Nutrition Strategies to Maximize Mitochondrial Function for Health, Performance, and Longevity

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Disclosure

I disclose the following financial relationships

Team Dietitian
Philadelphia 76ers

Nutrition Affairs
Amazentis SA
(parent company of Timeline Nutrition)

All interests for this individual have been mitigated

Objectives

1. **Why should we care about mitochondria?**

2. **How does aging affect our mitochondria?**

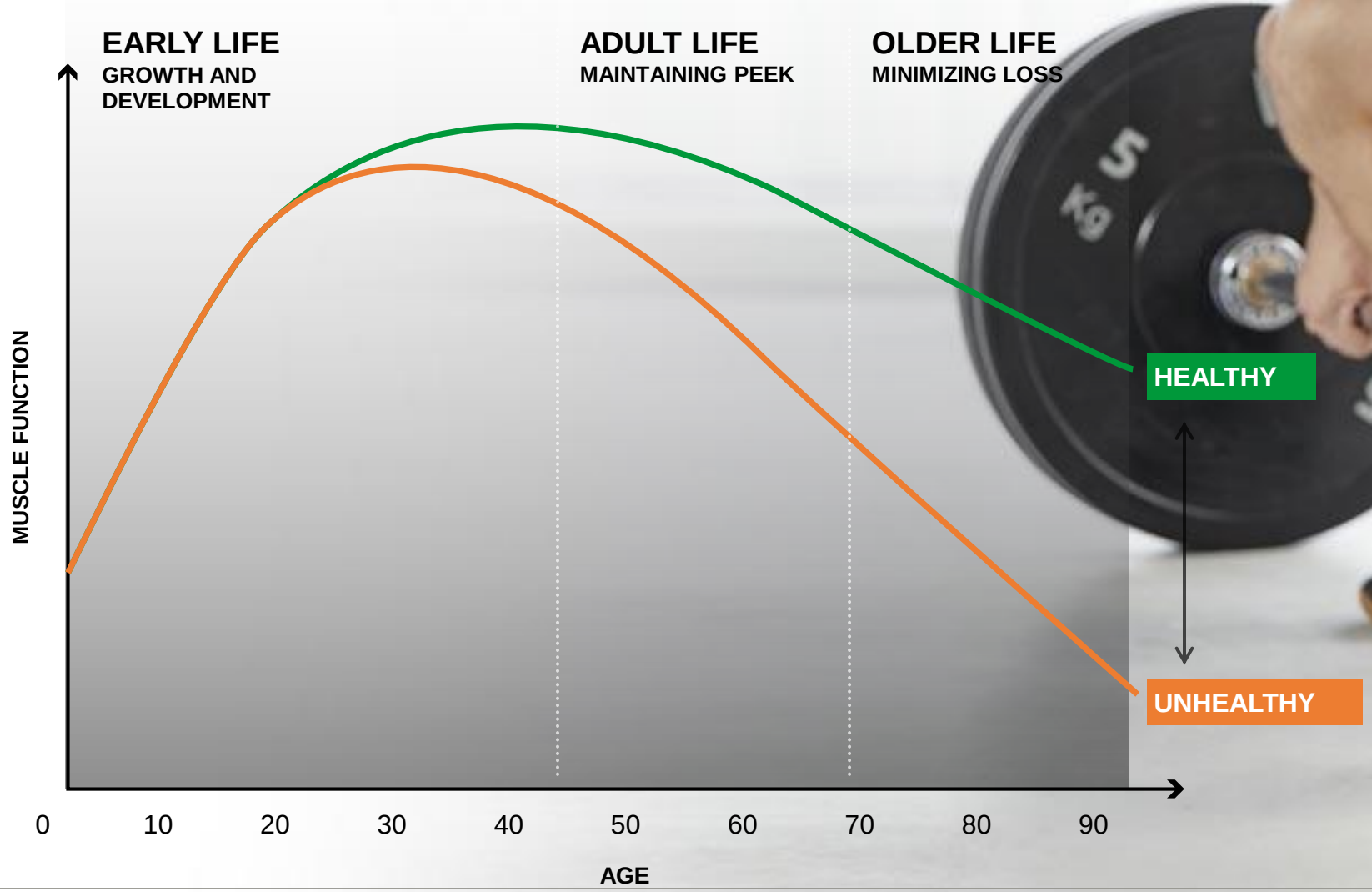
3. **How do we keep our mitochondria vibrant?**
   1. Diet
   2. Exercise
   3. Supplements

4. **What nutrition strategies are available for optimizing mitochondrial health?**
   1. NMN
   2. CoQ10
   3. Urolithin A

Muscle Aging Starts In Our 30s

Hand grip strength declines 10% every decade.

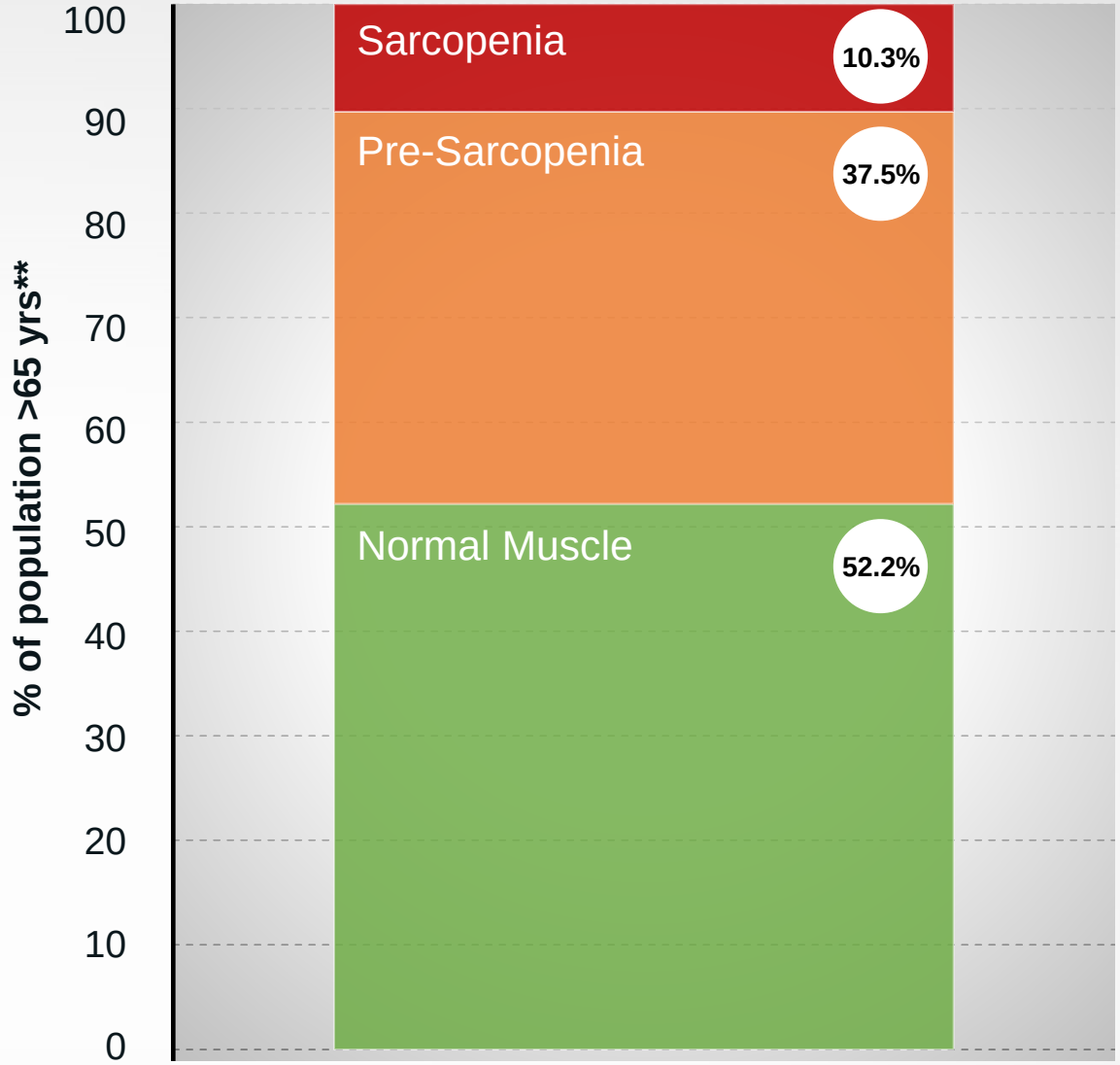
Early intervention strategies are needed.



