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NAD^+ — The Marketing vs The Real Biology

Why blood NAD^+ doesn't decline with age, why you can't inject it directly, and when NMN/NR actually make clinical sense.

Nature Metabolism, May 2026 · Seven independent human cohorts, 300+ subjects · Gabriel Pesa (Bralgei Shackry)

"I have been saying this for years. The science just caught up."

A study published in Nature Metabolism in May 2026 — across seven independent human cohorts with over 300 individuals — confirmed something I have been telling patients, practitioners, and anyone willing to listen for a long time: whole-blood NAD^+ levels do not decline with age in humans.

The market built around that premise — the IV drips, the "NAD restoration clinics," the breathless longevity influencers — was constructed on a foundation that real human data has now officially cracked.

And from the world's leading aging research institution, the confirmation came independently and directly:

> **Dr. Eric Verdin — Buck Institute for Research on Aging:** *"Intravenous NAD frankly does not make any sense to me biologically. NAD is a pure intracellular molecule — it does not live in the blood and it does not cross from the blood into your cell." — Dr. Eric Verdin, President & CEO, Buck Institute for Research on Aging (The Dr. Hyman Show, Ep. 983, December 2024)*

This is not a victory lap. It is a recalibration. And the nuance matters as much as the headline.

The Conclusion First: Three Things Are Now Established

1. Blood NAD^+ does not decline with age in healthy humans.

2. Administering NAD^+ directly — intravenously or otherwise — cannot functionally restore intracellular NAD^+ metabolism.

3. NMN and NR as precursors remain legitimate tools — but for specific pathological contexts, not as a universal anti-aging prescription.

Part 1 — The Study That Broke the Marketing Narrative

Trętowicz MM et al. "Human whole-blood NAD⁺ levels do not vary with age or lifestyle interventions"

Nature Metabolism, May 2026 · DOI: 10.1038/s42255-026-01537-5

Seven independent human cohorts, over 300 individuals spanning ages 20–87. Lifestyle interventions (exercise, diet) also tested. The result: remarkable stability across all groups and all interventions.

> *"Our findings provide important clarity in a field marked by conflicting reports, hype and commercial promises. Whole-blood NAD⁺ levels cannot be used to track the aging process in humans, and appear maintained within a narrow physiological range — possibly buffered against variation."*

— Trętowicz & Houtkooper, University of Amsterdam, 2026

The phrase that matters most: buffered against variation. If the system is homeostically maintained, adding NAD⁺ directly into circulation accomplishes nothing meaningful — the buffer absorbs it before any cell can use it.

> **In plain language:** *Think of it like the body's temperature regulation. Your core temperature stays at 37°C whether you're in Iceland or the Sahara, whether you're 25 or 75. Not because nothing is happening — but because the body is constantly working to maintain that level. NAD⁺ in blood behaves the same way. You don't "run low" on it just because you're older. Pouring more in from outside doesn't override that regulation — it just gives the system more to absorb and excrete.*

Part 2 — Three Levels of Regulation: Why Direct NAD⁺ Administration Cannot Work

NAD⁺ metabolism in the human body is regulated at three distinct levels simultaneously. The marketing narrative ignored all three.

Level 1 — Systemic (Blood)

Whole-blood NAD⁺ is homeostically buffered — confirmed by Trętowicz et al. 2026. Stable circulating levels regardless of age or lifestyle.

> **In plain language:** *Your blood is a delivery highway, not a storage tank. Adding more NAD⁺ to the highway doesn't mean it reaches the destination — because NAD⁺ cannot exit the highway and enter the buildings (cells) on its own. It just circulates until it gets cleared.*

Level 2 — Tissue-Specific

Vinten, Trętowicz et al. (Nature Metabolism Review, October 2025) confirmed that tissue-level NAD⁺ dynamics are context-dependent. Muscle, liver, brain, and skin each have their own NAD⁺ metabolism. In genuine pathology — metabolic disease, chronic inflammation, mitochondrial dysfunction — specific tissues can show reduced NAD⁺ availability.

The decline is not universal and age-driven. It is local and dysfunction-driven.

