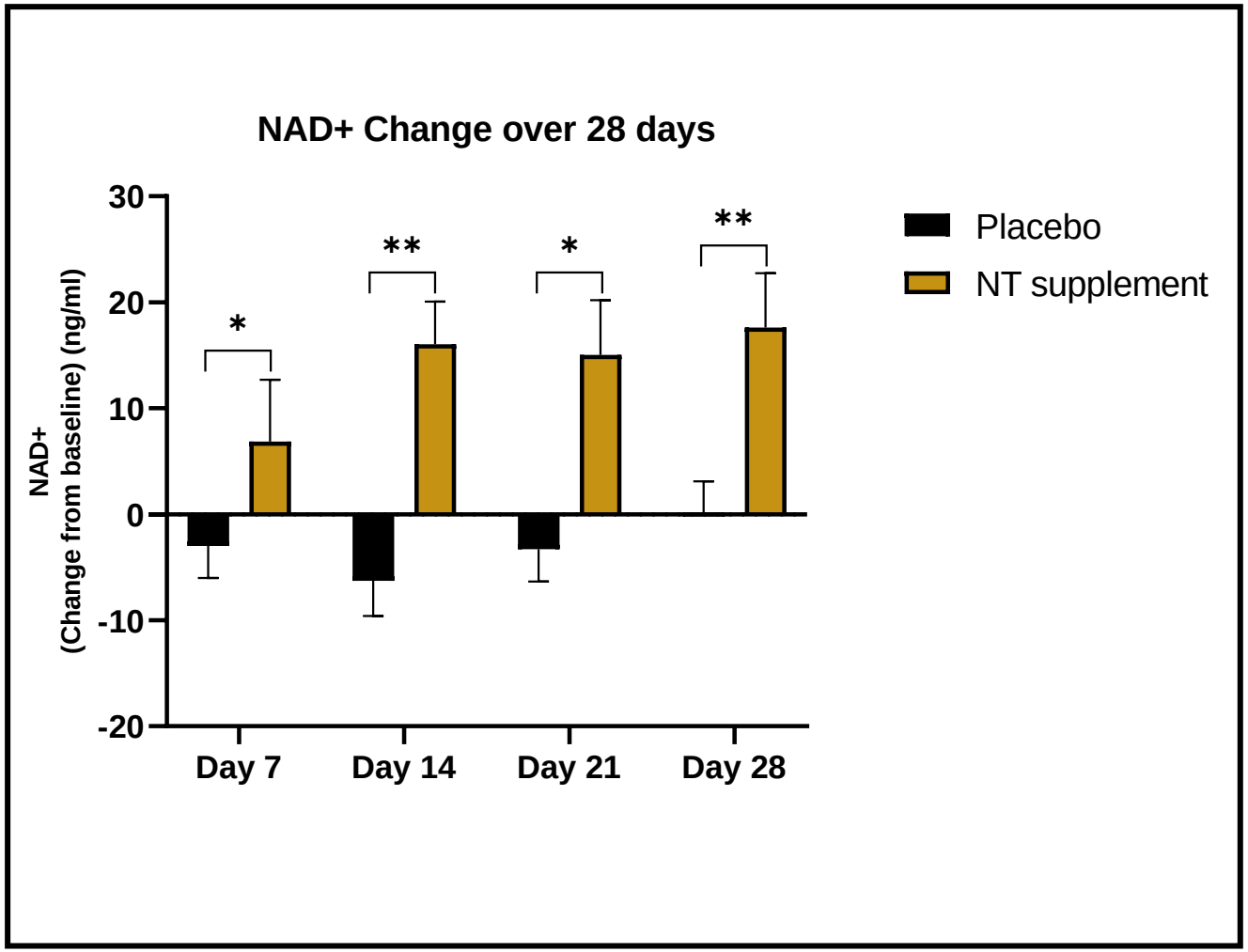
[1]Department of Applied Sciences, Northumbria University, Northumberland Road, Newcastle upon Tyne NE1 8ST, UK. [2]Nuchido Ltd. Dissington Hall, Dalton, Northumberland NE18 0AD, UK. [3]Present address: Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Blegdamsvej 3B, Mærsk Tårnet, 7, Sal 2200 København N, Denmark. [4]These authors contributed equally: John D. Henderson, Sophia N. Z. Quigley. ✉email: nichola@nuchido.com; dianne.ford@northumbria.ac.uk