Age-Related Decline In Muscle Function: A Tremendous Unmet Need

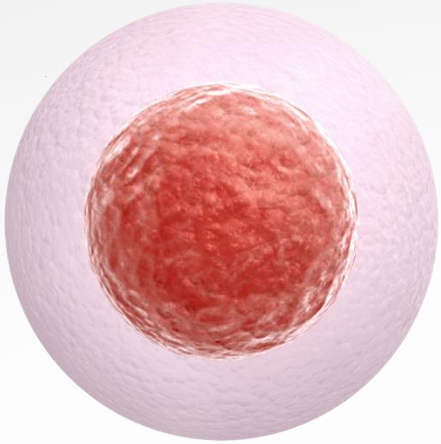
There are ~56 million people 65 years and older projected by 2020 in the US alone

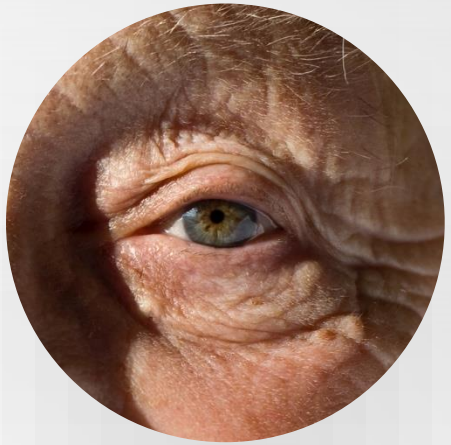
Worldwide, there will be more than 1 billion people over 65 years old by 2030



*JAGS Vol 52, 80-85, 2004 **US Censes 2014 est. in 2020

Mitochondrial Origin of Aging





Mitochondria

Decline in mitochondrial health & function

Cell

Age-associated cellular decline

Organ

Weakened organ or system (e.g. muscle)

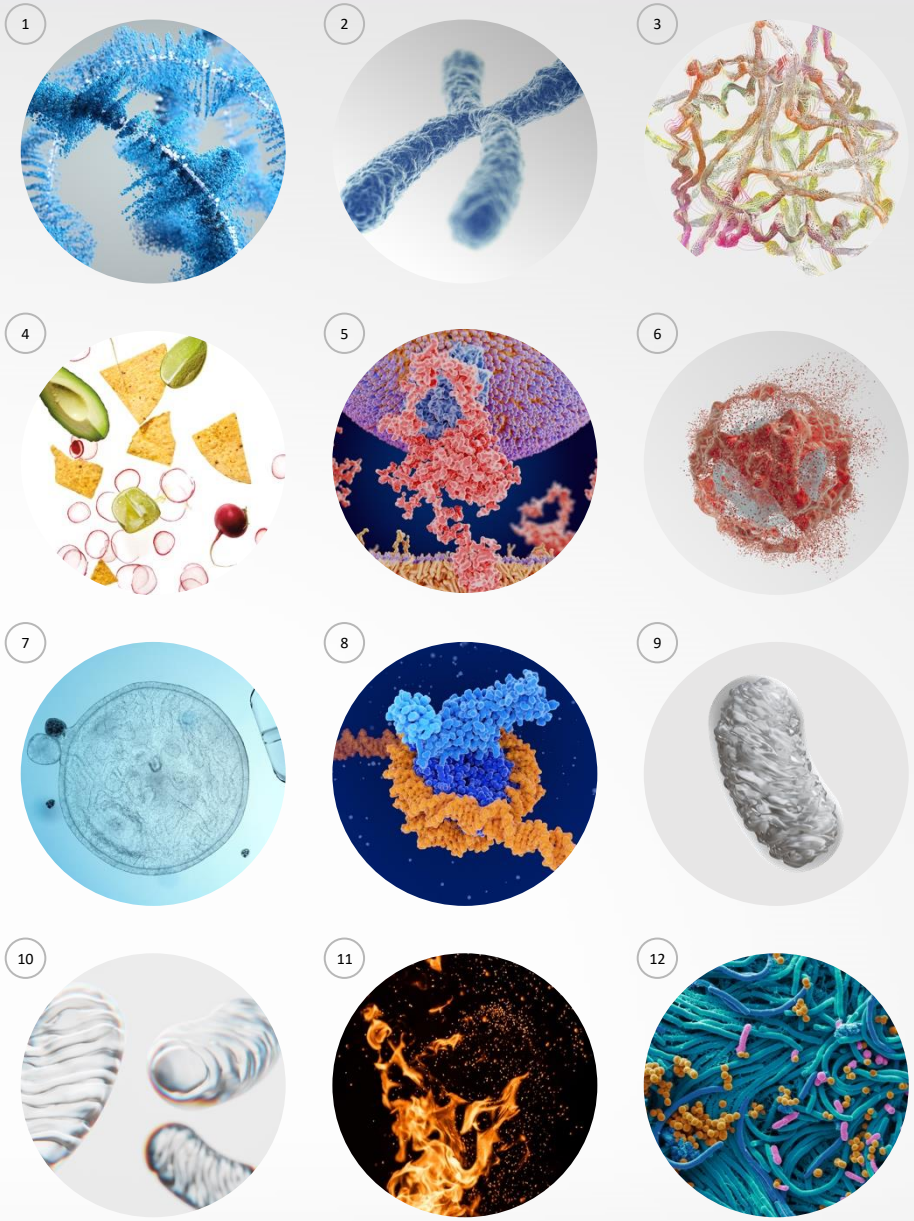
Body

Decline in function & onset of health issues (e.g. fatigue, reduced strength & mobility)

AGING

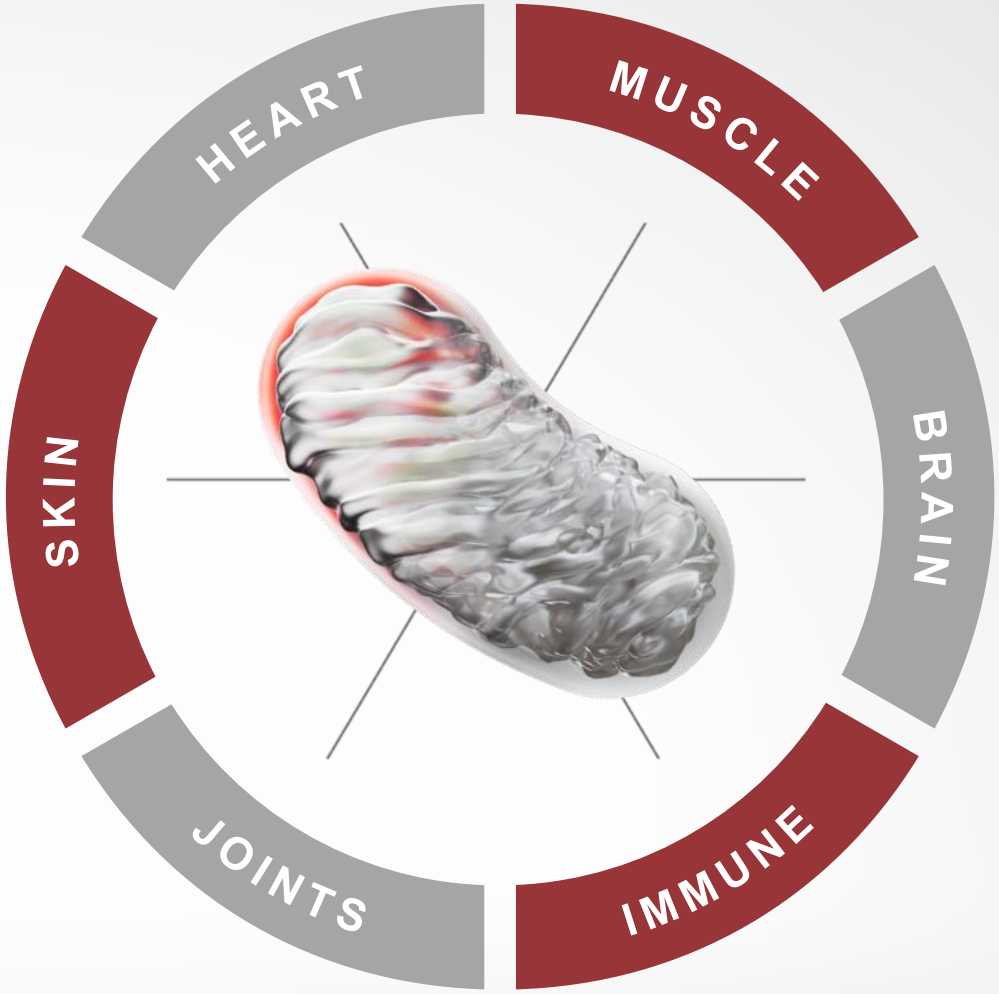
Biological Hallmarks of Aging

1. Genomic Instability
2. Telomere Attrition
3. Loss of Proteostasis
4. Deregulated Nutrient Sensing
5. Altered Intracellular Communication
6. Cellular Senescence
7. Stem Cell Exhaustion
8. Epigenetic Alterations
9. **Mitochondrial Dysfunction**
10. **Decline in Macroautophagy (e.g. Mitophagy)**
11. **Chronic Inflammation**
12. Gut Microbiome Dysbiosis



