Metabolic Health and Longevity in an Aging Population

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Overview

- Metabolic disease as a cause and consequence of aging
- Longevity predictors that act through metabolic health
  - Why favourite longevity markers may be largely about metabolic health
- Metabolic health as a risk multiplier
- Disease-specific outcomes with a slight brain bias

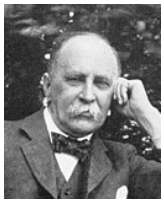
2

What is aging?

- Candle theory
  - Direct correlation between birthday candles and mortality risk
- Evolutionary theories
  - Antagonistic pleiotropy, disposable soma, developmental
- Damage/epigenetic based theories
  - Free radical/oxidative, DNA damage, (replicative) senescence, inflammaging, loss of information (epigenetic drift)

3

How did medicine historically think about aging?

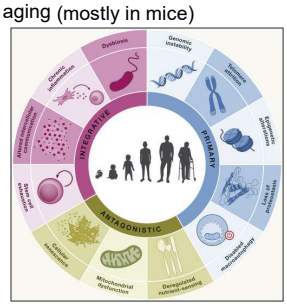


"The real work of life is done before the fortieth year… after the sixtieth year [men are] useless."
- Sir William Osler, Founder of Johns Hopkins Hospital

4

Can we measure aging?

- "Hallmarks" of aging (mostly in mice)

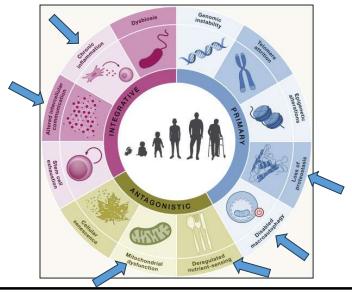


López-Otín et al., Cell 2023

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Many of the hallmarks of aging are metabolic

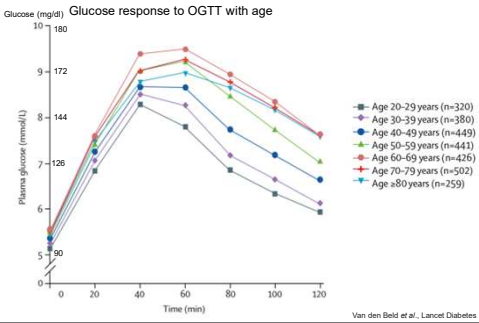
- "Hallmarks" of aging



López-Otín et al., Cell 2023

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Metabolic Health Declines with Age… If you Survive

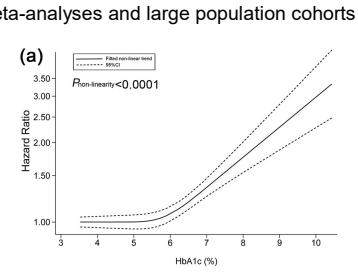


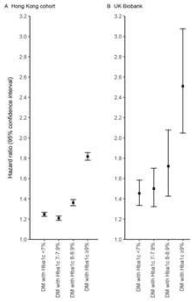
Van den Beld *et al.*, Lancet Diabetes Endocrinol. 2018

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(pre)diabetic HbA1c predicts mortality

- Meta-analyses and large population cohorts

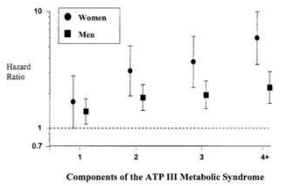




Zhong *et al.*, Sci Rep 2016; Guembe *et al.*, Cardiovasc Diabetol 2020

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MetS dose-response and CVD risk



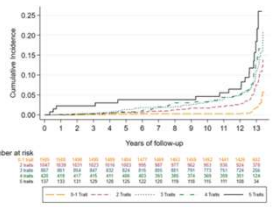


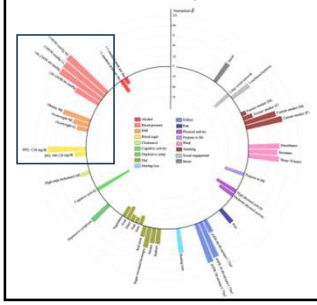
Fig. 2 Kaplan–Meier estimates of the cumulative incidence of primary endpoint events—myocardial infarction, stroke, or mortality from cardiovascular causes—according to the number of metabolic syndrome traits (0–1 trait, 2 traits, 3 traits, 4 traits, and 5 traits) in the Rivana cohort (n = 3976)

McNeill *et al.*, Diabetes Care 2005; Guembe *et al.*, Cardiovasc Diabetol 2020

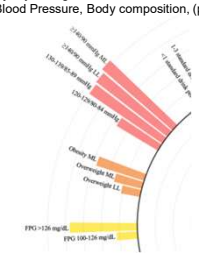
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Metabolic risk factors and brain-related disability

- 182 meta-analyses in dementia, stroke, and depression



Majority of largest risk factor are metabolic:
- Blood Pressure, Body composition, (pre)diabetes, CKD



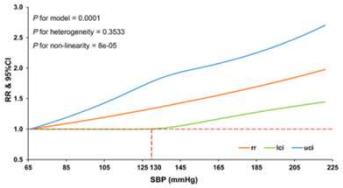
Seriff *et al.*, J Neurol Neurosurg Psychiatry 2025

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A large proportion of dementias may be preventable

- The Lancet commission estimates 45% (potentially conservative)
  - Projected to be 1st or 2nd highest cause of death by 2030
- Two of the most important risk factors are metabolic
  - Hypertension, (pre)diabetes