Published in partnership with the Japanese Society of Anti-Aging Medicine

npj

RESULTS : NAD+

NAD+ levels in whole blood increase after 7 days of treatment

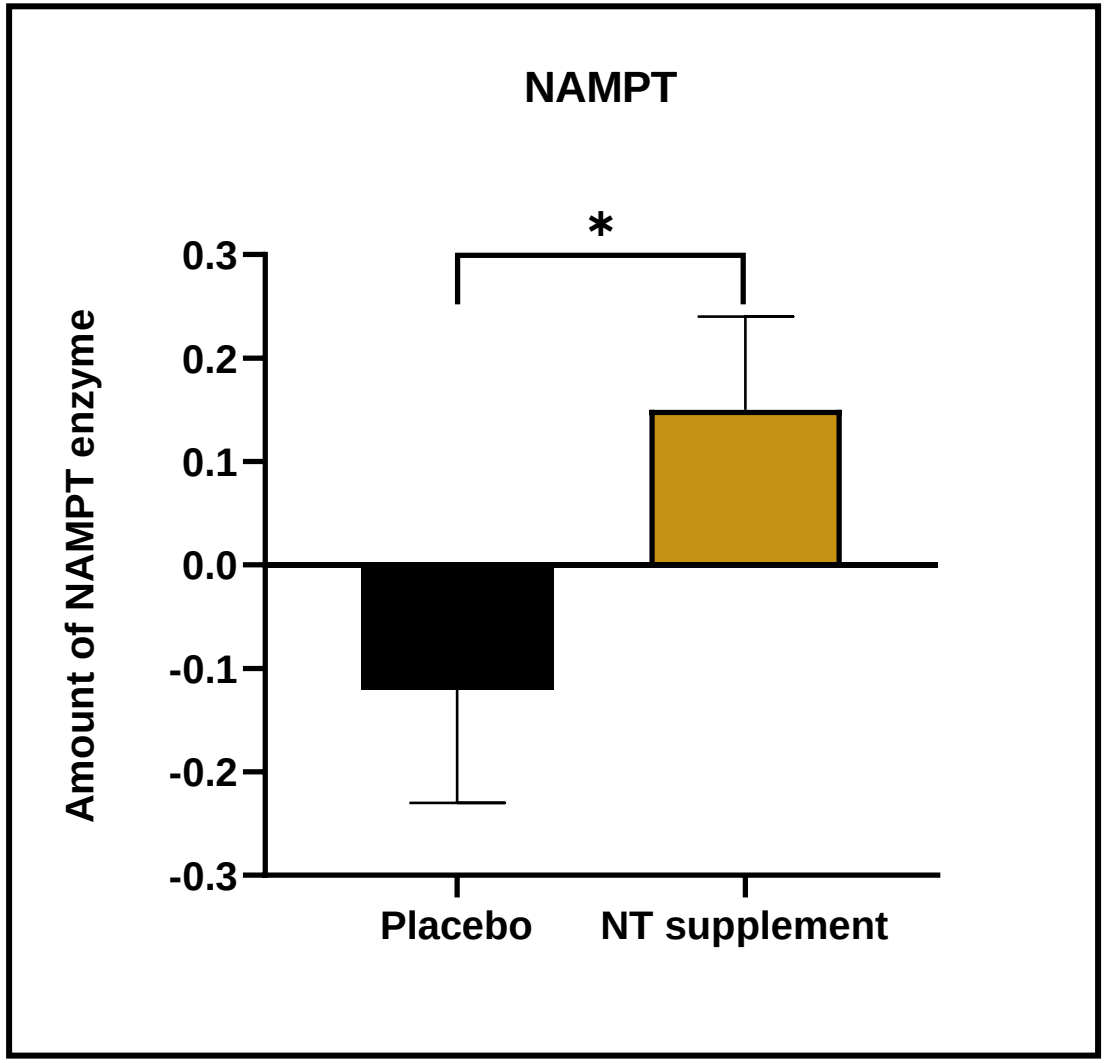


RESULTS : NAMPT

Increased expression of the NAD+ recycling enzyme NAMPT

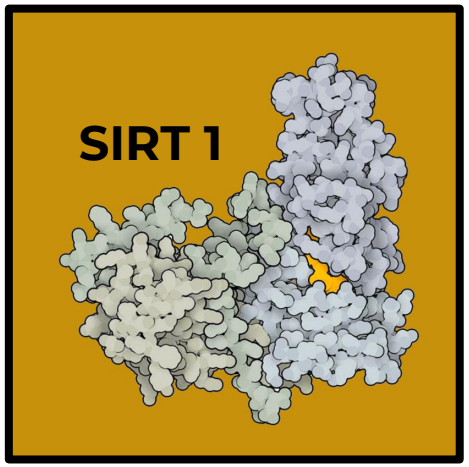
↑ NAMPT

