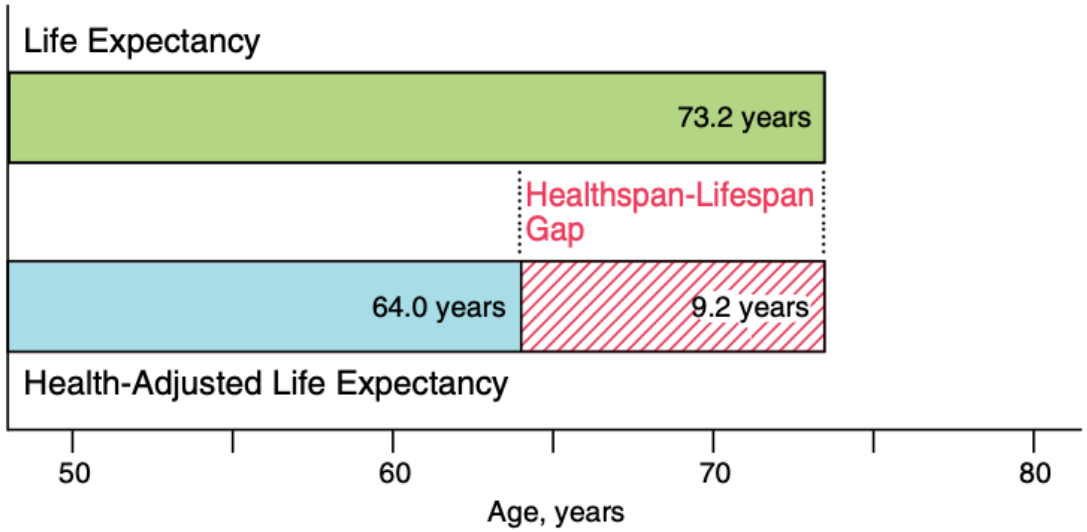
REVERSING THE BIOLOGICAL CLOCK: LESSONS LEARNED IN GEROSCIENCE

OVERVIEW

1. Introduction
2. What is ageing?
3. The key hallmarks of ageing
4. Why is autophagy imperative to counter cellular ageing?
5. How do pH changes aggravate ageing processes and contribute to chronic disease?
6. What is NMN and how does it promote longevity?
7. Which dietary and lifestyle interventions are supportive of healthy ageing?

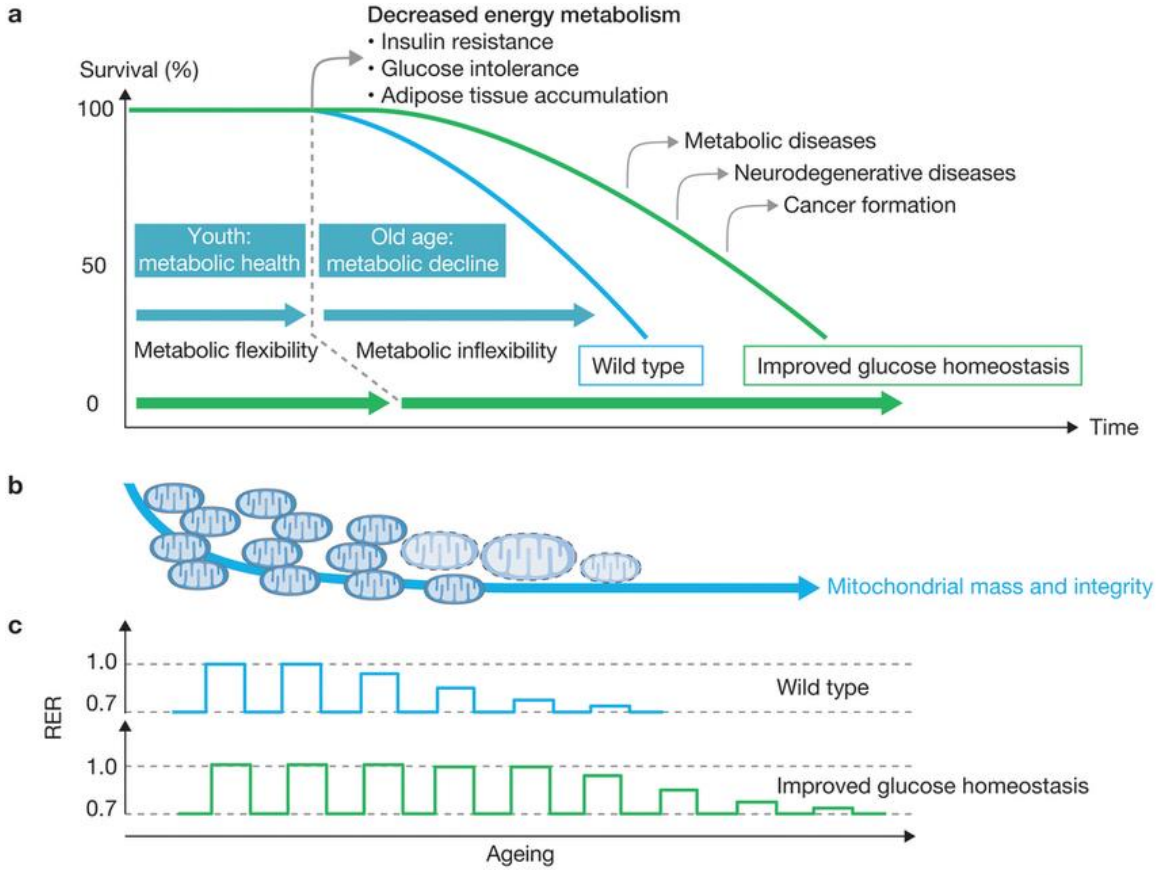
THE HEALTHSPAN-LIFESPAN GAP

- Since the mid-twentieth century, **life expectancy has increased by three decades**
- Unfortunately, **healthspan has not followed suit,** largely due to the **mass of chronic diseases which plague the growing older population**



Garmany, A., Yamada, S., & Terzic, A. (2021). Longevity leap: Mind the healthspan gap. *npj Regenerative Medicine*, *6*(1), 1-7.

METABOLIC FLEXIBILITY CONTROLS HEALTHSPAN & LIFESPAN



Riera, C. E., & Dillin, A. (2015). Tipping the metabolic scales towards increased longevity in mammals. *Nature cell biology*, *17*(3), 196-203.

WHAT IS AGEING?

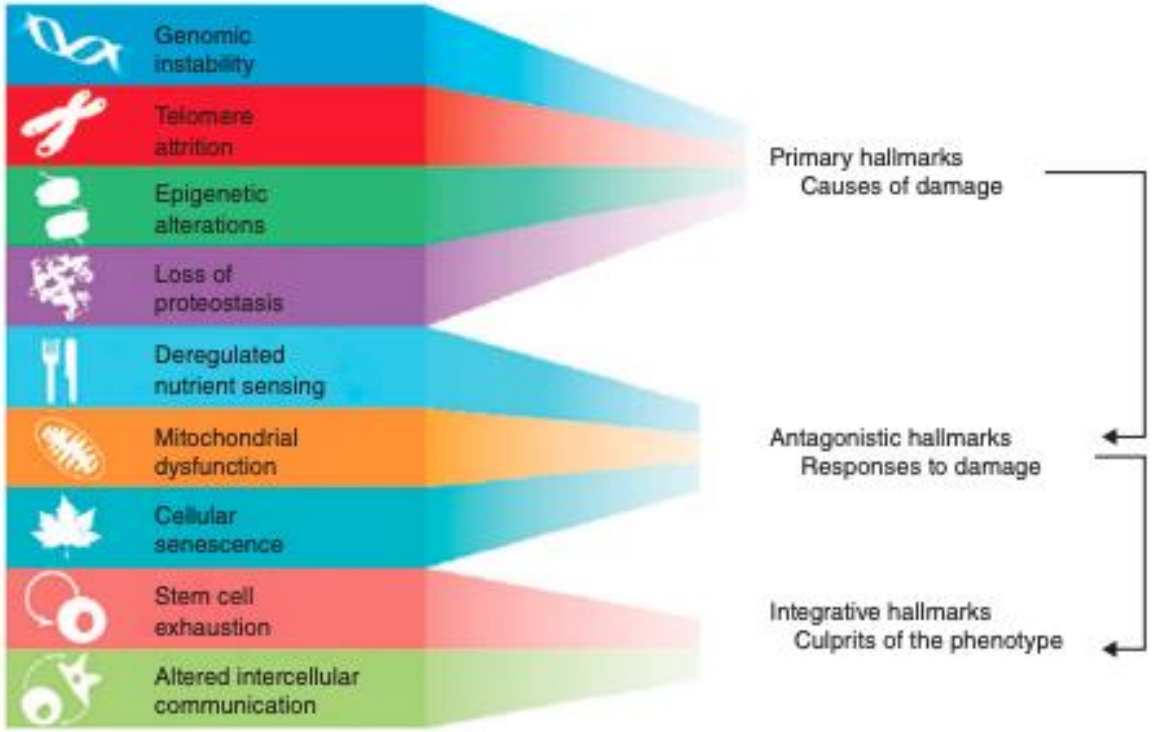
- Telomere shortening
- Higher probability of disease
- Accumulation of intracellular and extracellular waste

HALLMARKS OF AGEING

- Age is a leading risk factor for several common diseases, including type 2 diabetes, cancer, Alzheimer's disease and heart disease
- 58% of chronic disease-related mortality transpires in individuals over 70 years of age

Aunan, J. R., Watson, M. M., Hagland, H. R., & Søreide, K. (2016). Molecular and biological hallmarks of ageing. *Journal of British Surgery*, *103*(2), e29-e46.
Garmany, A., Yamada, S., & Terzic, A. (2021). Longevity leap: Mind the healthspan gap. *npj Regenerative Medicine*, *6*(1), 1-7.