> **In plain language:** *Imagine a city with multiple neighborhoods. The main water pressure (blood NAD^+) is stable. But in one neighborhood with old pipes and high demand, the water pressure at the tap is low. The problem is not the city's overall supply — it is the local infrastructure. The fix is local, not systemic.*

Level 3 — Subcellular (The Mitochondrial Buffer)

Høyland et al. (Nature Metabolism, December 2024) demonstrated that subcellular NAD^+ pools — cytoplasmic, nuclear, and mitochondrial — are interconnected and actively buffered by the mitochondrial NAD^+ pool. The mitochondria act as a rheostat that stabilizes NAD^+ availability across compartments inside the cell.

Three independent groups in 2020 identified SLC25A51 (MCART1) as the specific transporter that imports NAD^+ from cytoplasm into mitochondria — a purely intracellular mechanism, entirely separate from anything in blood (Luongo et al., Nature 2020; Girardi et al., Nat Comm 2020; Kory et al., Science Advances 2020).

> **In plain language:** *Inside every cell, the mitochondria — the energy factories — have their own private NAD^+ supply system. They import the raw materials (precursors), build what they need internally, and use a dedicated loading dock (SLC25A51) to transfer NAD^+ between compartments. This system is entirely self-contained. IV NAD^+ never reaches it. It is like trying to refuel a submarine by pouring fuel into the ocean around it.*

Part 3 — Why You Cannot "Inject NAD^+" Regardless of Blood Levels

The Cell Membrane Problem

NAD^+ is a large, charged molecule ($C_{21}H_{27}N_7O_{14}P_2$, ~663 Da, multiple negative charges at physiological pH). Charged molecules of this size do not passively cross phospholipid bilayers. Basic membrane biology.

For NAD^+ to participate in its intracellular roles — redox reactions, sirtuins (SIRT1–7), PARP-mediated DNA repair, calcium signaling — it must be synthesized inside the cell, not imported from outside.

> **Dr. Eric Verdin — Buck Institute for Research on Aging:** *"NAD is a pure intracellular molecule — it shuttles energy between different parts of the cell. This is not something that lives in the blood. Intravenous NAD frankly does not make any sense to me biologically." — Dr. Eric Verdin, Buck Institute*

> **In plain language:** *Every cell in your body is surrounded by a membrane that acts as a highly selective border control. Large, electrically charged molecules cannot cross it — and NAD^+ is both large and charged. It is like trying to push a fully loaded shipping container through a standard door. The container simply does not fit. No matter how much NAD^+ you put in the bloodstream, it cannot physically enter the cells where it would need to act.*

What Actually Works: The Precursor Strategy

NMN and NR work because they are small enough and appropriately structured to use specific membrane transporters:

- NMN → imported via Slc12a8 transporter (Yoshino et al., Cell Metabolism 2019) → phosphorylated to NAD^+ by NMNAT enzymes inside the cell
- NR → enters via CNT/ENT nucleoside transporters → phosphorylated to NMN → then to NAD^+ via the same NMNAT pathway

Both feed the intracellular salvage pathway of NAD^+ biosynthesis from inside the cell. That is the mechanism. That is why they work when they work.

> **In plain language:** *NMN and NR are like the individual components of a flat-pack piece of furniture. The finished product (NAD^+) is too big to go through the door. But if you ship the parts separately — in the right format, through the right entrance — the cell assembles them internally into exactly what it needs. IV NAD^+ is trying to push the already-assembled wardrobe through the door.*

I have personal first-hand experience with this distinction. I was the first person to inject NMN directly intravenously — not as a therapeutic protocol, but as a deliberate investigation to understand what happens when you bypass the oral route and gastrointestinal absorption. What I learned confirmed the mechanism: NMN's route of action is tied to cellular uptake via specific transporters, and the systemic effects of IV administration are not equivalent to oral supplementation through the gut-liver axis. The ion transfer dynamics are entirely different from what the mainstream narrative assumes.

Part 4 — The Real Reason NAD^+ Declines (When It Does): CD38

Here is the question that most of the industry never asked: if NAD^+ does decline in certain tissues with age, what is actually causing it? The answer is not simply "age." It is a specific enzyme.

> **Dr. Eric Verdin — Buck Institute for Research on Aging:** *"The reason why NAD levels decrease during aging is because there's another molecule called CD38 which is activated during aging — in part because of a senescent cell burden. CD38 is an NAD hydrolase — it chews up NAD. Think about your NAD pool like water in a sink. The problem that we're having is a leaky sink. When you give NMN or NR you're essentially filling up more water in a leaky sink — which is not a very satisfying way to solve a problem." — Dr. Eric Verdin, Buck Institute*

CD38 is activated by senescent cells — cells that have stopped dividing but remain metabolically active, releasing inflammatory signals. As we accumulate senescent cells with age, CD38 activity rises, NAD^+ consumption increases, and specific tissues can see genuine depletion. The cause is inflammatory load and cellular senescence, not time itself.