Mitochondria Are The Bedrock Of Good Health

- Healthy cells rely on healthy mitochondria.
- Optimal function optimizes health and is particularly essential to heart, kidney, eye, brain and muscle function.



Mitochondrial Upkeep

Diet

Exercise

Supplements

Mitochondrial Optimization Through Diet

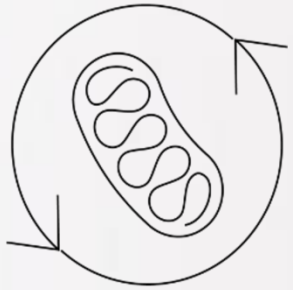
Intermittent fasting

Many different definitions and approaches

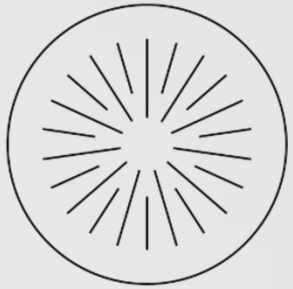
Antioxidants & polyphenols

Over 8000 polyphenols with a wide range of bioavailability and effectiveness

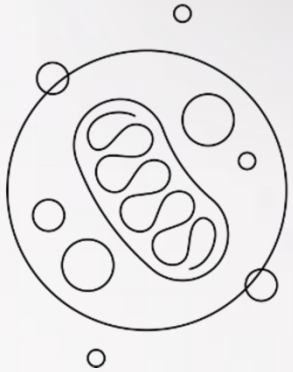
Mitochondrial Optimization Through Exercise



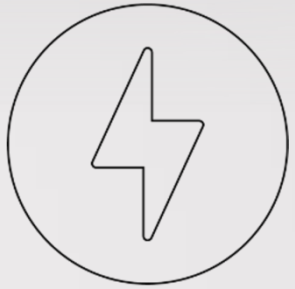
Endurance training triggers biogenesis
= more mitochondria*



The more mitochondria you have, the more energy you produce



HIIT training increases respiration
= more efficient mitochondria**



Produce more power

*Donato DMD, et al. *American Journal of Physiology-Endocrinology and Metabolism*. 2014
**Huertas JR, et al. *Oxidative medicine and cellular longevity*. 2019

Mitochondrial Optimization Through Supplements

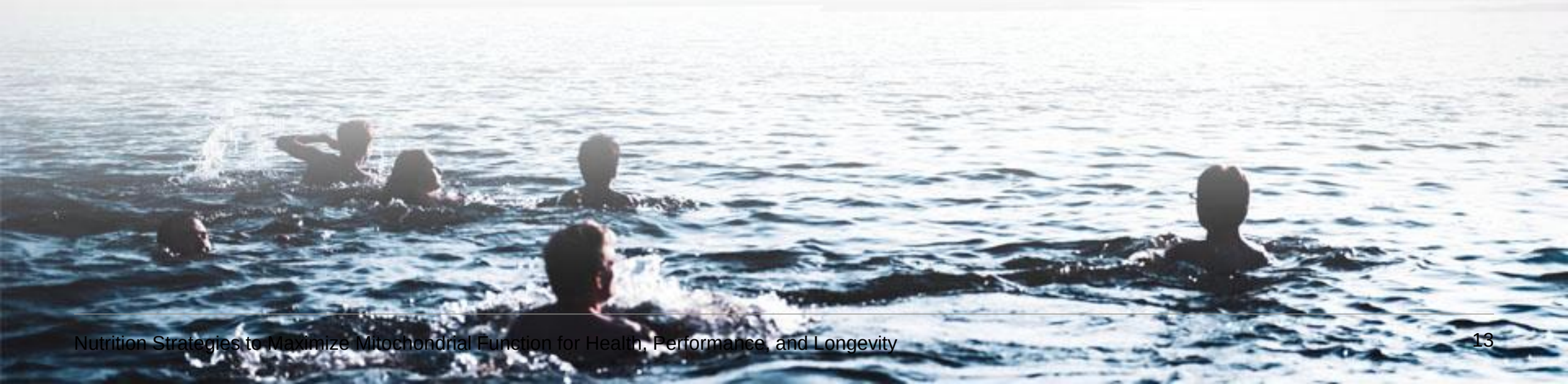
FDA: “Dietary supplements are intended to add to or supplement the diet and are different from conventional food.”

- Vitamins, minerals, macronutrients, ergogenic aids and other metabolites

- Unregulated by the FDA for safety & efficacy
- Third-party testing crucial
- Look for certification label

Mitochondrial Optimization Through Supplements

1. **Nicotinamide Mononucleotide (NMN)**
2. **CoQ_{10}**
3. **Urolithin A**



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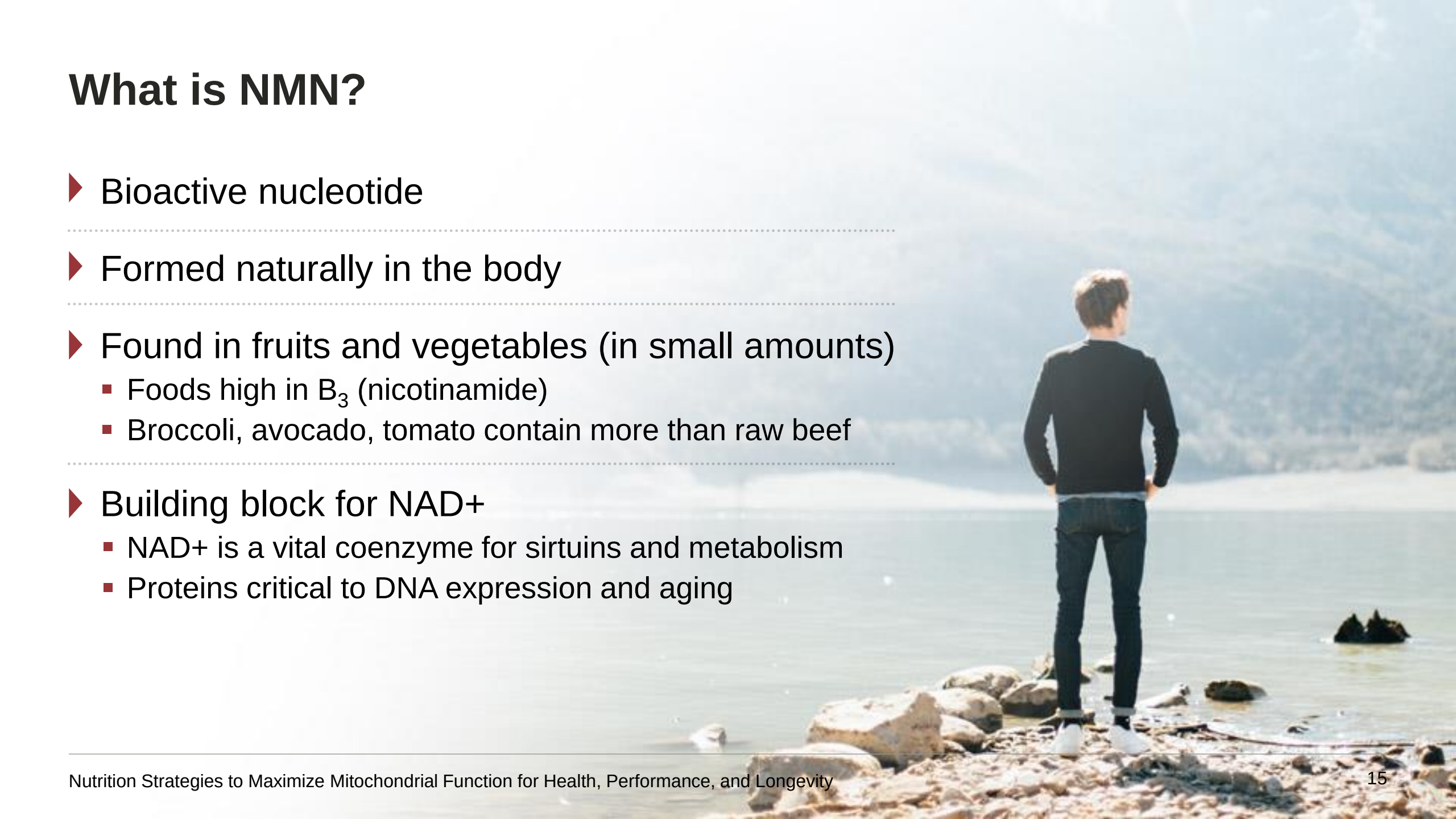
Nicotinamide Mononucleotide (NMN)