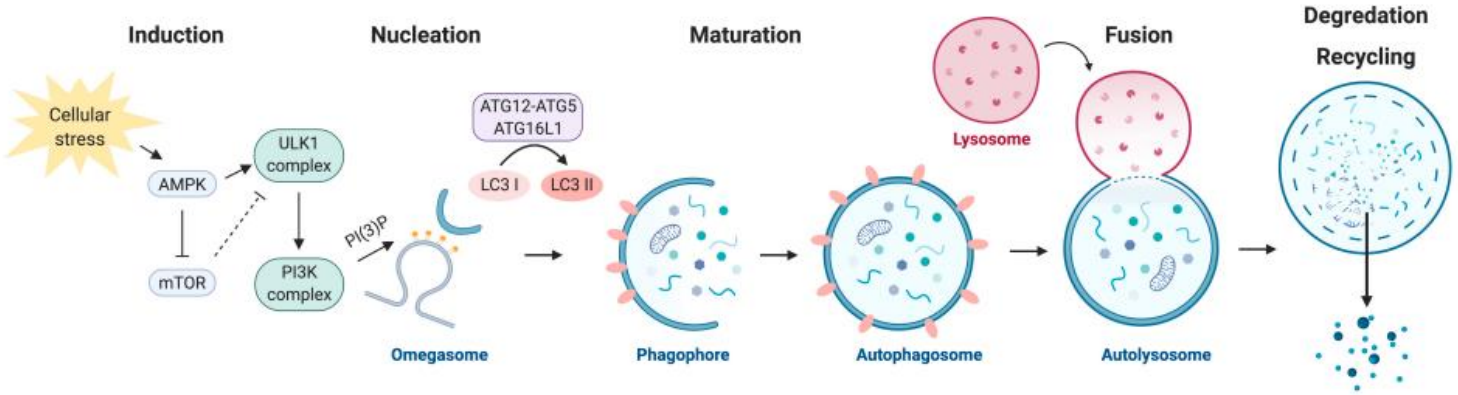
A CLOSER LOOK AT THE 9 HALLMARKS OF AGEING



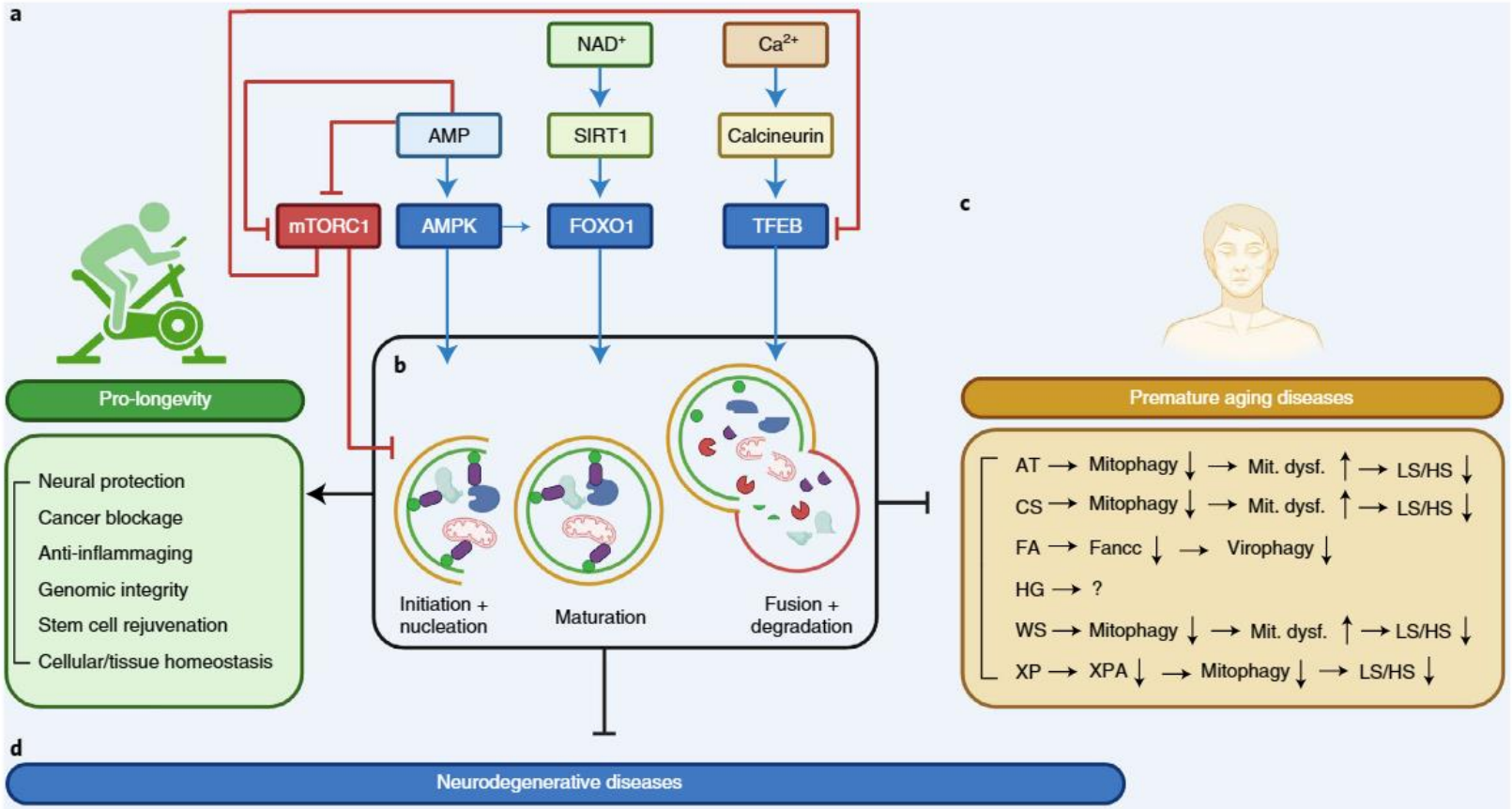
Aunan, J. R., Watson, M. M., Hagland, H. R., & Søreide, K. (2016). Molecular and biological hallmarks of ageing. *Journal of British Surgery*, *103*(2), e29-e46.
Garmany, A., Yamada, S., & Terzic, A. (2021). Longevity leap: Mind the healthspan gap. *npj Regenerative Medicine*, *6*(1), 1-7.

STRATEGIES FOR REVERSING THE BIOLOGICAL CLOCK

Reduction of intracellular waste - autophagy

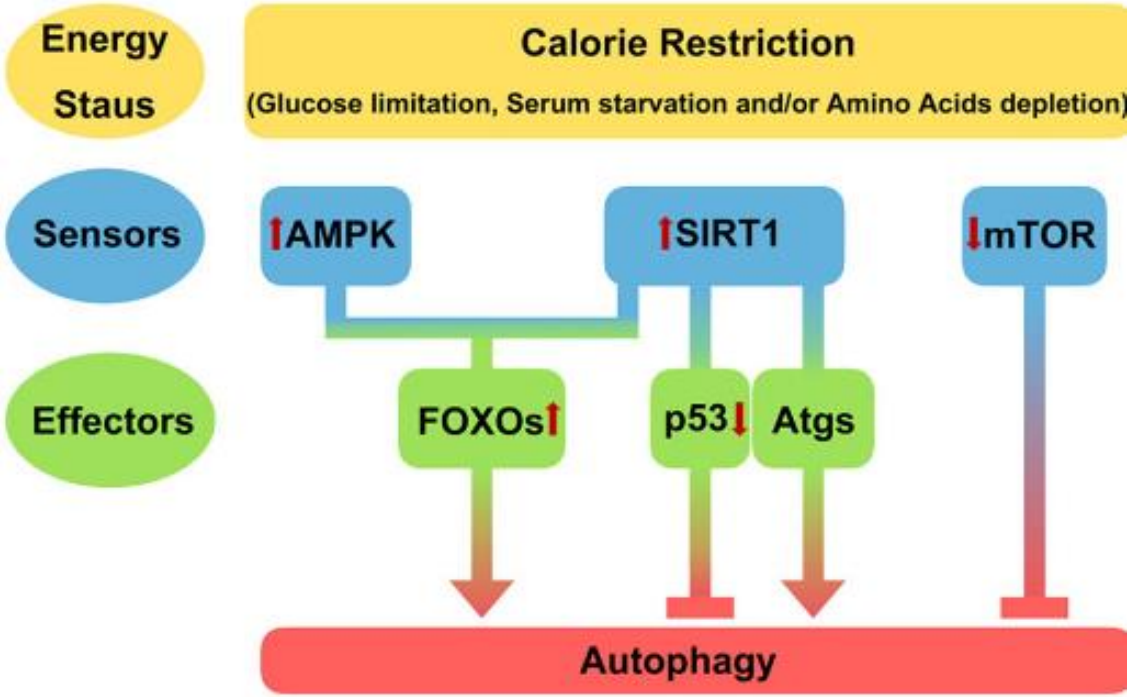


Chang, N. C. (2020). Autophagy and stem cells: self-eating for self-renewal. *Frontiers in Cell and Developmental Biology*, *8*, 138.



Aman, Y., Schmauck-Medina, T., Hansen, M. *et al.* Autophagy in healthy aging and disease. *Nat Aging* **1**, 634–650 (2021).

THE REGULATION OF AUTOPHAGY BY SIRT1 UNDER CALORIE RESTRICTION



Lee, I. H. (2019). Mechanisms and disease implications of sirtuin-mediated autophagic regulation. *Experimental & molecular medicine*, *51*(9), 1-11.