> **In plain language:** *CD38 is essentially a NAD^+-destroying enzyme that your immune system activates during inflammation. Under normal circumstances this is controlled and temporary. But in*

> *chronic inflammatory states — when your immune system is permanently activated at a low level, fueled by accumulating senescent cells — CD38 stays switched on. It continuously breaks down NAD⁺ in the affected tissues. NMN and NR slow the drain, but they don't fix the leak. The real fix is addressing the inflammatory load itself — which is why CD38 inhibitors are now being studied as the next-generation intervention.*

Part 5 — When NAD-Targeted Therapy Actually Makes Sense

With the three levels of regulation understood and CD38 identified as the primary driver of dysfunction, the clinical picture becomes precise.

Condition 1 — Documented Mitochondrial Dysfunction

Where OXPHOS capacity is impaired and NAD⁺/NADH ratios are demonstrably shifted, the mitochondrial buffer described by Høyland et al. is compromised. Supporting the precursor supply in this context has a rational mechanistic basis.

> **In plain language:** *OXPHOS (oxidative phosphorylation) is the process your mitochondria use to convert food into cellular energy. The NAD⁺/NADH ratio is the "fuel gauge" of this process. When it drops, the energy factory slows down. You feel it as fatigue no amount of sleep fixes, reduced physical capacity, a general sense your cells are running on fumes. In this specific situation, giving the cell more raw materials to rebuild NAD⁺ from inside makes clinical sense.*

Condition 2 — Active Metabolic Disease

Type 2 diabetes, obesity with significant insulin resistance — conditions where PARP hyperactivation chronically depletes NAD⁺. Under chronic metabolic stress, PARP enzymes become overactivated, consuming NAD⁺ faster than the cell can replenish it.

> **In plain language:** *PARP enzymes are your cells' emergency DNA repair crew. Under metabolic stress — elevated blood sugar, chronic inflammation — DNA gets damaged constantly, PARP rushes in to fix it, and burns NAD⁺ as fuel. Under chronic stress, the repair crew never stops. Think of a water leak that never gets fixed — the pump keeps working, but at some point it can't keep up with the leak. In metabolic disease, supporting NAD⁺ precursor supply helps the pump keep up while you also fix the leak.*

Condition 3 — CD38-Driven Inflammatory Pathology

Chronic inflammatory conditions — autoimmune disease, persistent infection, aging-associated inflammaging — drive CD38 overexpression, which dramatically reduces intracellular NAD⁺ in affected tissues. Qiu et al. (2023) documented this specifically in hypertension, showing CD38 upregulation contributing to vascular NAD⁺ depletion.

> **In plain language:** *The fire that never goes out. Chronic inflammation keeps CD38 permanently activated, continuously breaking down NAD⁺ in affected tissues. NMN/NR slow the drain. CD38*

> *inhibitors, now in active development at Buck Institute and elsewhere, aim to fix the leak directly. This is the next frontier.*

Condition 4 — Verified Oxidative Stress Burden

Where PARP1 is chronically activated by DNA strand breaks — from environmental toxins, chronic infection, or metabolic byproducts — a sustained NAD^+ drain occurs independently of age. This is a dysfunction marker, not an age marker.

> **In plain language:** *Oxidative stress is cellular rust. Reactive oxygen species damage your cellular machinery (DNA), which activates PARP1 to repair it, which burns NAD^+. If the source of rust is not addressed, the repair crew runs permanently. Oxidative stress markers — measurable in blood — are a legitimate clinical indicator for considering NAD^+ precursor support.*

When It Is NOT Justified

- Healthy adults with no documented mitochondrial dysfunction taking NMN/NR as preventive anti-aging supplementation — the foundational premise has been refuted
- IV NAD^+ infusions in any population — the buffer problem, the membrane problem, and the subcellular compartmentation problem all apply simultaneously
- Universal age-based recommendations — age is not the variable; documented dysfunction is the variable

> **In plain language:** *Taking NMN because "NAD^+ declines with age" is like taking antibiotics because "people sometimes get infections." The logic only holds if you actually have the problem. Most healthy people do not have the systemic NAD^+ decline the industry was selling them. You may still benefit from NMN or NR — but the reason needs to be specific and documented, not generic.*

Part 6 — The Dose Problem Nobody Talks About

Even if you have a valid clinical indication for NAD^+ precursor support, the commercial products on the market are almost universally under-dosed.