- Shade, C. *Integrative Medicine.* 2020
- Liao, B., et al. *JISSN*. 2021
- Yoshino, M., et al. *Science.* 2021
- Akasaka et al. *Geriatric Gerontology Int.* 2023
- Methuselah Foundation. 2022

What is NMN?

- Bioactive nucleotide
- Formed naturally in the body
- Found in fruits and vegetables (in small amounts)
  - Foods high in B_3 (nicotinamide)
  - Broccoli, avocado, tomato contain more than raw beef
- Building block for NAD+
  - NAD+ is a vital coenzyme for sirtuins and metabolism
  - Proteins critical to DNA expression and aging



Why is NAD+ important?

- NAD+ participates in >50% of all physiologic processes
  - Mitochondrial biogenesis, oxidative stress alleviation, etc

- Increasing NAD+ levels leads to boosted energy production and cellular repair

Why should we care about NMN?

Both NMN levels and the conversion of NMN to NAD+ decline with age

NAD+ levels drop to approx. ½ by middle-age

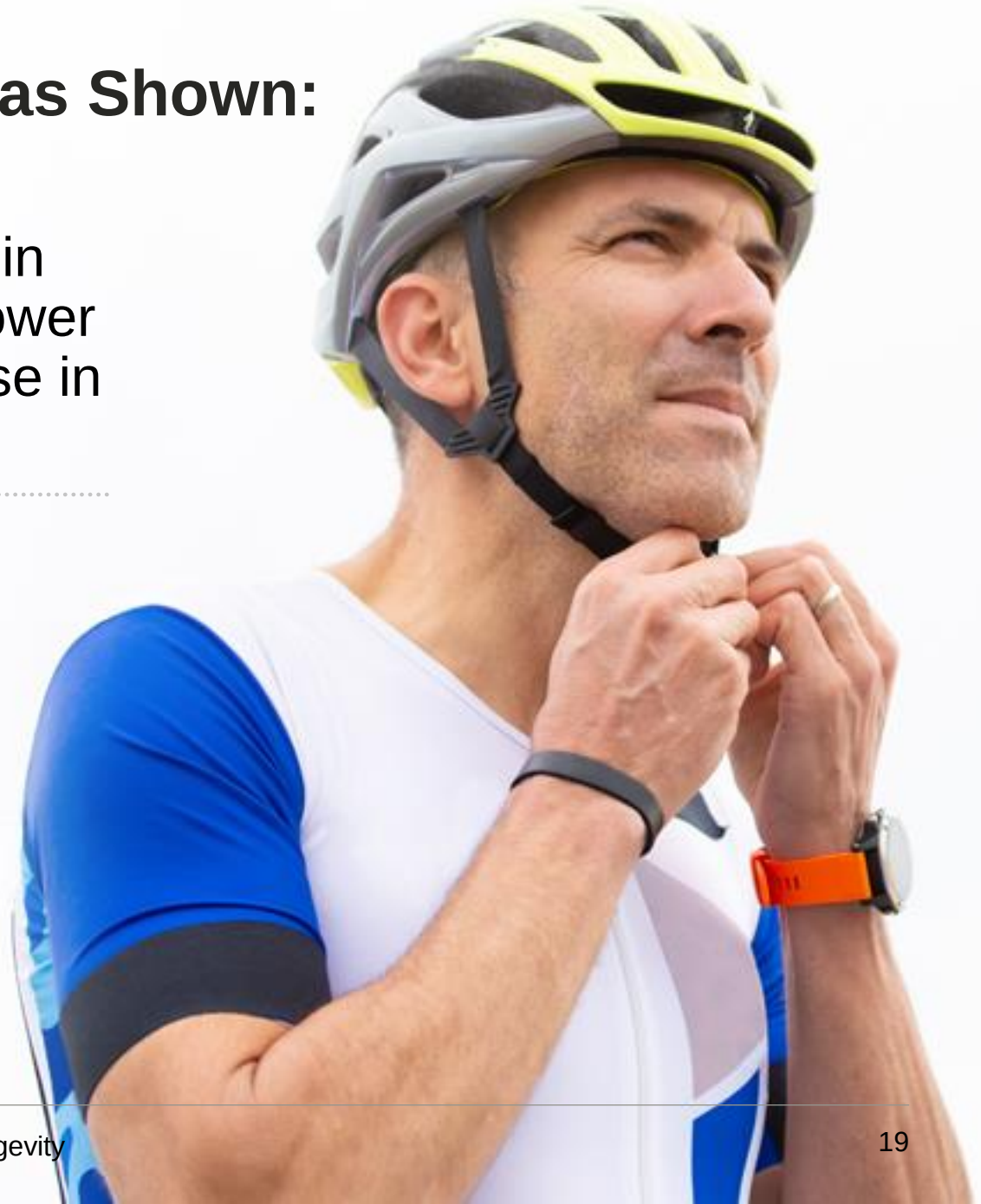
Levels of the enzyme that catalyses the conversion of nicotinamide (B3) to NMN also decreases with age

NMN supplementation in mice has shown:

- Decreased age-associated weight gain
- Increased energy metabolism and physical activity
- Increased insulin sensitivity
- Increased eye function
- Increased mitochondrial metabolism
- Prevention of age-related changes in gene expression
- Restoration of skeletal muscle
- Ameliorated cognitive decline in Alzheimer’s model
- Decreased ROS
- Possible increased integrity of BBB

NMN Supplementation in Humans has Shown:

- No differences in BMI or %BF, no changes in HRmax, RERmax, HRR, o2-pulse, peak power or workload, or VO2max overall for any dose in amateur, healthy runners over 6 weeks
- Increased muscle insulin sensitivity, insulin signaling and remodeling in overweight or obese women with prediabetes
- No improvement in grip strength or walking speed in older males with diabetes and impaired physical performance



NMN is No Longer Readily Available

- As of October 2022, FDA has banned NMN sale as a supplement
  - A drug developer is asking FDA to approve NMN as a drug
  - Protects production of NMN from the unregulated space of supplements
  - Can no longer be sold as a supplement

2

CoQ_{10}

- Drobnic F, et al. *Nutrients*. 2022
- Gutierrez-Marisacal et al. *Int. J of Molecular Sciences*. 2020
- Mantle et al. *Antioxidants*. 2020
- Mantle et al. *Int. J of Molecular Sciences*. 2023

Ubiquinone vs. Ubiquinol vs. CoQ_{10}

Coenzyme Q_{10} (CoQ_{10})