THE CONNECTION BETWEEN NAD+, SIRTUINS & AUTOPHAGY

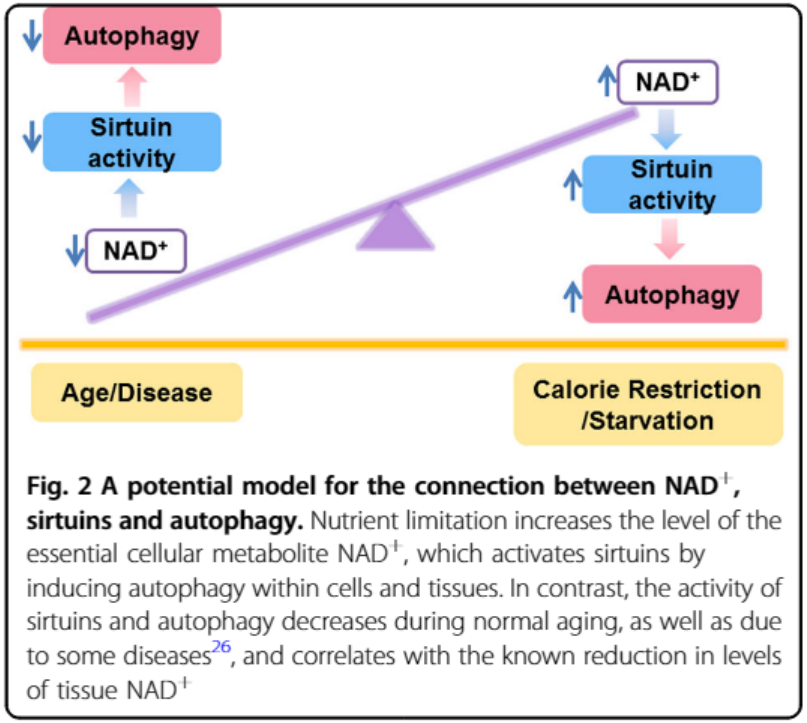
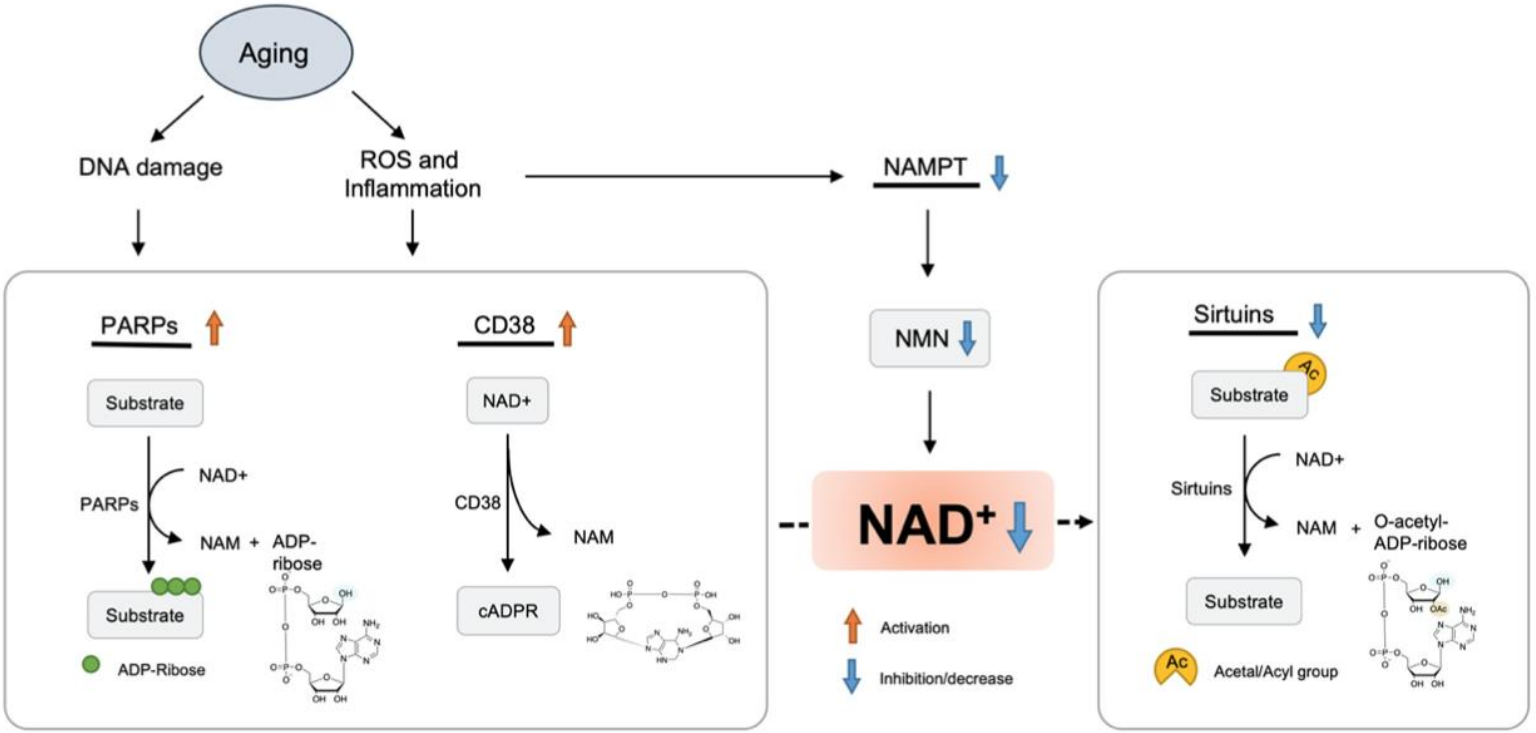


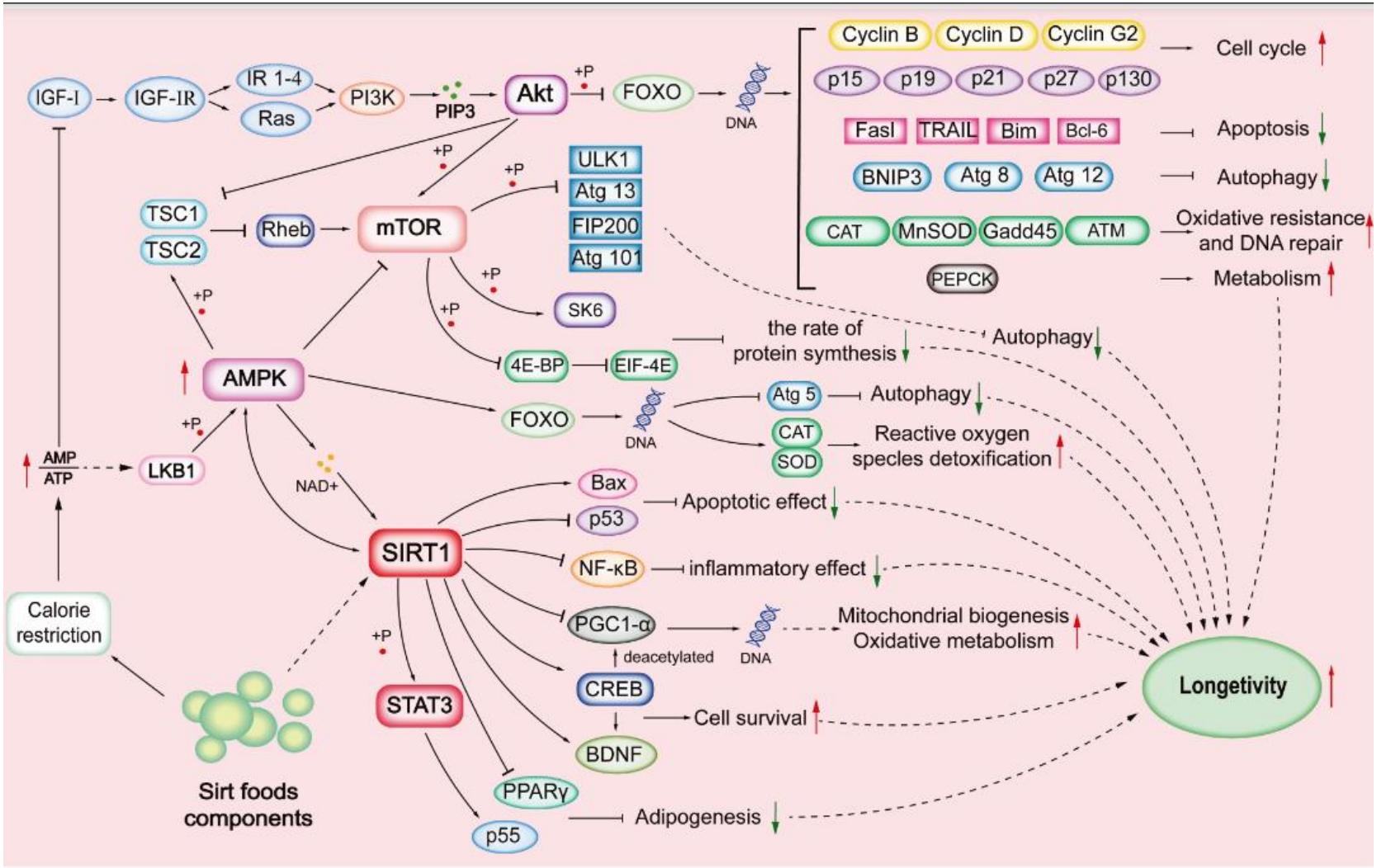
Fig. 2 A potential model for the connection between NAD$^+$, sirtuins and autophagy. Nutrient limitation increases the level of the essential cellular metabolite NAD$^+$, which activates sirtuins by inducing autophagy within cells and tissues. In contrast, the activity of sirtuins and autophagy decreases during normal aging, as well as due to some diseases[26], and correlates with the known reduction in levels of tissue NAD$^+$

Lee, I. H. (2019). Mechanisms and disease implications of sirtuin-mediated autophagic regulation. *Experimental & molecular medicine*, *51*(9), 1-11.

NAD+ BIOSYNTHETIC PATHWAYS DECLINE WITH AGE



Hong, W., Mo, F., Zhang, Z., Huang, M., & Wei, X. (2020). Nicotinamide mononucleotide: a promising molecule for therapy of diverse diseases by targeting NAD+ metabolism. *Frontiers in cell and developmental biology*, *8*, 246.



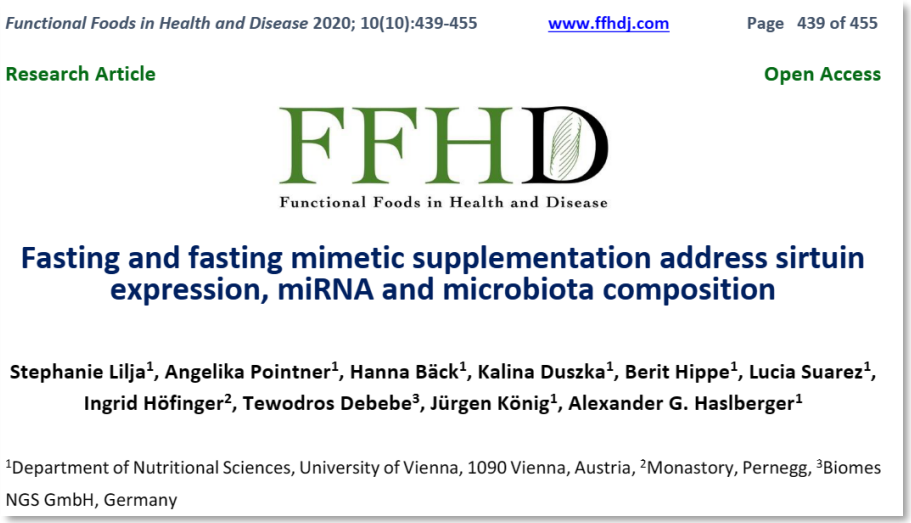
Akan, O.D.; Qin, D.; Guo, T.; Lin, Q.; Luo, F. Sirtfoods: New Concept Foods, Functions, and Mechanisms. *Foods* **2022**, *11*, 2955.

TOP 20 SIRT FOODS

- Kale
- Red wine
- Strawberries
- Onions
- Soy
- Parsley
- Extra virgin olive oil
- Dark chocolate (85% cocoa)
- Matcha green tea
- Buckwheat
- Turmeric
- Walnuts
- Arugula (rocket)
- Bird's eye chili
- Lovage
- Medjool dates
- Red chicory
- Blueberries
- Capers
- Coffee

Akan, O.D.; Qin, D.; Guo, T.; Lin, Q.; Luo, F. Sirtfoods: New Concept Foods, Functions, and Mechanisms. *Foods* **2022**, *11*, 2955.