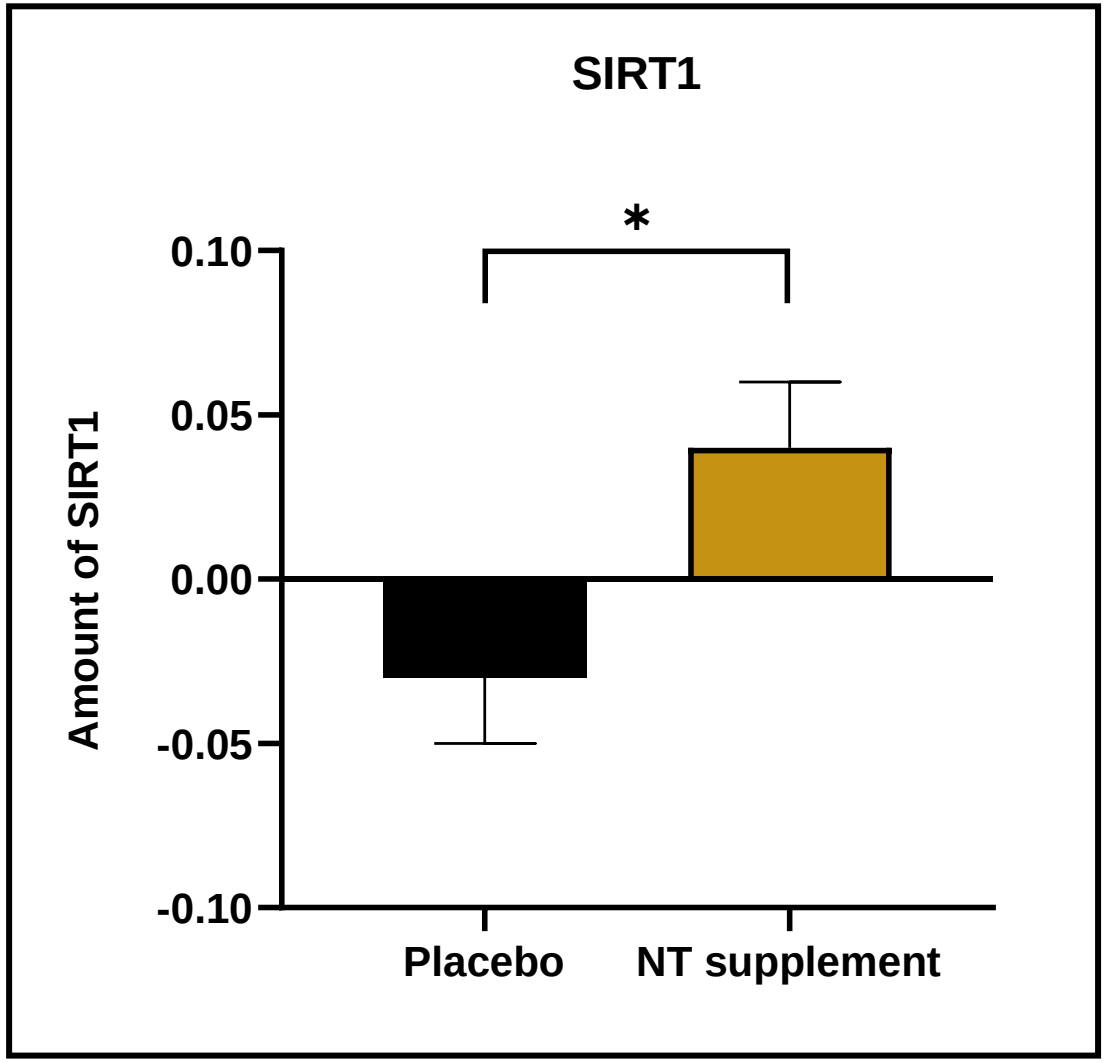
NAD+ RECYCLING



RESULTS : SIRT1

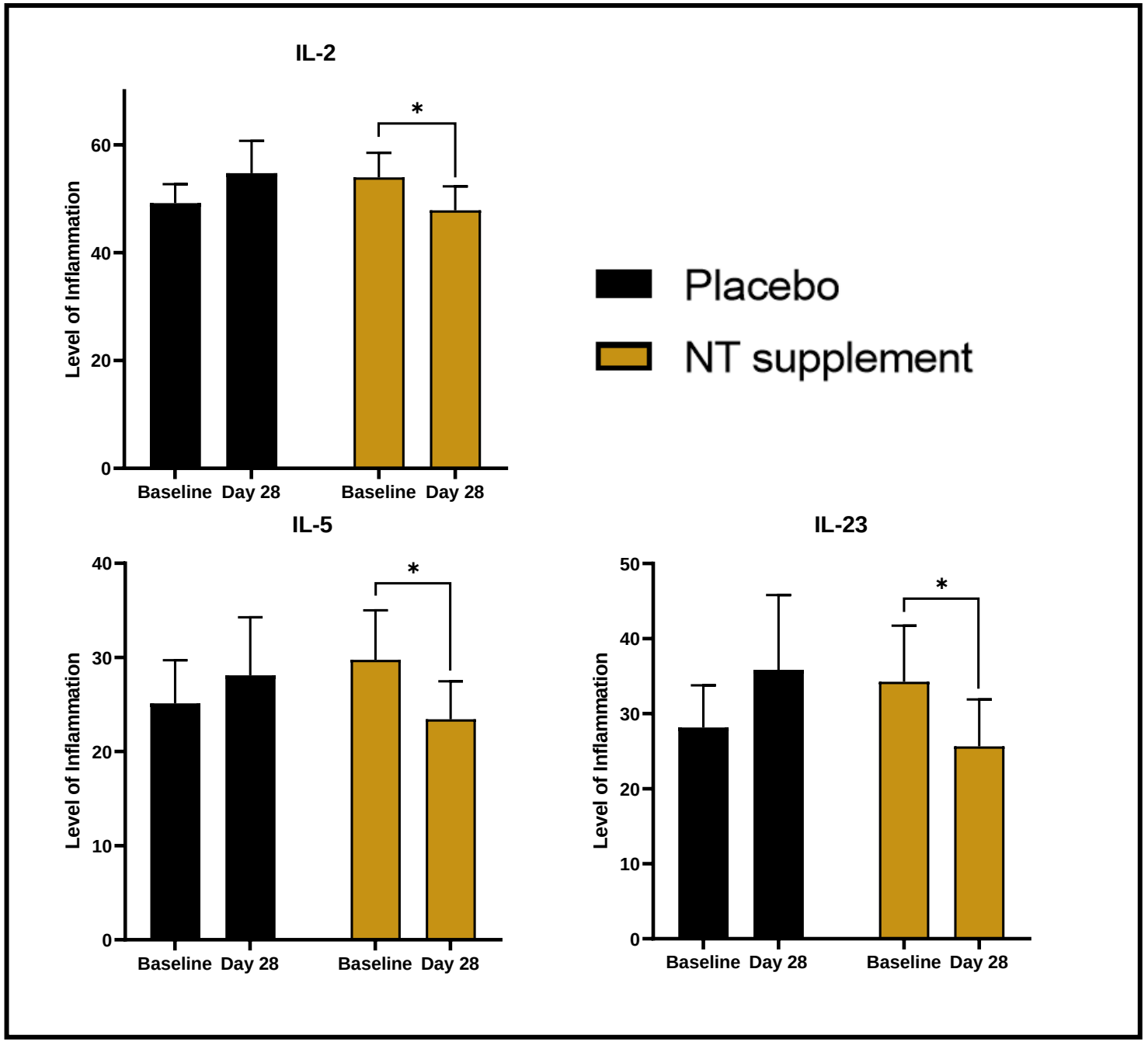
Increased expression of the longevity protein SIRT1