Ubiquinone = oxidized form of CoQ10

Primary form found within the body

Ubiquinol = reduced form of ubiquinone

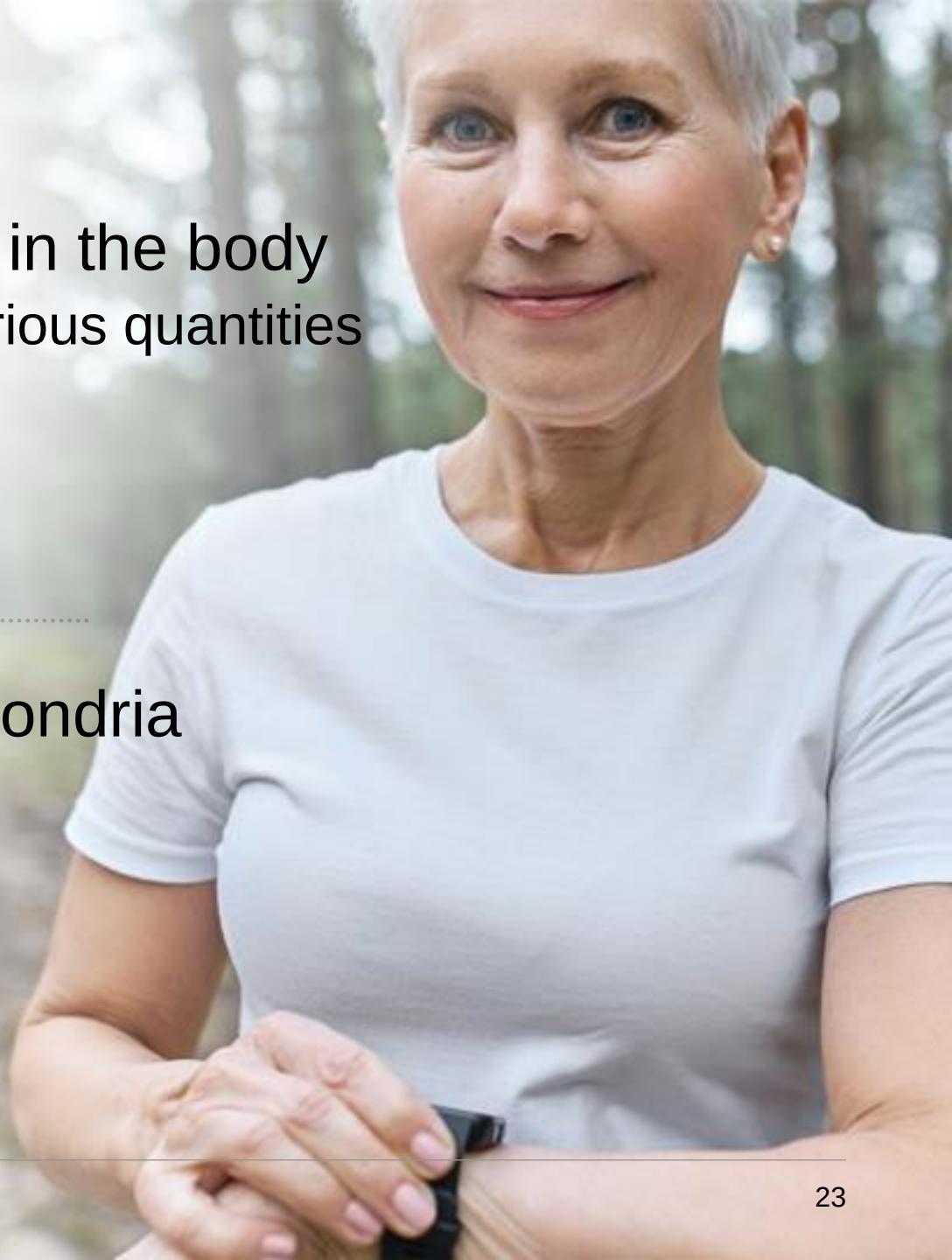
Ubiquinol is 6-10x more bioavailable than ubiquinone

Constant inter-conversion between two forms

Ubiquinol is not “active” form of CoQ_{10}

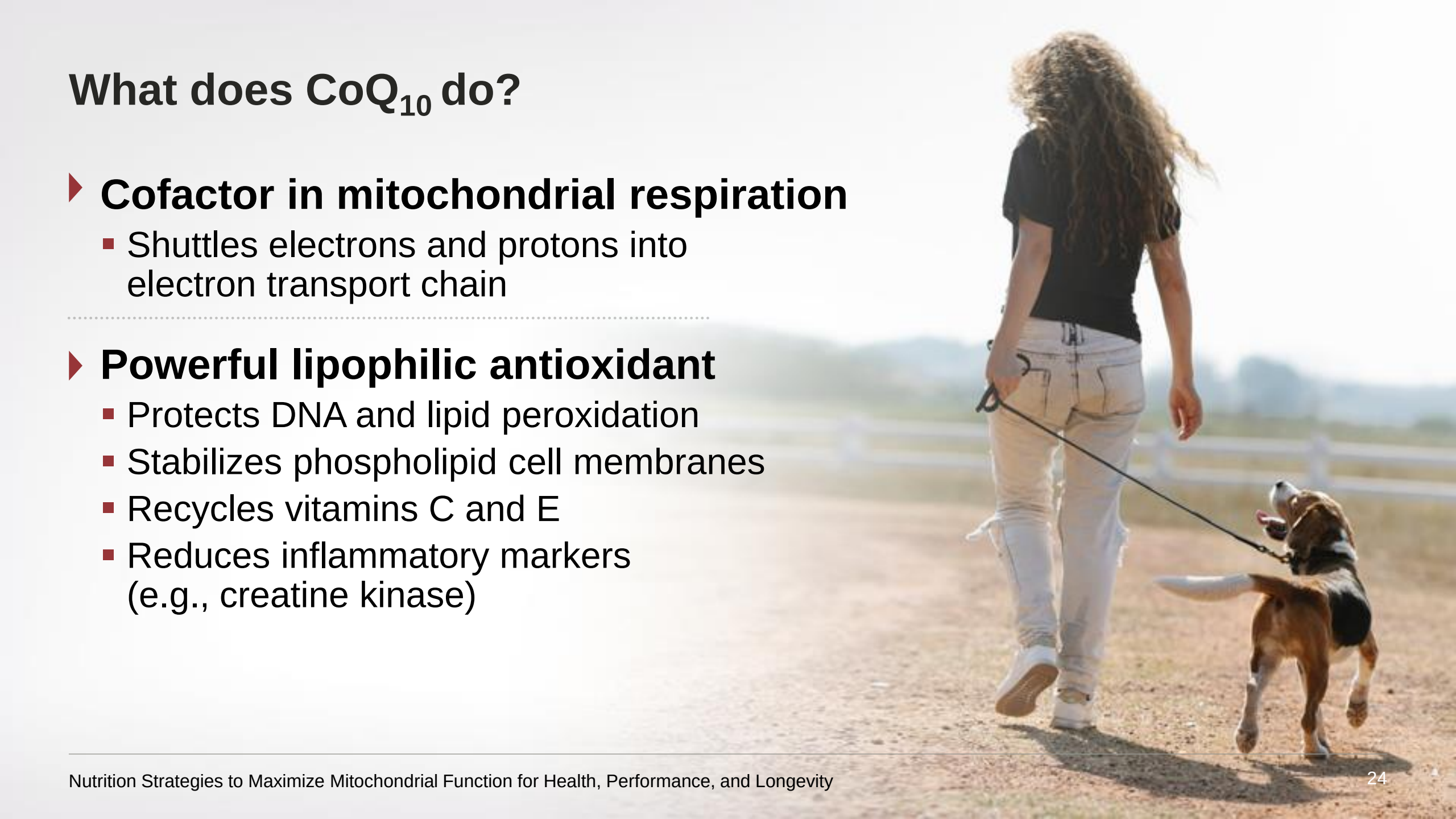
What is CoQ_{10}?

- Only lipid-soluble antioxidant produced in the body
  - Found in all subcellular compartments in various quantities across tissues
  - All cells except red blood cells have the capacity to manufacture it
- Approx. 50% of CoQ10 found in mitochondria
- Transported in blood as ubiquinol bound to LDL and VLDL



What does CoQ_{10} do?