FASTING PROMOTES LONGEVITY



Functional Foods in Health and Disease 2020; 10(10):439-455 www.ffhdj.com Page 439 of 455

Research Article Open Access

FFHD
Functional Foods in Health and Disease

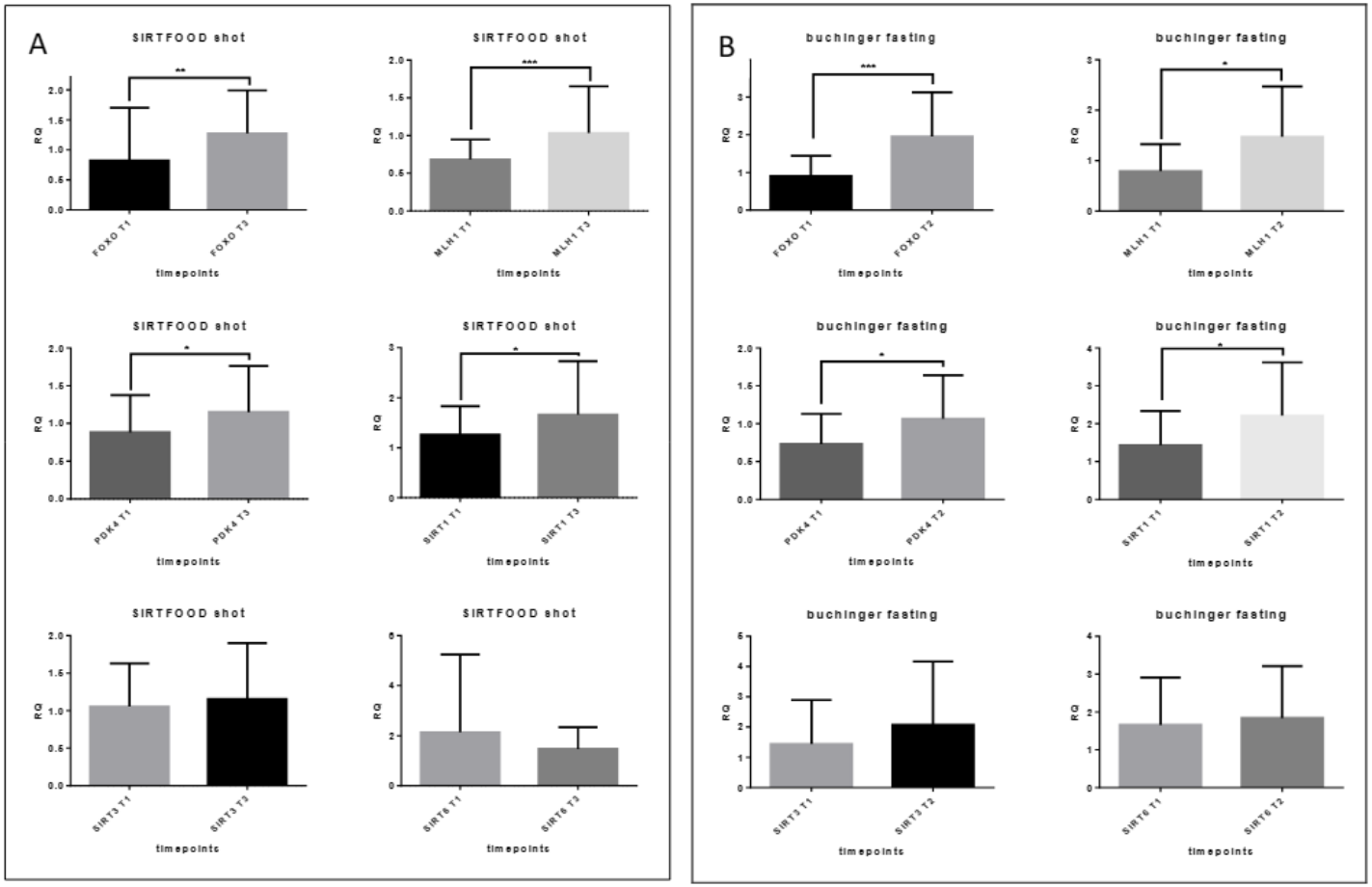
Fasting and fasting mimetic supplementation address sirtuin expression, miRNA and microbiota composition

Stephanie Lilja[1], Angelika Pointner[1], Hanna Bäck[1], Kalina Duszka[1], Berit Hippe[1], Lucia Suarez[1], Ingrid Höfinger[2], Tewodros Debebe[3], Jürgen König[1], Alexander G. Haslberger[1]

[1]Department of Nutritional Sciences, University of Vienna, 1090 Vienna, Austria, [2]Monastory, Pernegg, [3]Biomes NGS GmbH, Germany

Conclusions: Our results confirm the effects of fasting on longevity associated mechanisms but also suggest that SIRTFOOD shot intervention addresses some of these effects.

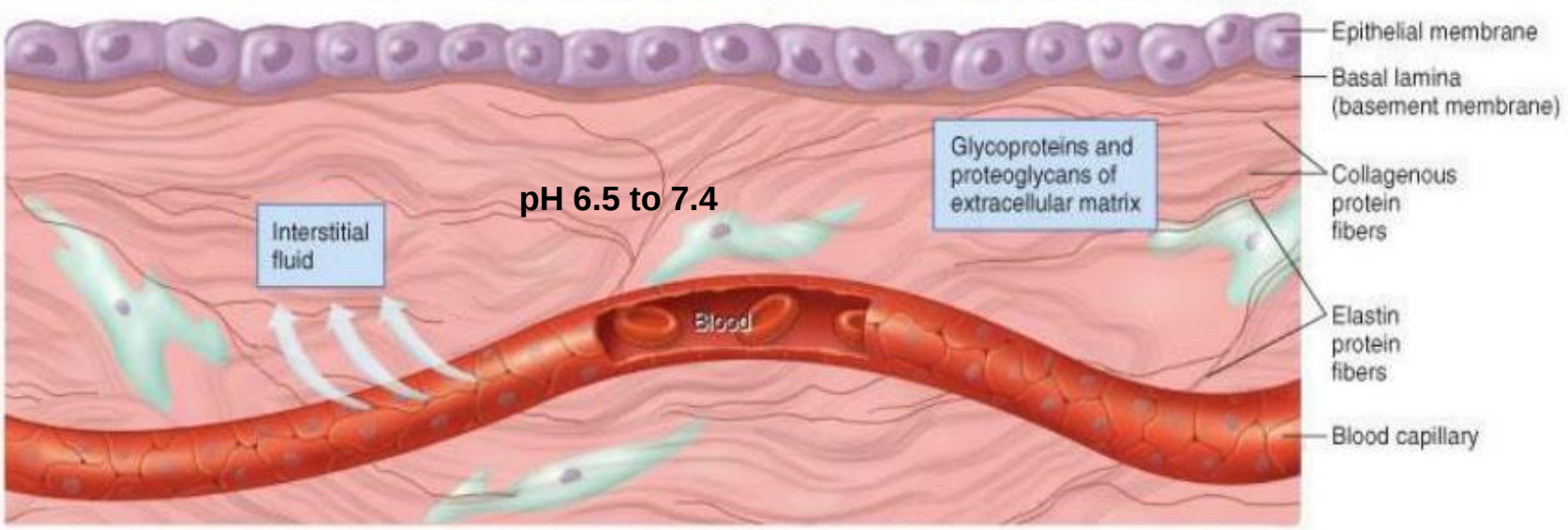
Lilja, S., Bäck, H., Duszka, K., Hippe, B., Suarez, L., Höfinger, I., ... & Haslberger, A. (2020). Fasting and fasting mimetic supplementation address sirtuin expression, miRNA and microbiota composition. *Functional Foods in Health and Disease*, *10*(10), 439-455.



Lilja, S., Bäck, H., Duszka, K., Hippe, B., Suarez, L., Höfinger, I., ... & Haslberger, A. (2020). Fasting and fasting mimetic supplementation address sirtuin expression, miRNA and microbiota composition. *Functional Foods in Health and Disease*, *10*(10), 439-455.