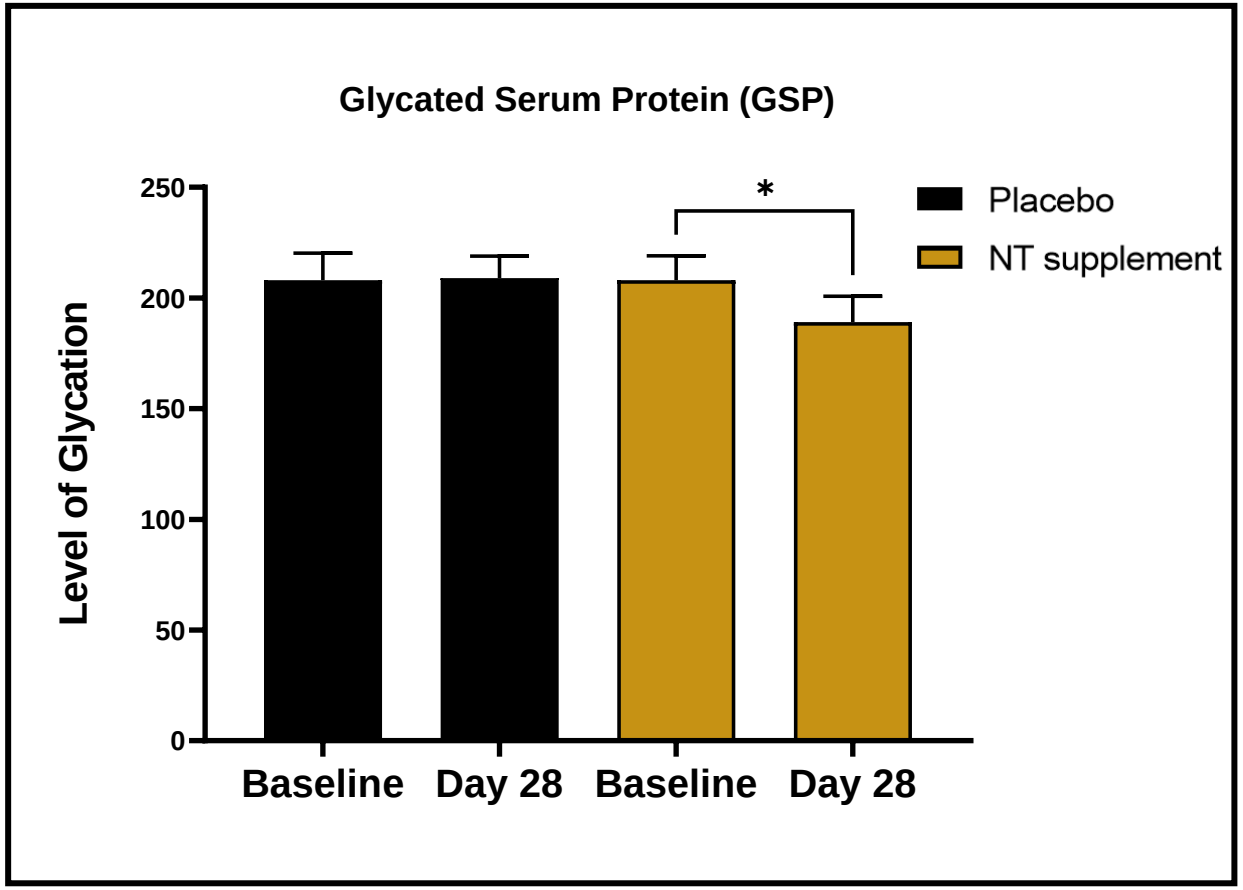
RESULTS : INFLAMMATION

Reduction in circulating inflammation (a key driver of ageing)