- **Cofactor in mitochondrial respiration**
  - Shuttles electrons and protons into electron transport chain
- **Powerful lipophilic antioxidant**
  - Protects DNA and lipid peroxidation
  - Stabilizes phospholipid cell membranes
  - Recycles vitamins C and E
  - Reduces inflammatory markers (e.g., creatine kinase)



Supplementation with CoQ_{10} in humans has shown:

Benefits for patients with dyslipidemia

Reduced triglycerides and total cholesterol, increased HDL

Benefits for patients with hypertension & COPD

Direct effect on endothelium with improvement of smooth muscle activity & reduced inflammation

Benefits for patients with chronic heart failure & myocardial infarction

Reduced rate of major adverse events

Supplementation with CoQ_{10} in humans has shown:

Benefits for patients with non-alcoholic fatty liver disease

Reduced levels of AST and GGT, TNF-α, & hs-CRP

Potential benefits for patients with neurodegenerative conditions

- **Reduced oxidative stress**
- **Poor diffusion through BBB in animal models**

Potential benefits for athletes

- **Anti-inflammatory activity could benefit highly active**
  - No benefit observed in moderately active or sedentary
- **Anti-inflammatory effect would be protective and aid recovery, not directly benefitting performance**

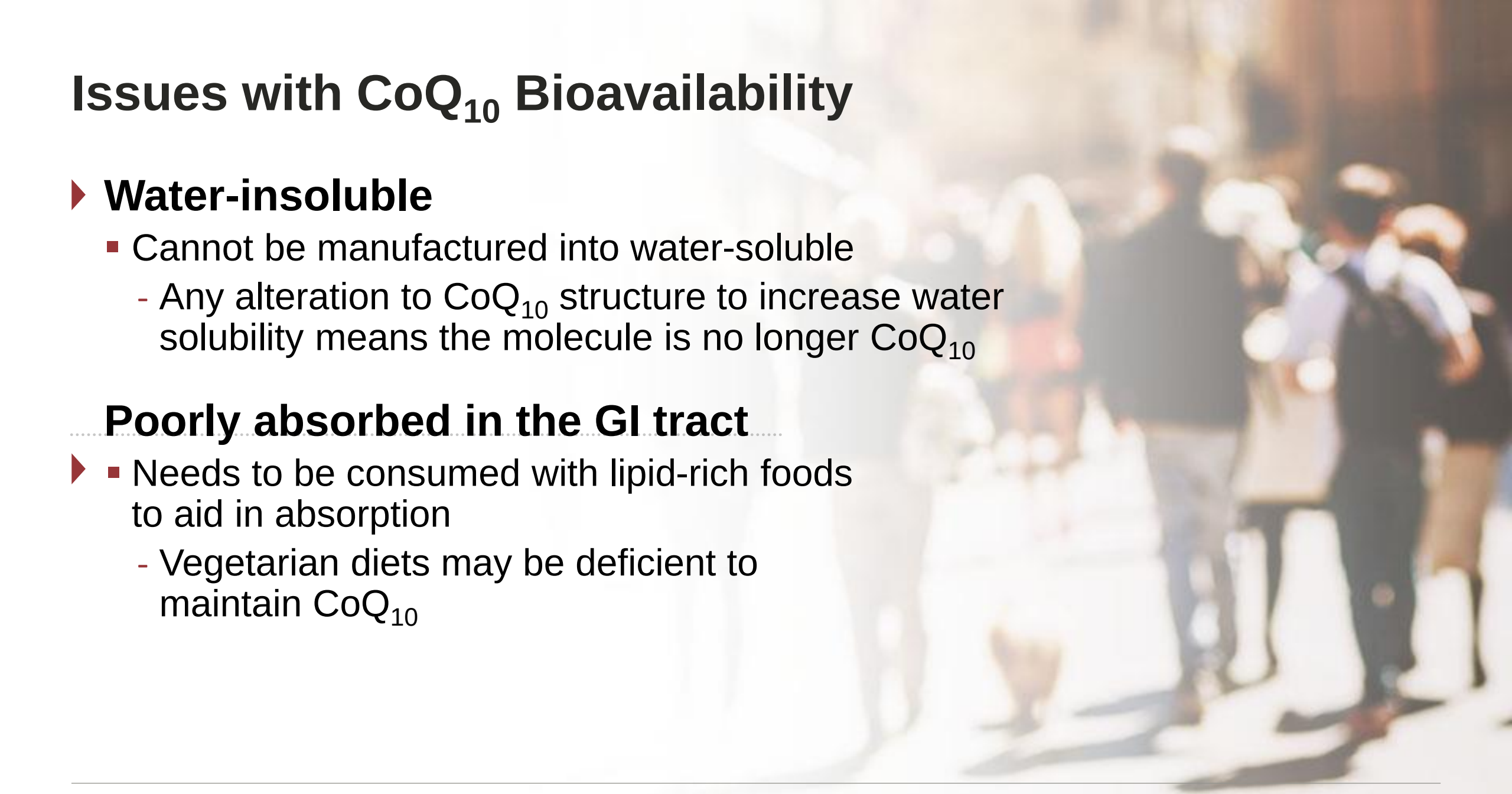
Supplementation with CoQ_{10}

- **Ubiquinone used more often in RCTs**
- **Ranges in studies from 100 to 1200mg/day**
  - Some studies suggest 2400mg divided into 3 doses throughout the day for those who are deficient
- **Estimated daily requirement from endogenous or exogenous sources is 500mg**
  - Based on average turnover time of 4 days in tissue
  - Approx. 5mg ingested from food per day

Issues with CoQ_{10} Bioavailability

- **Water-insoluble**
  - Cannot be manufactured into water-soluble
    - Any alteration to CoQ_{10} structure to increase water solubility means the molecule is no longer CoQ_{10}

- **Poorly absorbed in the GI tract**
  - Needs to be consumed with lipid-rich foods to aid in absorption
    - Vegetarian diets may be deficient to maintain CoQ_{10}



Issues with CoQ_{10} Bioavailability

CoQ_{10} can only be absorbed in GI tract as individual molecules

- Uptake pathway begins with emulsification and micelle formation with fatty components of food
- Raw CoQ_{10} is manufactured as crystals and cannot be absorbed in that state
    - Crystals must be dissociated into individual molecules
- Not all CoQ_{10} manufacturers have demonstrated that they have achieved this dissociation
- Without crystal dispersion to individual molecules, bioavailability reduced to 75%

3

Urolithin A

- Singh A., et al. *Euro J Clin Nutr*. 2022.
- Andreux PA, et al. *Nature Metabolism*. 2019.
- Liu S et al. *JAMA Network Open*. 2022
- Singh A, et al. *Cell Rep Med*. 2022

What is Urolithin A?

- **A naturally occurring postbiotic produced by gut microbiome after eating certain precursor foods**