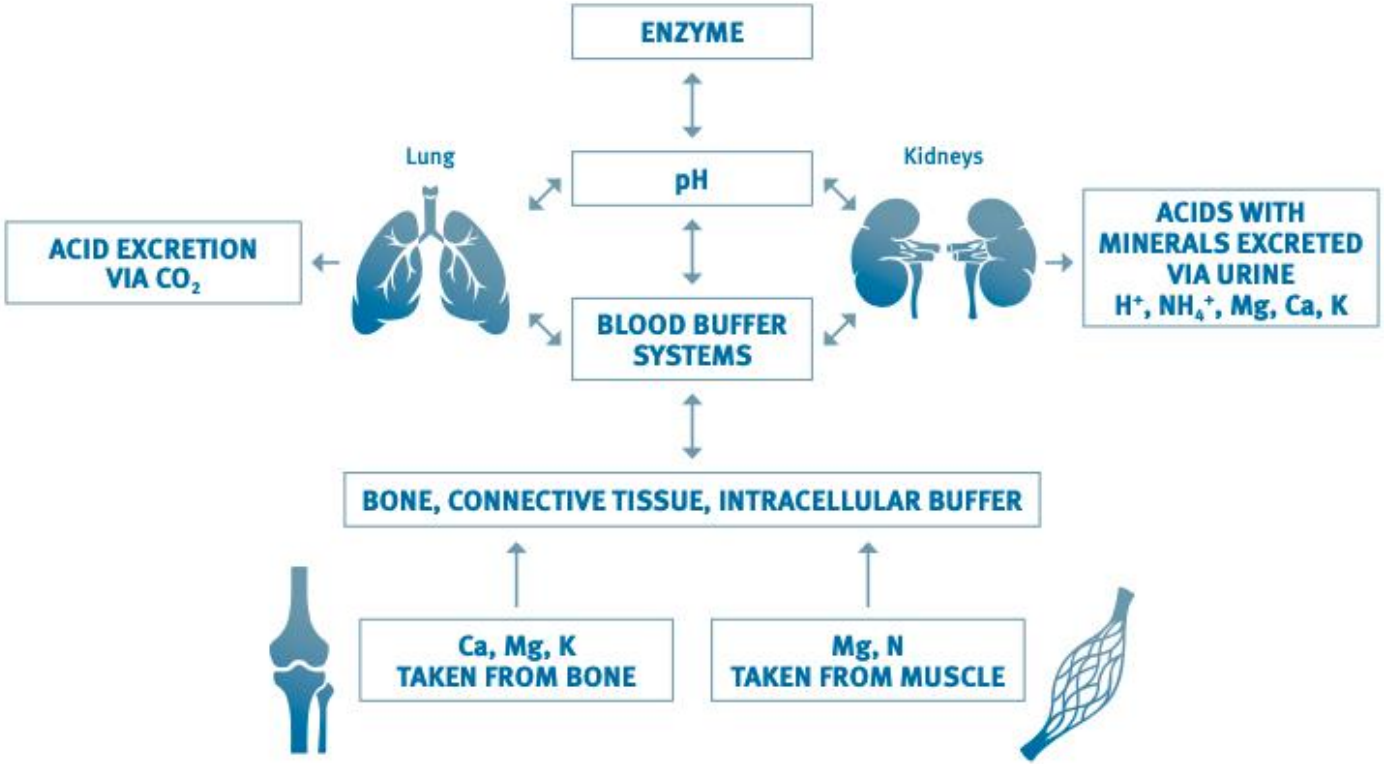
PH & AGEING

tissue



pH 6.5 to 7.4

REGULATION OF ACID-BASE METABOLISM

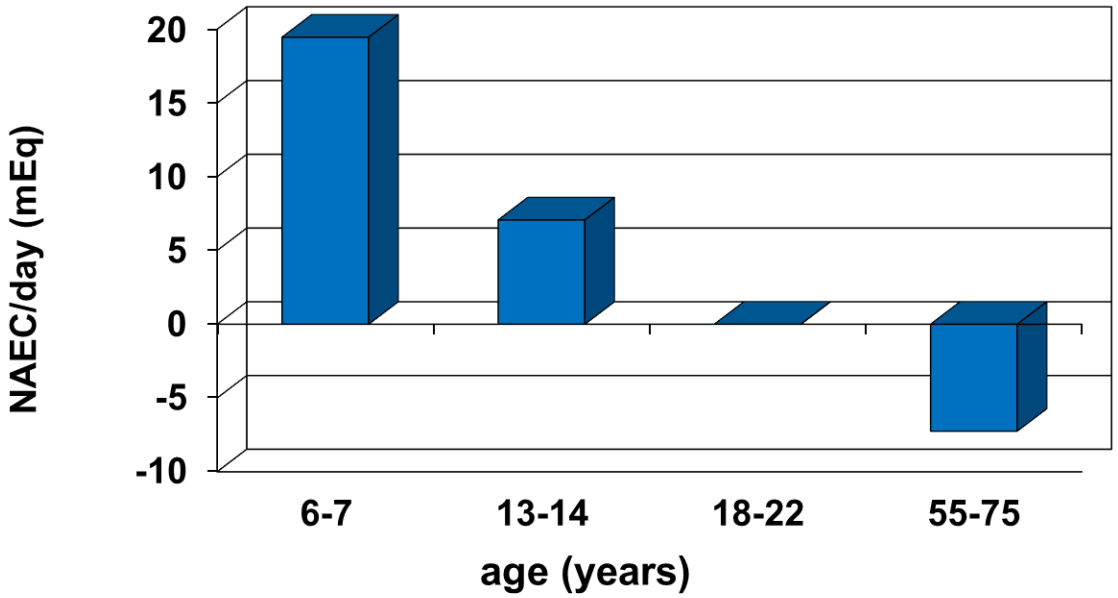


Vormann, J., & Goedecke, T. (2006). Säure-Basen-Haushalt: Latente Azidose als Ursache chronischer Erkrankungen. *Schweizerische Zeitschrift für Ganzheitsmedizin/Swiss Journal of Integrative Medicine*, *18*(5), 255-266.

CAUSES OF LATENT ACIDOSIS

- High intake of acidic food ingredients, mainly protein and phosphates.
- Low intake of alkaline foods (vegetables, fruits) in our usual diet.
- Protein metabolism - sulphur-containing amino acids: methionine/cysteine → glucose + urea + SO_4^{2-} + 2 H^+
- Dieting and fasting
- Strenuous activity (athletes)
- Acute or chronic inflammation

RELATIVE ACID EXCRETION CAPACITY (NAEC) IN HEALTHY PEOPLE OF DIFFERENT AGES



Berkemeyer, S., Vormann, J., Günther, A. L., Rylander, R., Frassetto, L. A., & Remer, T. (2008). Renal net acid excretion capacity is comparable in prepubescence, adolescence, and young adulthood but falls with aging. *Journal of the American Geriatrics Society*, *56*(8), 1442-1448.

DIETARY ACID LOAD & TYPE 2 DIABETES RISK

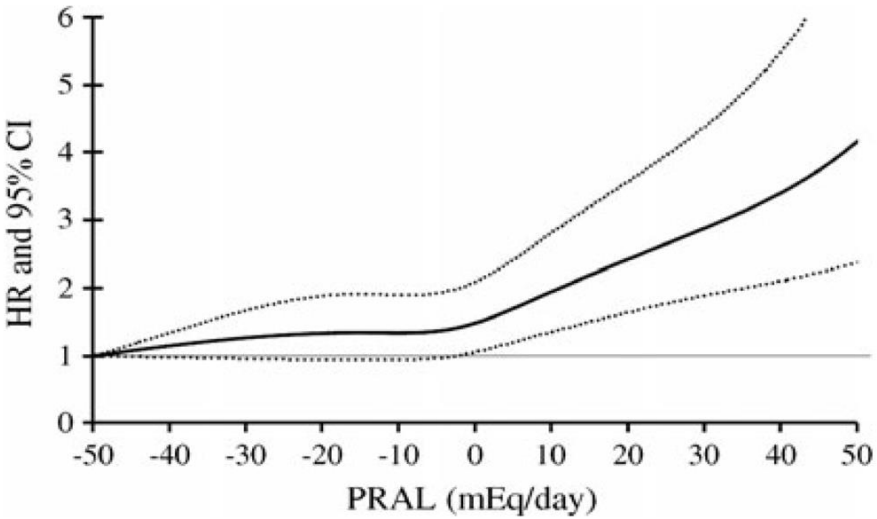


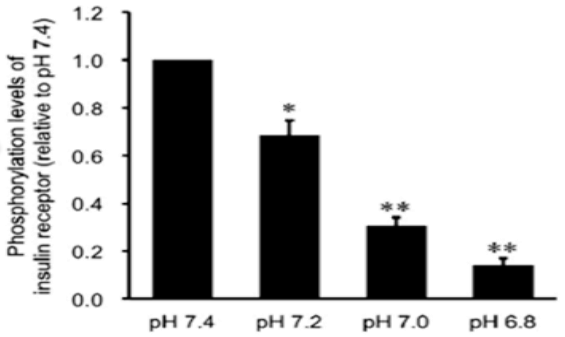
Fig. 1 Cubic spline regression model between PRAL score and risk of type 2 diabetes (E3N-EPIC cohort data, N=66,485).

Fagherazzi et al. Dietary acid load and risk of type 2 diabetes: the E3N-EPIC cohort study. Diabetologia. 2014 Feb;57(2):313-20.

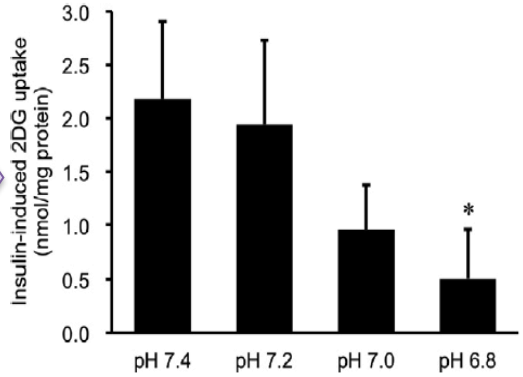
INSULIN RECEPTORS AND PH

- Higher fasting insulin after induction of acidosis.
- Glucose uptake decreased at low pH.
- Insulin receptors (and AKT phosphorylation) decreased in low pH media.

Insulin receptor activation



Uptake of glucose into the cell



Hayata, M et al. (2014). The serine protease prostasin regulates hepatic insulin sensitivity by modulating TLR4 signalling. *Nature communications*, *5*, 3428

life

MDPI

Article

Exercise Training, Intermittent Fasting and Alkaline Supplementation as an Effective Strategy for Body Weight Loss: A 12-Week Placebo-Controlled Double-Blind Intervention with Overweight Subjects

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2 NuOmix Research k.s. Applied Nutriomic Research, Martin, 81106 Bratislava, Slovaki; werner@nuomix-research.com
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4 Institute of Sport Science, Martin-Luther-University of Halle-Wittenberg, 06108 Halle, Germany; till-meyer@gmx.net
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* Correspondence: kuno.hottenrott@sport.uni-halle.de

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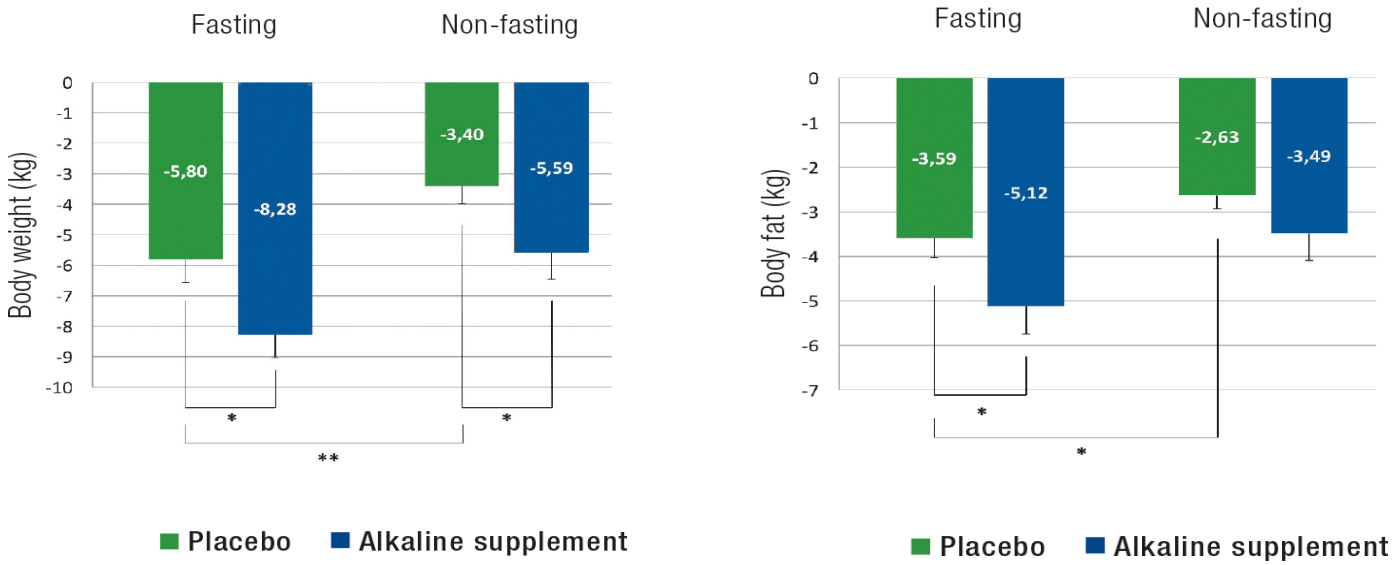
Hottenrott, K., Werner, T., Hottenrott, L., Meyer, T. P., & Vormann, J. (2020). Exercise training, intermittent fasting and alkaline supplementation as an effective strategy for body weight loss: A 12-week placebo-controlled double-blind intervention with overweight subjects. *Life*, *10*(5), 74.