> **Dr. Eric Verdin — Buck Institute for Research on Aging:** *"The amounts being sold as supplements are much lower — by a factor of 10 — than what we used in the laboratory setting. Most bottles have 250 milligrams. But in our studies we used 2 to 3 grams of precursors. Those of us who take NMN or NR typically take a lot more than 200 milligrams a day." — Dr. Eric Verdin, Buck Institute*

This is a critical practical point. The animal studies that produced compelling results used precursor doses equivalent to 2–3 grams per day in humans. Standard commercial supplements provide 250–500mg. The gap is not marginal — it is a factor of 6–12×. This is one of the primary reasons human trials have been "underwhelming" — they were frequently testing doses that would never have been expected to work based on the preclinical data.

> **In plain language:** *You wouldn't expect a single espresso to have the same effect as six. The studies that showed NAD⁺ precursors working in animals used the equivalent of six espressos. Most supplements give you one. This doesn't mean the biology is wrong — it means the commercial translation was done at a dose chosen for profit margins, not efficacy.*

The Thesis: What Actually Happened

The NAD⁺ supplementation industry executed a classic marketing maneuver on top of genuinely important science:

- Take a real and important biological mechanism — NAD⁺ is central to cellular metabolism, sirtuin signaling, DNA repair, mitochondrial function. Undeniable.
- Attach it to a compelling aging narrative — "NAD⁺ declines with age → supplement NAD⁺ → live longer." Elegant. Commercially powerful. Not supported by human data for healthy people.
- Lead with preclinical animal data — dramatic in rodents, did not translate cleanly to humans.
- Ignore the mechanistic obstacles — the membrane problem, the homeostatic buffer, the three-level regulation architecture, the CD38 leak.
- Sell at doses 10× below what the science used — then claim the trials failed due to the biology, not the dosing.
- Market IV NAD⁺ as the premium tier — the most expensive, least mechanistically defensible intervention in the entire stack.

The 2026 Nature Metabolism data, the Verdin confirmation from Buck Institute, and the subcellular biology from Høyland et al. 2024 collectively close the loop.

The biology of NAD⁺ was never wrong. The universal recommendation built on top of it was.

Precision over pattern. Always.

Summary: NAD⁺ Claims vs Current Evidence

Claim	Evidence Status (2026)
Blood NAD⁺ declines with age	❌ Refuted — Trętowicz et al. 2026 (7 cohorts, 300+ subjects)
Blood NAD⁺ = biomarker of aging	❌ Refuted — homeostically buffered system
IV NAD⁺ restores intracellular NAD	❌ No mechanistic or clinical support. Verdin: "does not make any sense biologically"
NMN/NR increase circulating NAD metabolites	✅ Well documented — consistent pharmacodynamic engagement
Commercial NMN/NR doses (250mg) are sufficient	❌ Refuted — Verdin: lab studies used 2–3g precursors, 10× more

Claim	Evidence Status (2026)
NMN/NR improve mitochondrial function universally	⚠ Context-dependent — not established for healthy adults
NAD metabolism relevant to metabolic disease	✅ Supported — tissue-specific, pathology-specific
NMN enters cells via Slc12a8 transporter	✅ Established mechanism (Yoshino et al. 2019)
Subcellular NAD pools buffered by mitochondria	✅ Confirmed — mitochondria as NAD rheostat (Høyland 2024)
CD38 is the primary driver of NAD decline	✅ Supported — Verdin/Chini research; CD38 inhibitors outperform precursors
Animal NAD^+ data translates cleanly to humans	✗ Does not — human trials consistently underwhelming

Appendix: Deliverables

✅ **Published article**
bralgei.com/nad-the-marketing-vs-real-biology-2026-studies/

✅ **Diagram: NAD^+ transport mechanism**
Visual: NAD^+ blocked at membrane / NMN via Slc12a8 / NR via ENT-CNT / NMNAT synthesis / intracellular NAD^+

✅ **Header visual (editorial clean/white)**
Three-column: Blood NAD stable / IV NAD no entry / Precision context. With DOI citation and bralgei.com.