- **Precursors = ellagitannins**
  - Pomegranates, berries & nuts

Natural Urolithin A Production

Does occur

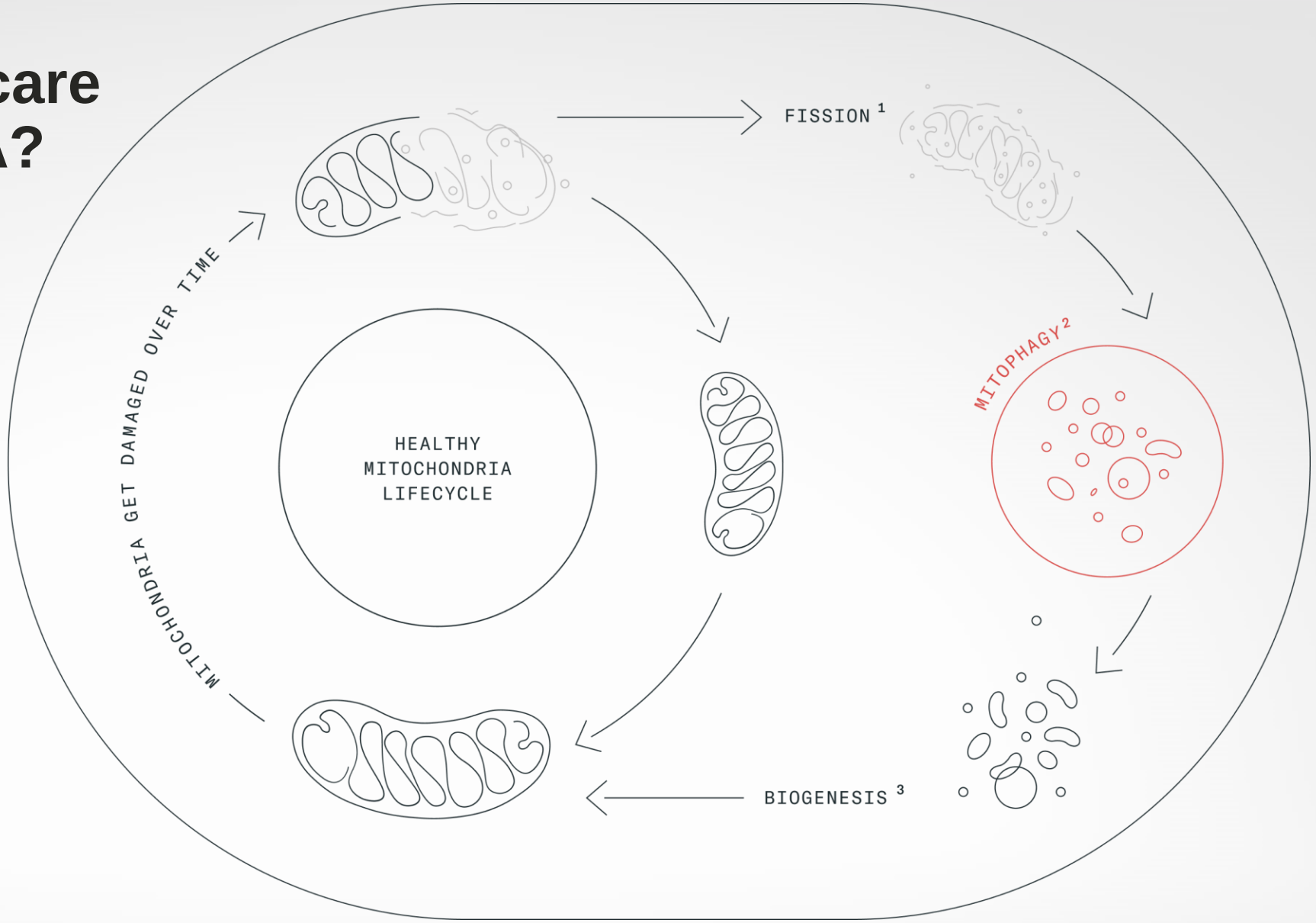
because the gut transforms ellagitannins into urolithins, hence why urolithin A is a post-biotic.

However…

… only 30-40% people produce Urolithin A in meaningful quantities after eating ellagitannins.

Why should we care about Urolithin A?

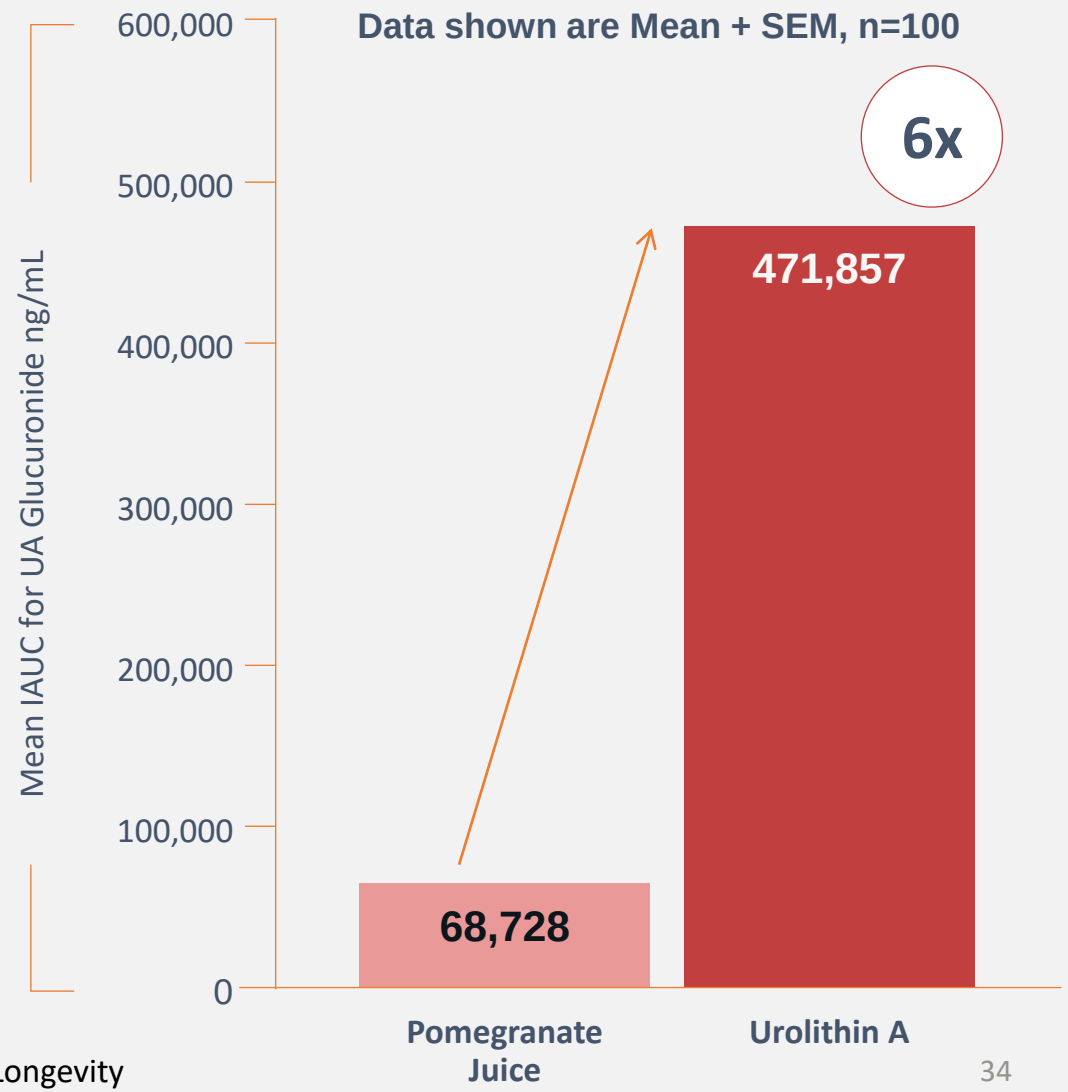
- **Stimulates mitophagy process**
  - Dysfunctional mitochondria are recycled & repackaged into new, healthy mitochondria



Supplementation with Urolithin A in humans has shown:

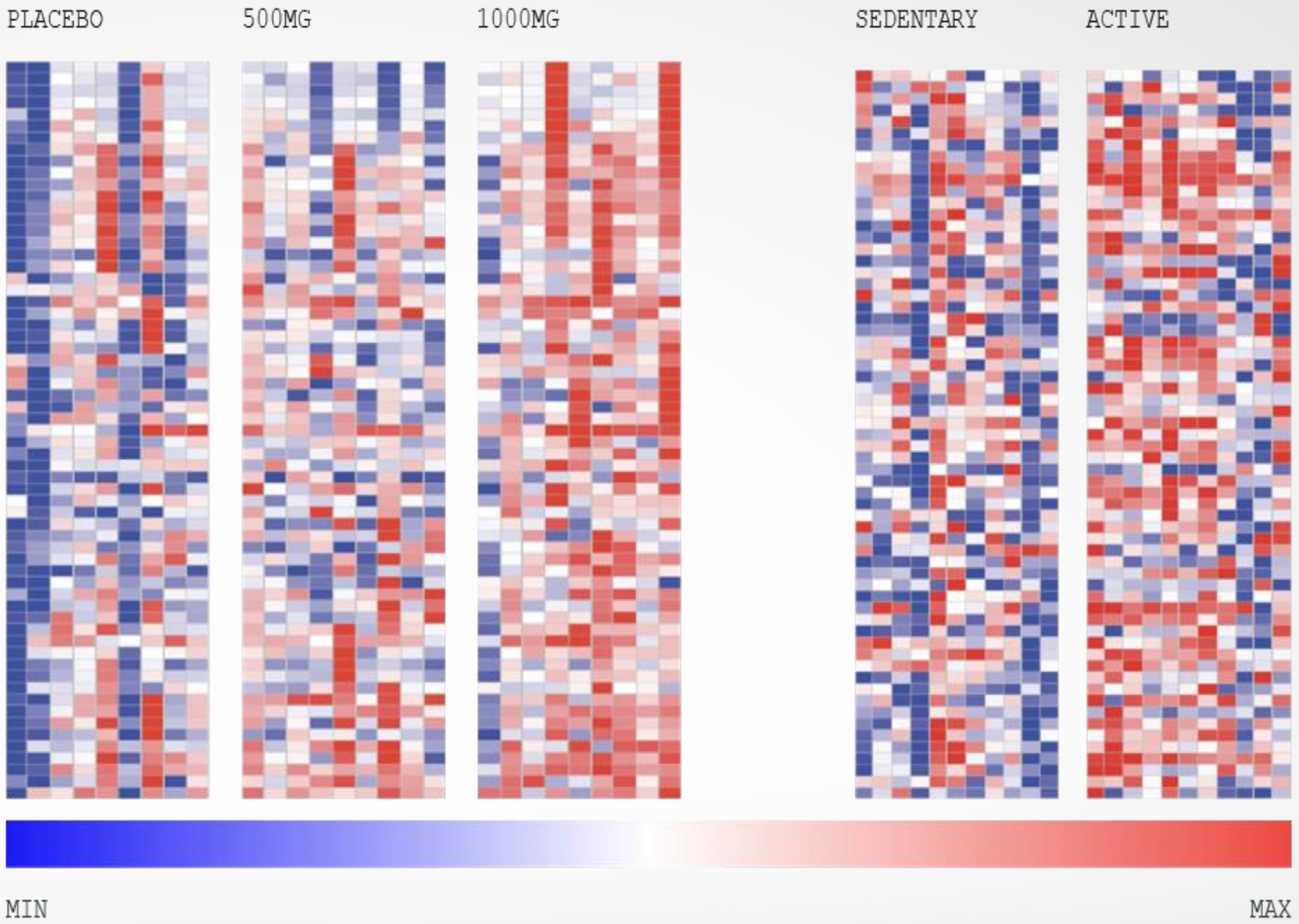
- A way to circumvent the issue of ellagitannin bioavailability and provide 6x more urolithin A into the blood stream than pomegranate juice consumption