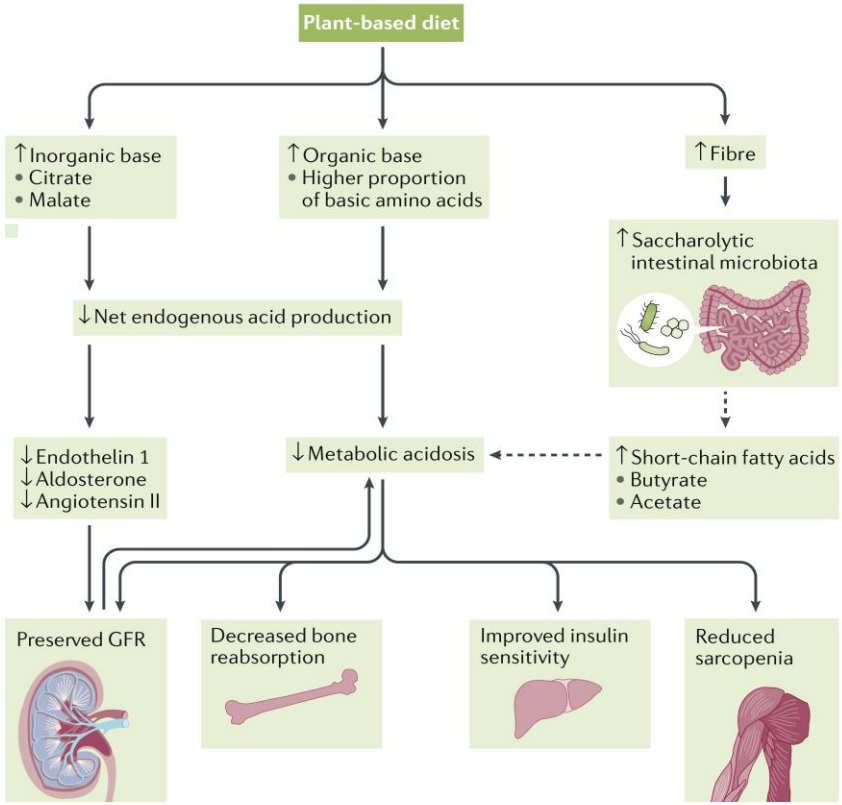
RESULTS: WEIGHT



Body weight loss (left) and body fat loss (right) with fasting and non-fasting subjects taking placebo and alkaline supplement. * $p < 0.05$; ** $p < 0.01$

Hottenrott, K., Werner, T., Hottenrott, L., Meyer, T. P., & Vormann, J. (2020). Exercise training, intermittent fasting and alkaline supplementation as an effective strategy for body weight loss: A 12-week placebo-controlled double-blind intervention with overweight subjects. *Life*, *10*(5), 74.

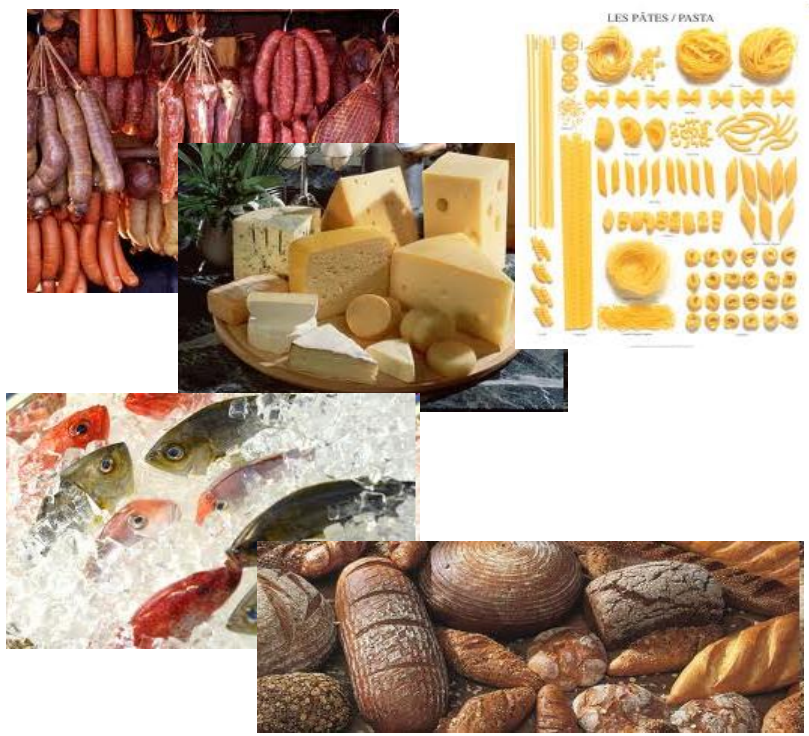
PLANT FOOD INTAKE & ACID-BASE HOMEOSTASIS



Carrero, J. J., González-Ortiz, A., Avesani, C. M., Bakker, S. J., Bellizzi, V., Chauveau, P., ... & Fouque, D. (2020). Plant-based diets to manage the risks and complications of chronic kidney disease. *Nature Reviews Nephrology*, *16*(9), 525-542.

ACIDIC VERSUS ALKALINE FOODS

acidic food (positive PRAL)



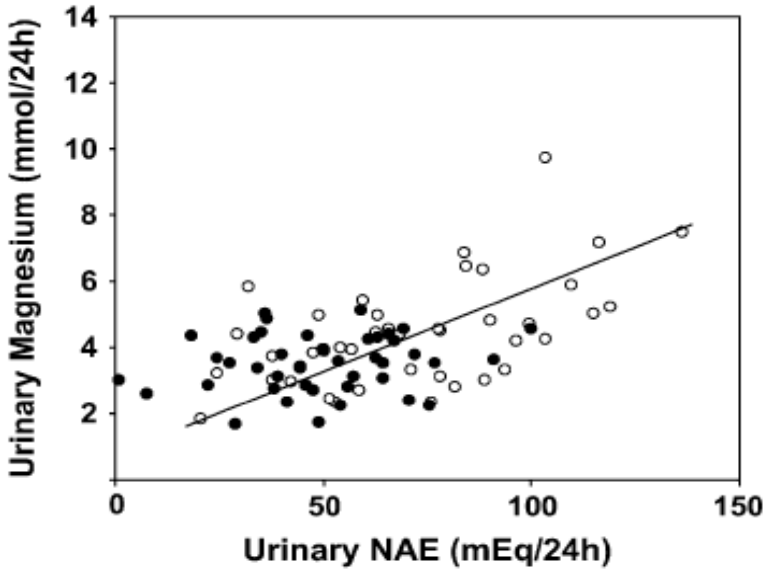
alkaline food (negative PRAL)

The Journal of Nutrition
Nutritional Epidemiology

Acid-Base Status Affects Renal Magnesium Losses in Healthy, Elderly Persons[1]

Ragnar Rylander,[2]* Thomas Remer,[3] Shoma Berkemeyer,[3] and Jürgen Vormann[4]

[2]University of Göteborg, Gothenburg, Sweden; [3]Research Institute of Child Nutrition, 44225 Dortmund, Germany; and [4]Institute for Prevention and Nutrition, 85733 Ismaning, Germany



Rylander, R., Remer, T., Berkemeyer, S., & Vormann, J. (2006). Acid-base status affects renal magnesium losses in healthy, elderly persons. *The Journal of nutrition*, *136*(9), 2374-2377.

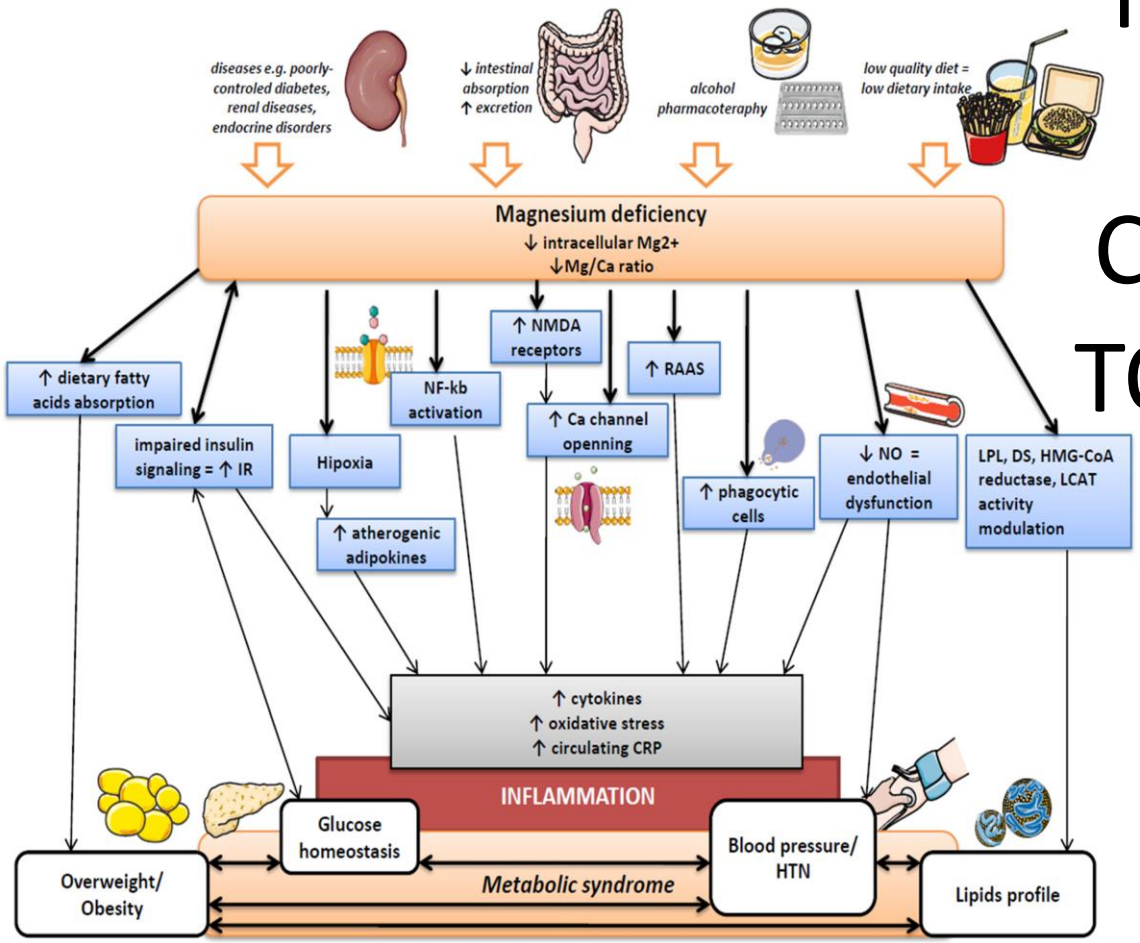
Magnesium Deficiency

What Is Our Status?