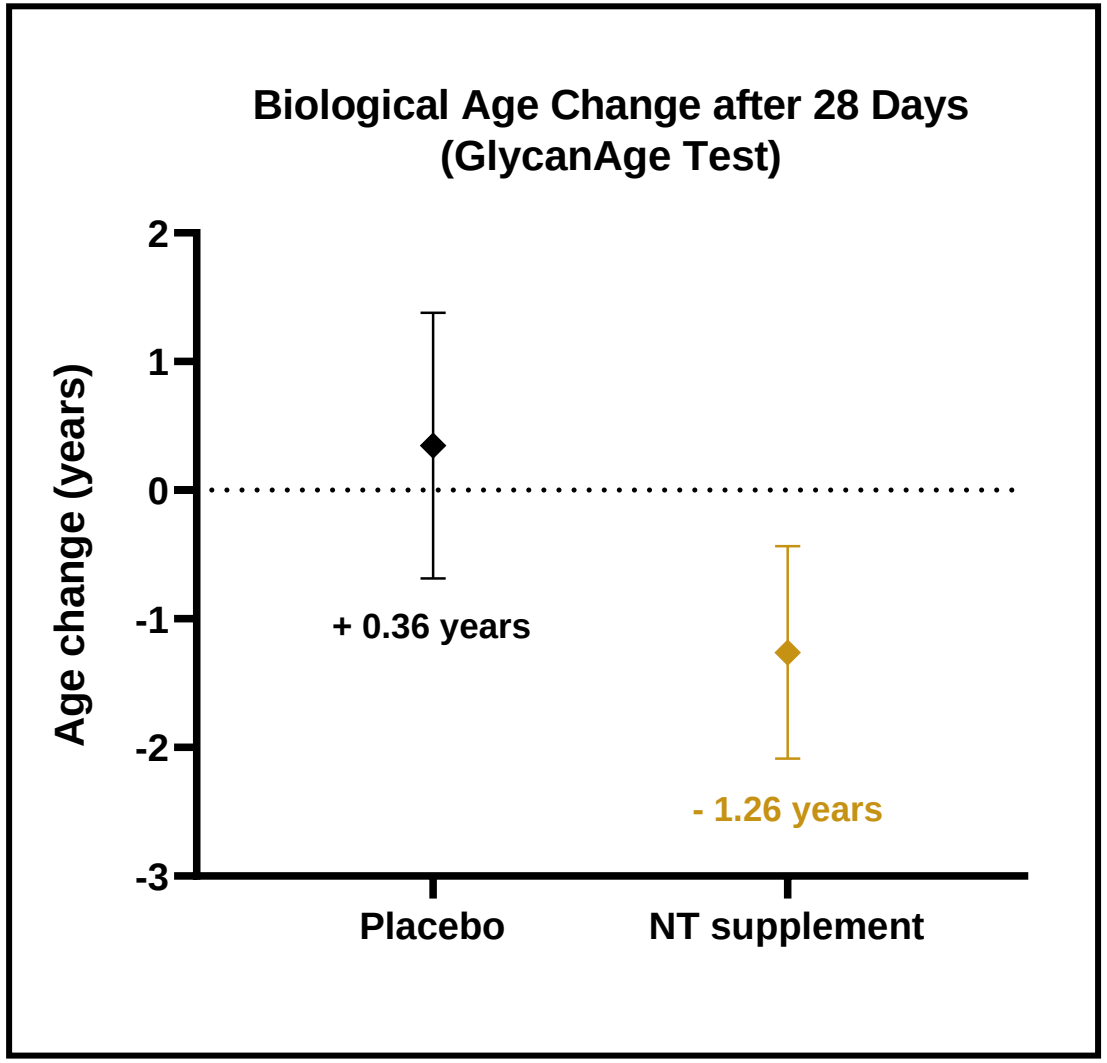
RESULTS : GLYCATION

Reduction in levels of glycation (a biomarker of skin and cardiovascular ageing)



RESULTS : BIOLOGICAL AGE

Reversal of biological age



REPORTED BENEFITS

Top 5 reported benefits:

- ✓ Increased physical energy
- ✓ Increased mental energy and reduction of brain fog
- ✓ Improved recovery
- ✓ Improved sleep
- ✓ Improved hair/skin/nails growth and quality

I've been taking TIME+ each day as recommended for nearly three weeks now and sleeping extremely well, in fact I've not slept like this in years and real want to continue taking your product.
Roland Bonnici

I feel my body repairs from weight training more quickly like when I was younger also, I have been able to lift more weight without any tendon or joint ache whereas before Nuchido I was decreasing my weights.
Ges Conway

I train 4-5 times a week and noticed that my recovery has improved together with a small improvement in scores, times etc. Can't attribute this to anything else other than TIME+ as all other routines have remained the same.
Paul Davis

I have to say I see a big difference when I take Nuchido and when I don't take it and I live a healthy lifestyle! It's pretty scary to admit to be honest.
Samantha Guveli

This has completely changed my life; I have been taking this for 1 month. I have been going so hard in the gym, have been maxing out, increasing my weight and I am not sore, I am significantly not sore, and I am an athlete and I have worked out my whole life.
Danielle Moinet

I am sleeping better (proven by my tracker and better HRV), feel refreshed instead of sluggish, clear mind and improved stamina when I exercise
Ana Jara

I am so glad I found this product my brain fog completely disappeared my memory has definitely improved and my tiredness has also greatly improved. Would highly recommend.
Lisa McNally

NUCHIDO TIME+

THANK YOU+

Visit us at stand B21

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LABORATORIES