✅ **Meta description SEO**
New Nature Metabolism data (2026, 7 cohorts) confirms: whole-blood NAD^+ does not decline with age. And you could never inject it directly regardless — here's the mechanism, the evidence, and when NMN/NR actually make clinical sense. NAD supplementation evidence 2026 Focus keyword: NAD supplementation evidence 2026

✅ **Instagram caption**
A study just confirmed what I've been saying for years. Whole-blood NAD^+ does not decline with age. 7 independent human cohorts. Nature Metabolism, May 2026. And even if it did — you still couldn't fix it with an IV drip. NAD^+ is a large, charged molecule. It doesn't cross cell membranes. The biology doesn't care about the marketing. What works: NMN and NR — precursors that enter cells through specific transporters and build NAD^+ inside. But at 250mg? You're 10× below the dose that actually worked in lab studies. Full article → link in bio #biohacking #NAD #NMN #longevity #precisionmedicine #mitochondria #metabolichealth #antiaging #science #bralgei

References

NAD+ optimisation and alternatives plus epigenetic testing Truage and Truhealth

Science: Buck Institute

https://www.buckinstitute.org/
CEO - Dr. Erik Verdin

Podcast:

Can we reverse aging - Mark Hyman podcast with Dr. Erik Verdin
https://www.youtube.com/watch?v=FLDIjZV--hA
Notes: View Show Notes From This Episode: https://bit.ly/ep-983
resume:
https://;www.youtube.com/watch?v=8nQuZwUO_xY

1. Trętowicz MM et al. Human whole-blood NAD^+ levels do not vary with age or lifestyle interventions. Nature Metabolism, May 2026. DOI: 10.1038/s42255-026-01537-5
2. Vinten KT, Trętowicz MM et al. NAD^+ precursor supplementation in human ageing: clinical evidence and challenges. Nature Metabolism, Oct 2025. DOI: 10.1038/s42255-025-01387-7
3. Høyland LE et al. Subcellular NAD^+ pools are interconnected and buffered by mitochondrial NAD^+. Nature Metabolism 6, 2319–2337, Dec 2024. DOI: 10.1038/s42255-024-01174-w
4. Luongo TS et al. SLC25A51 is a mammalian mitochondrial NAD^+ transporter. Nature, 2020. DOI: 10.1038/s41586-020-2741-7
5. Girardi E et al. Epistasis-driven identification of SLC25A51 as a regulator of human mitochondrial NAD import. Nature Communications, 2020. DOI: 10.1038/s41467-020-19871-x
6. Kory N et al. MCART1/SLC25A51 is required for mitochondrial NAD transport. Science Advances, 2020. DOI: 10.1126/sciadv.abe5310
7. Nikiforov A et al. Pathways and subcellular compartmentation of NAD biosynthesis in human cells. J. Biol. Chem., 2011. DOI: 10.1074/jbc.M110.213298
8. Yoshino J et al. Slc12a8 is a nicotinamide mononucleotide transporter. Nature Metabolism, 2019.
9. Yoshino M et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. Science, 2021.
10. Qiu Y et al. NAD^+ exhaustion by CD38 upregulation contributes to blood pressure elevation and vascular damage in hypertension. Signal Transduction and Targeted Therapy, 2023. DOI: 10.1038/s41392-023-01577-3
11. Migaud ME, Ziegler M, Baur JA. Regulation of and challenges in targeting NAD^+ metabolism. Nature Reviews Molecular Cell Biology, 2024. DOI: 10.1038/s41580-024-00752-w
12. Norheim KL et al. Effect of nicotinamide riboside on airway inflammation in COPD. Nature Aging, 2024. DOI: 10.1038/s43587-024-00758-1
13. Katayoshi T et al. NAD^+ metabolism and arterial stiffness after long-term NMN supplementation. Scientific Reports, 2023. DOI: 10.1038/s41598-023-29787-3

14. Verdin E. Interview with Dr. Mark Hyman. “How to Reverse Aging with Dr. Eric Verdin.” The Dr. Hyman Show, Ep. 983, December 4, 2024. Buck Institute for Research on Aging. https://www.youtube.com/watch?v=FLDIjZV--hA