Adela Hruby, PhD, MPH
Nicola M. McKeown, PhD

Low magnesium intake has been implicated in a broad range of cardiometabolic conditions, including diabetes, hypertension, and cardiovascular disease. Dietary magnesium and total body magnesium status are widely used but imperfect biomarkers in serum magnesium. Despite serum magnesium's limitations, it is nevertheless observed to be lower in those with cardiometabolic disease than in generally healthy people. Although some 50% of Americans do not meet recommended levels of magnesium intake, the extent of prevalent magnesium deficiency is unknown. Given magnesium's role in a multitude of chronic conditions that are increasingly common across the globe, here, we summarize recently published literature reporting prevalent hypomagnesaemia in generally representative populations and in populations with type 2 diabetes mellitus, metabolic syndrome, and obesity. On the basis of these studies, we estimate that up to a third of the general population may be magnesium deficient and that outside of acute clinical encounters or hospitalization, hypomagnesaemia is likely frequently overlooked in general clinical practice. Nutr Today. 2016;51(3):121–128

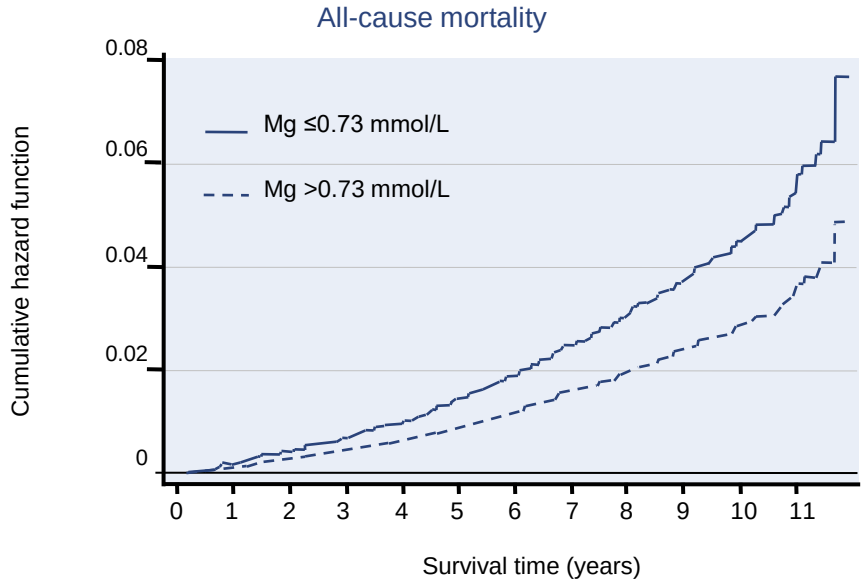
MAGNESIUM DEFICIENCY CONTRIBUTES TO METABOLIC DISEASE



Pelczyńska et al. The Role of Magnesium in the Pathogenesis of Metabolic Disorders. *Nutrients*. 2022; 14(9):1714.

LOW SERUM MG ASSOCIATED WITH HIGHER ALL-CAUSE MORTALITY

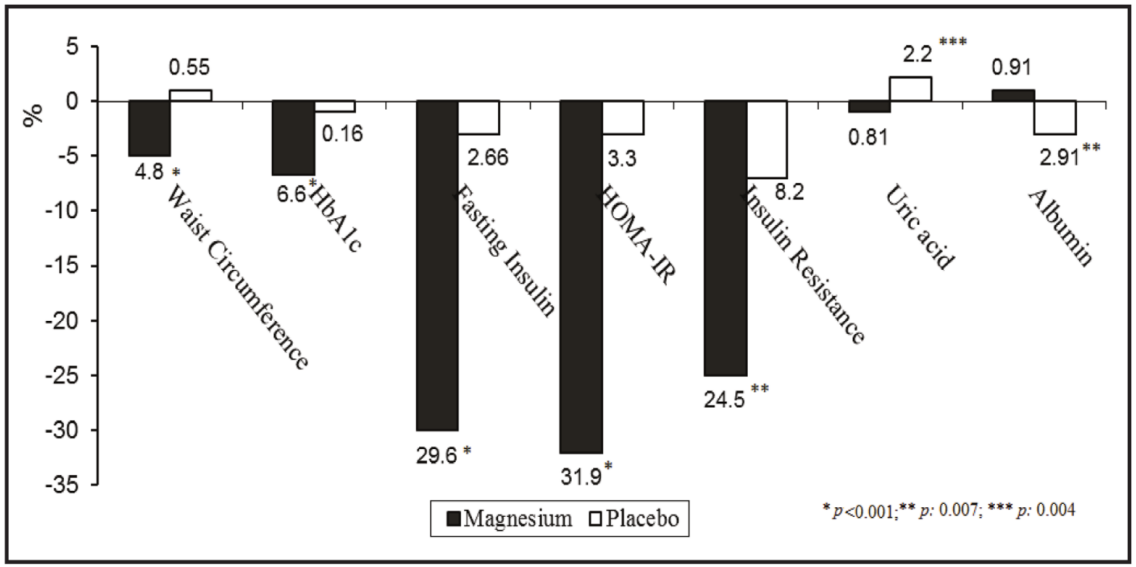
Five-year follow-up of the population-based Study of Health in Pomerania (SHIP) (n=4203, exclusion of subjects with Mg supplementation).



Reffelmann, T., Ittermann, T., Dörr, M., Völzke, H., Reinthaler, M., Petersmann, A., & Felix, S. B. (2011). Low serum magnesium concentrations predict cardiovascular and all-cause mortality. *Atherosclerosis*, *219*(1), 280-284.

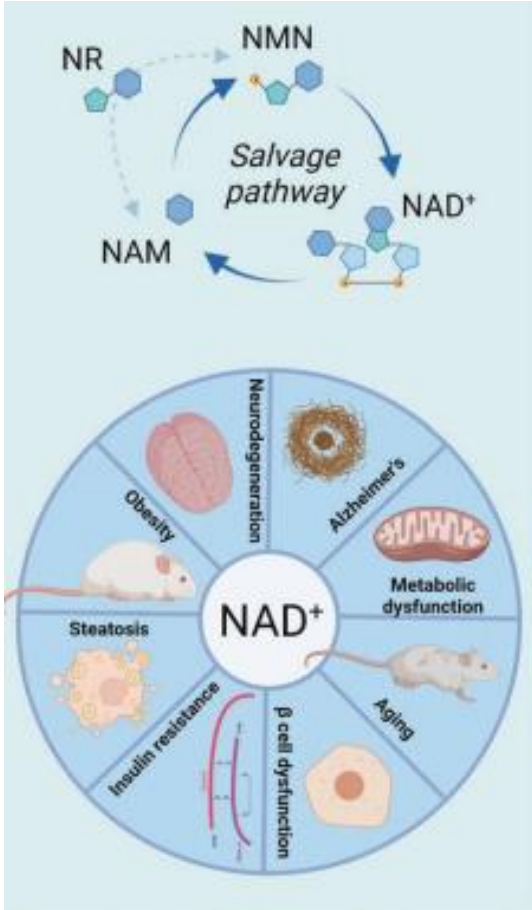
MAGNESIUM SUPPLEMENTATION IMPROVES METABOLIC PROFILE

Fig. 2. Significant mean changes by percentage in metabolic parameters after treatment in the study groups. HOMA-IR, homeostatic model assessment for insulin resistance, HbA1c, hemoglobin A1c.



Toprak O, Kurt H, Sarı Y, Şarkış C, Us H, Kırık A. Magnesium Replacement Improves the Metabolic Profile in Obese and Pre-Diabetic Patients with Mild-to-Moderate Chronic Kidney Disease: A 3-Month, Randomised, Double-Blind, Placebo-Controlled Study.
Kidney Blood Press Res. 2017;42(1):33-42.

NMN BOOSTS NAD+ LEVELS

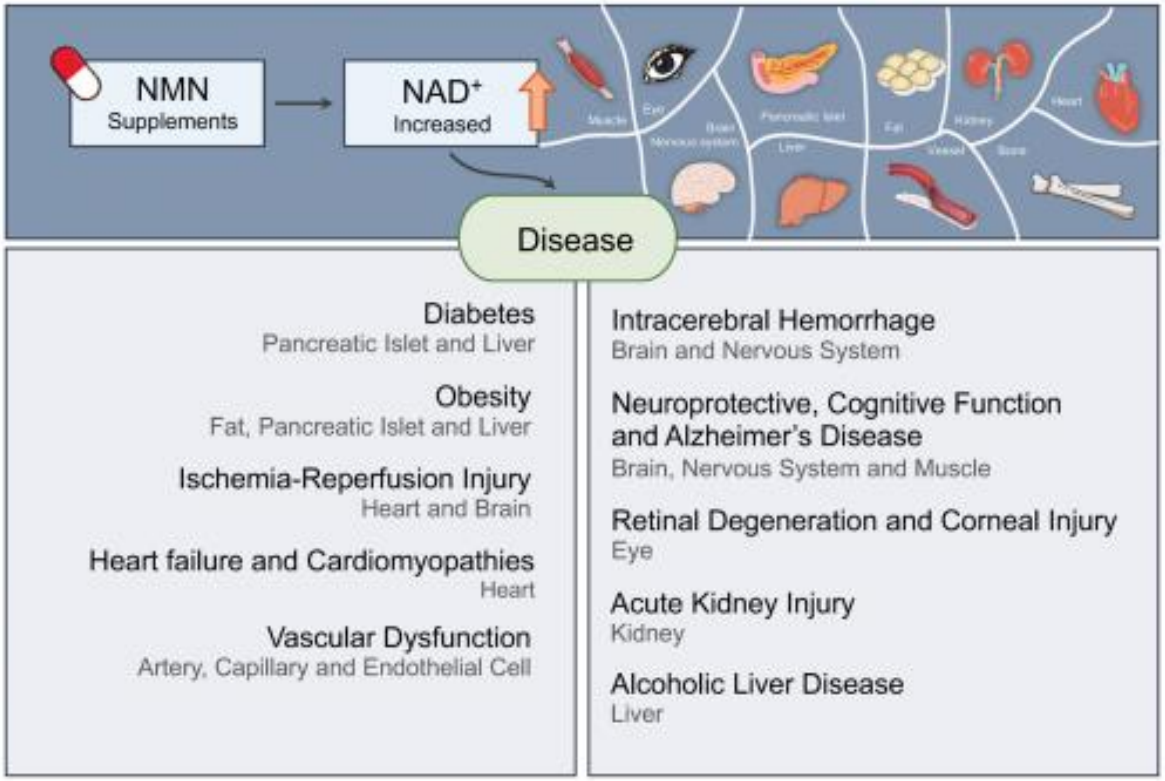


- To maintain metabolic flexibility, mitochondria require substrates, oxygen, and cofactors for energy production.
- Nicotinamide mononucleotide (NMN) is particularly important as the orally bioavailable precursor to NAD+, the essential coenzyme required for energy transduction and cell signalling.