Pomegranate juice =
31g sugar per 8oz glass



Supplementation with Urolithin A in humans has shown:

- Mitochondrial gene expression similar to aerobic exercise regimens

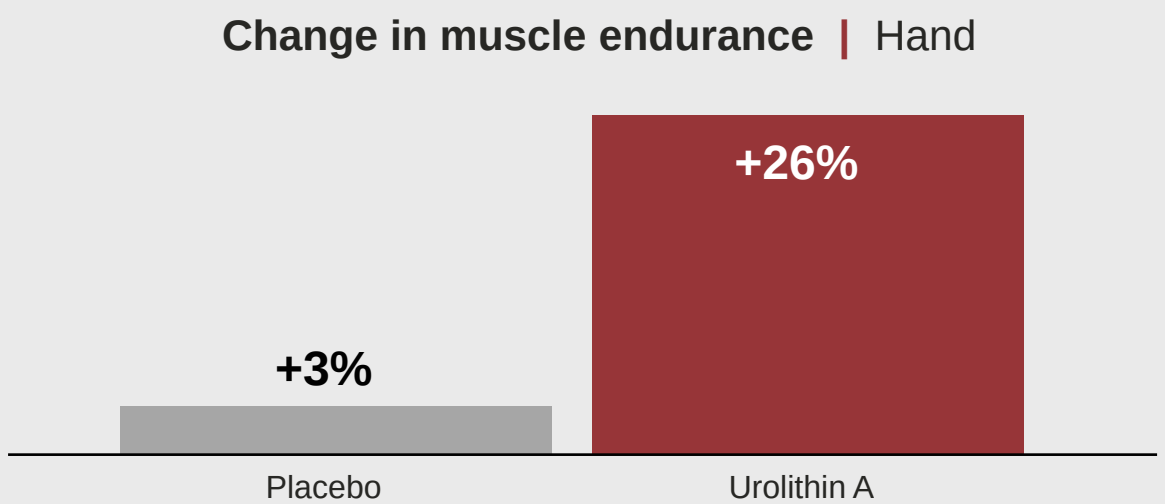


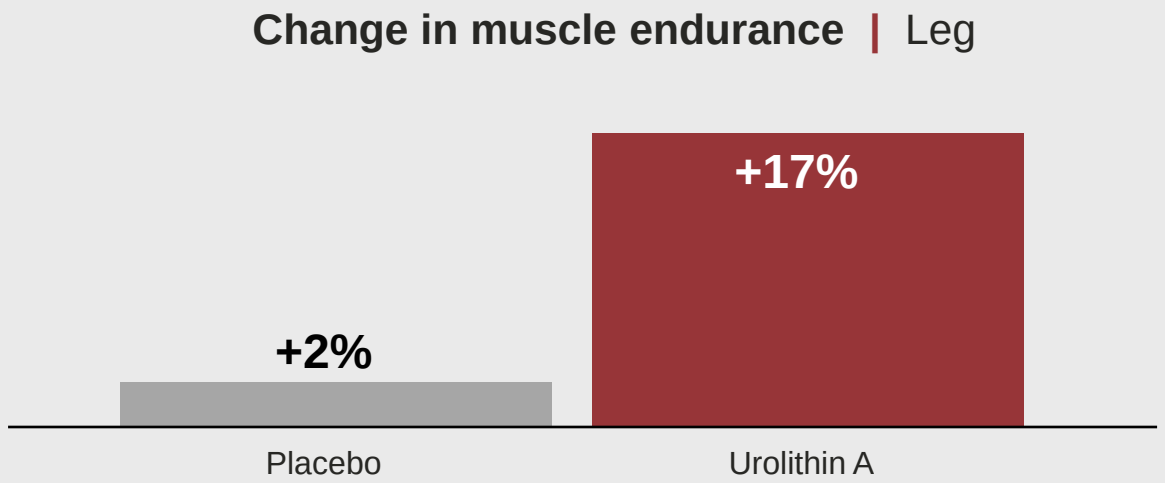
Heatmap represents genes that are the most significantly changed by the treatment within the GO_MITOCHONDRION genset

Supplementation with Urolithin A in humans has shown:

- Increased muscle endurance up to 17% (leg) and 26% (hand) after 8 weeks in older adults

- Increased muscle strength (leg) by up to 21% after 16 weeks in middle-age adults





Supplementing with Urolithin A

500mg per day

No upper limit established

Plateau of benefits seen at 1000mg per day

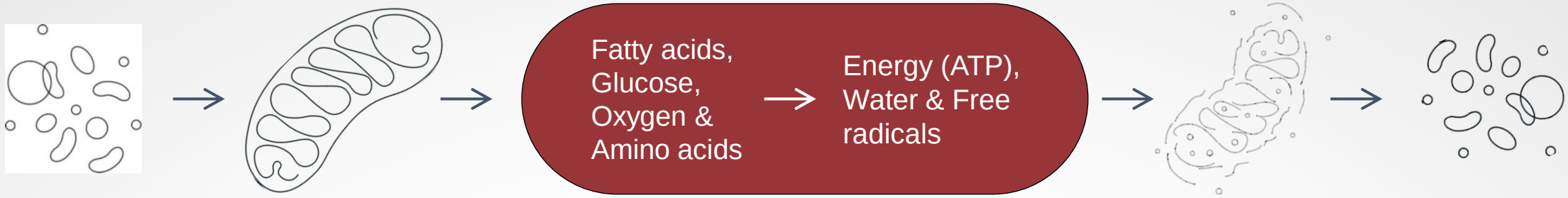
Should be taken at consistent time of day

Can be morning, afternoon, or night

Can be taken fasted or fed

Soft gel, food extract powders, protein powder

Nutritional Options for Mitochondrial Bioenergetics



	Biogenesis	Energy Production	Mitophagy
Pathways to Target	Creation of new mitochondria	Optimal functioning of mature mitochondria	Clearance of damaged mitochondria
Nutrition-Based Bioactives	**Urolithin A** **NMN**	**CoQ10**	**Urolithin A**

Conclusion

1

Mitochondrial decline & dysfunction are hallmarks of muscle loss and aging

2

Keeping the mitochondria healthy for as long as possible is key to longevity

3

Appropriate diet, exercise, & supplement strategies can aid in mitochondrial health quest

4

Future research should continue to investigate the impact of mitochondrial health supplements to unlock the key to ameliorate the aging process

Thank you!