Alegre GFS, Pastore GM. NAD+ Precursors Nicotinamide Mononucleotide (NMN) and Nicotinamide Riboside (NR): Potential Dietary Contribution to Health. Curr Nutr Rep. 2023 Sep;12(3):445-464. doi: 10.1007/s13668-023-00475-y. Epub 2023 Jun 5. PMID: 37273100; PMCID: PMC10240123

Roos, J., Zinngrebe, J., & Fischer-Posovszky, P. (2021). Nicotinamide mononucleotide: a potential effective natural compound against insulin resistance. *Signal transduction and targeted therapy*, *6*(1), 310.

NMN SUPPORTS METABOLIC FLEXIBILITY

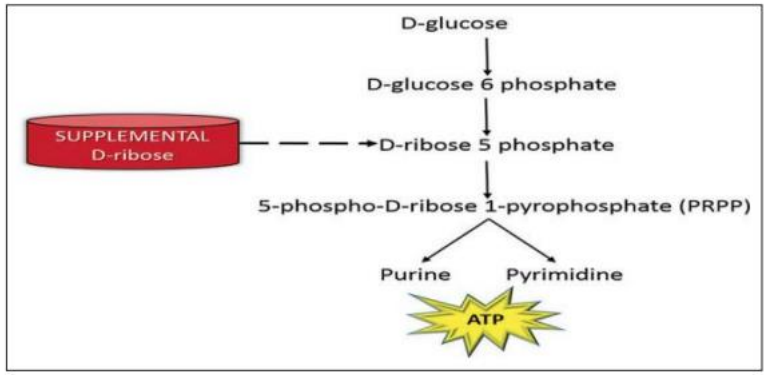


NMN supports metabolic flexibility via NAMPT and NAD+ production.

Hong, W., Mo, F., Zhang, Z., Huang, M., & Wei, X. (2020). Nicotinamide mononucleotide: a promising molecule for therapy of diverse diseases by targeting NAD+ metabolism. *Frontiers in cell and developmental biology*, *8*, 246.

NMN & D-RIBOSE: A POWERFUL DUO FOR METABOLIC HEALTH

- **D-ribose** acts as a co-substrate during the salvage pathway for NAD+, facilitating the conversion of NMN to NAD+.
- Studies supporting the combination of 240 mg/day NMN and 1280 mg/day D-ribose demonstrate improvements in:
- high energy phosphates;
- blood glucose levels;
- insulin sensitivity;
- ATP/AMP ratios; and
- salivary cortisol reduction.



Xue, Y., Shamp, T., Nagana Gowda, G. A., Crabtree, M., Bagchi, D., & Raftery, D. (2022). A Combination of Nicotinamide and D-Ribose (RiaGev) Is Safe and Effective to Increase NAD+ Metabolome in Healthy Middle-Aged Adults: A Randomized, Triple-Blind, Placebo-Controlled, Cross-Over Pilot Clinical Trial. Nutrients, 14(11), 2219. https://doi.org/10.3390/nu14112219

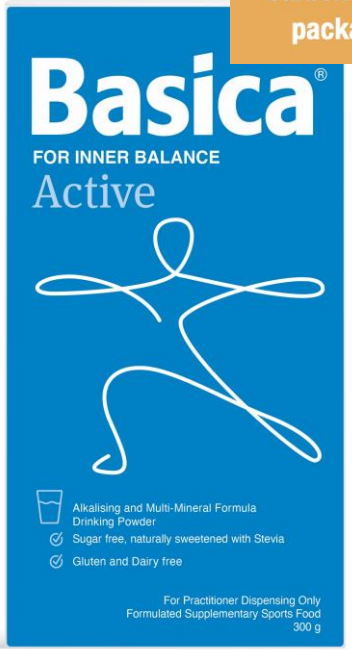
SUMMARY

- Healthspan is contingent on metabolic flexibility, the ability to switch between glucose and fatty acid utilisation depending on availability.
- Induction of autophagy, the reduction of intracellular waste, promotes metabolic flexibility and supports healthy ageing.
- Calorie restriction, i.e. intermittent fasting, initiates autophagy and increases NAD+ levels. Reduced NAD+ is associated with metabolic and age-related diseases.
- Relative acid excretion capacity (NAEC) declines with age, further increasing susceptibility to disease.
- Daily supplementation with alkalising minerals aids the maintenance of healthy pH and supports longevity.
- Nicotinamide mononucleotide (NMN) increases NAD+ levels, supports metabolic flexibility and aids the prevention of age-related disease.

BASICA ACTIVE – KEY FEATURES

- ✓ **OPTIMAL ALKALISATION:** Contains alkalising minerals in “citrate” form (potassium, magnesium, molybdenum, selenium, chromium, calcium and zinc)
  - **Potassium & Magnesium** for electrolyte balance, and muscle & nervous system function
  - **Magnesium** for energy metabolism & reduction of fatigue
  - **Calcium** necessary for normal bone structure & enhanced bone mineral density
  - **Vitamins C, B2 and Zinc** contribute to cell protection from free radical damage
- ✓ **SUITABLE FOR SENSITIVE PATIENTS:** Sulfite Free formula does not disturb digestive processes
- ✓ **OPTIMAL BIOAVAILABILITY:** Calcium carbonate and citric acid, when added to water, effervesce to produce calcium citrate, thereby supplying ‘citrates’ in a soluble form
- ✓ **PROVEN EFFICACY:** Alkalising mineral citrates for optimal pH balance backed by clinical trials

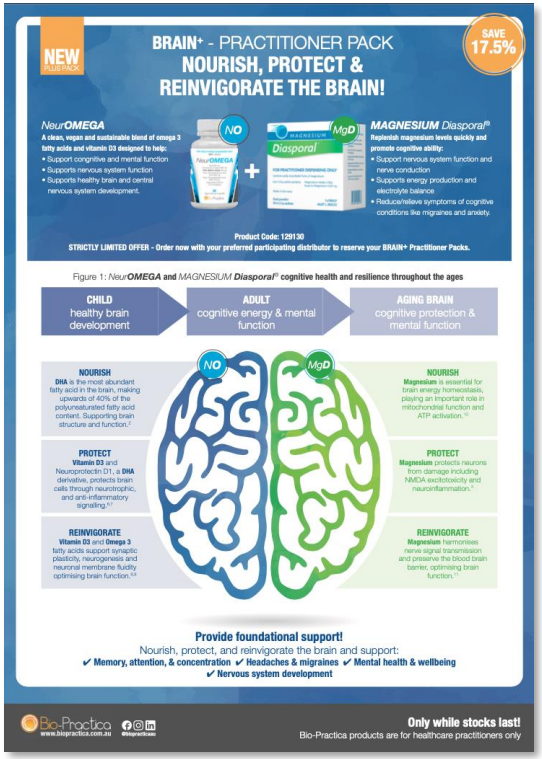
The same great tasting, effective formula now in carbon neutral packaging



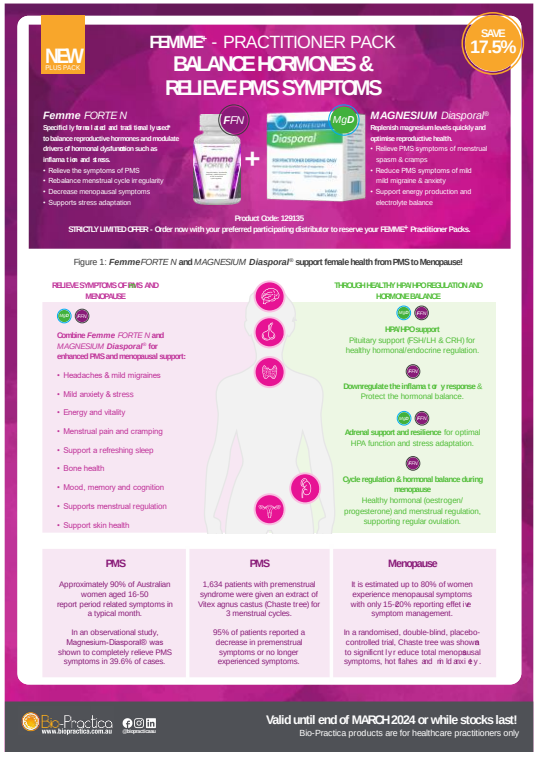
MAGNESIUM DIASPORAL– KEY FEATURES

- ✓ **PROVEN EFFICACY:** Backed by over 25 human clinical trials with 100 years of clinical use, MAGNESIUM Diasporal® has demonstrated efficacy in hormonal, musculoskeletal, cardiometabolic & nervous system health AND:
  - ✓ Relieves symptoms of mild migraines & anxiety
  - ✓ Supports energy production & general health and wellbeing
  - ✓ Supports musculoskeletal health, muscle function & bone health
  - ✓ Supports nerve conduction & nervous system health
  - ✓ Relieves menstrual cramps & symptoms of menstrual tension
  - ✓ Maintains cardiovascular system & heart health
- ✓ **PREMIUM QUALITY:** Free from sulfites & other allergens in state of the art manufacturing.
- ✓ **OPTIMAL BIOAVAILABILITY:** Superior absorption & fast delivery for Magnesium when and where it matters
- ✓ **HIGH STRENGTH MAGNESIUM 400:** Delivering 2058mg of TriMagnesium Dicitrate, twice the amount of elemental magnesium when compared to conventional magnesium citrate.

NEW PLUS PACKS!



BRAIN



FEMME

IMMUNE