SBP and cognitive disorders:
- Meta-analysis of >2.2M people

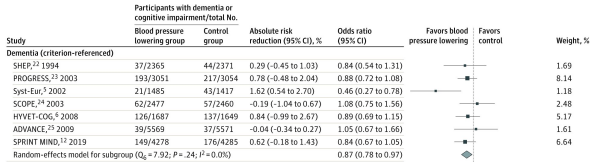


Livingston et al., Lancet 2024; Ou *et al.*, Cog Disord 2020

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Treating hypertension decreases dementia risk

- Meta-analysis of antihypertensive RCTs

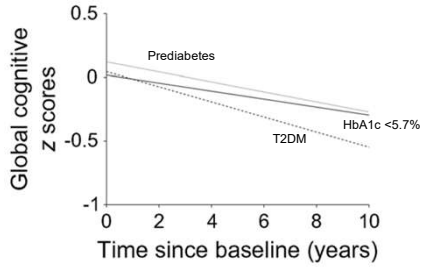


Hughes et al., JAMA 2020

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Diabetes, prediabetes and cognitive decline

- English Longitudinal Study of Ageing

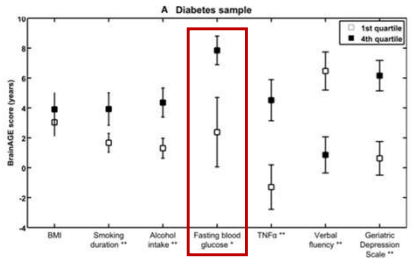


- Adjusted for age, sex, education, and 15 health status metrics

Zheng *et al.* Diabetologia 2018

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Blood glucose and BrainAge

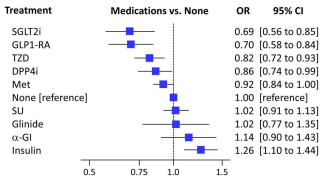


Franke and Gaser. Front Neurol 2019

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Type 2 Diabetes increases dementia risk

- Meta-analysis of 40 population studies
  - HR for dementia 1.53 (95% CI 1.38-1.70) in those with T2DM
- Network meta-analysis of observational studies and Rx RCTs
  - Likely driven by degree of glycemic control

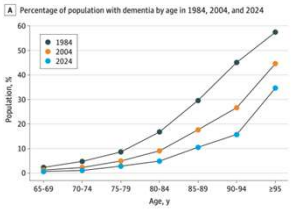


Nguyen et al., Alz Res Ther 2026; Ou *et al.*, Cog Disord 2020

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Evidence that we can move the needle

- Age-specific incidence of dementia is *decreasing*
  - Meta-analysis of several US and European cohorts
  - Thought to be due to major focus on preventing heart disease



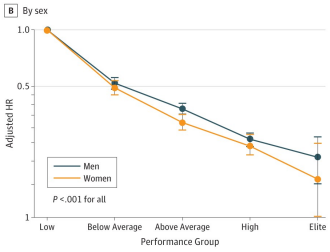
	Meta-analysis (random-effects)
All-cause dementia	0.87 (0.81–0.93)
Alzheimer disease	0.84 (0.76–0.92)

Wolters *et al.*, Neurology 2020; Stallard *et al.*, JAMA 2025

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Can we predict aging in humans?

- VO_2Max often considered "best" longevity predictor

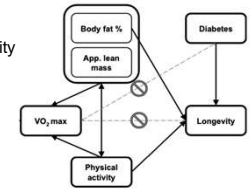


Mandsager *et al.*, JAMA Open Network, 2018

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VO_2Max is a proxy of metabolic health and activity

- Once you adjust for physical activity a lot of the signal disappears
  - 45-day longer life on average for each unit increase in VO_2Max
- 70,000 people in UK Biobank
  - VO_2Max not associated with longevity
- People with higher VO_2Max:
  - Are less sedentary
  - Are less likely to be obese
  - Have more muscle

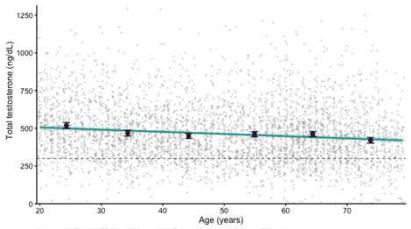


Mandsager *et al.*, JAMA Open Network, 2018; Jayedi *et al.*, Sports Med 2022

18

Does aging decrease testosterone in men?

- 3,791 men aged 20–79 in four NHANES cycles (2011–2023
  - Testosterone by gold-standard LC-MS/MS, morning draws only
- Average 15.1 ng/dL (−20.5 to −9.7 ng/dL) per decade decrease

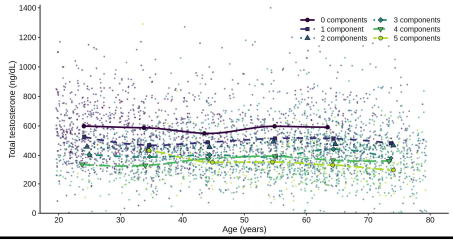


House et al., *Submitted*

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Testosterone remains stable within MetS groups

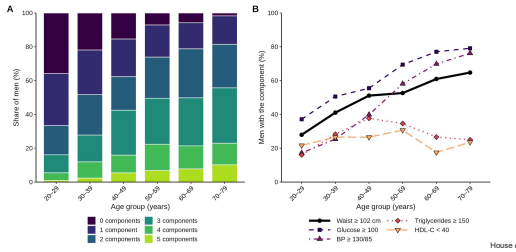
- Largest differentiator is number of MetS components
  - 40-60 ng/dL lower per component
  - Abdominal obesity has largest effect



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Is lower T with age a metabolic health signal?

- Testosterone is stable with age within MetS categories
- MetS categories become more common with age

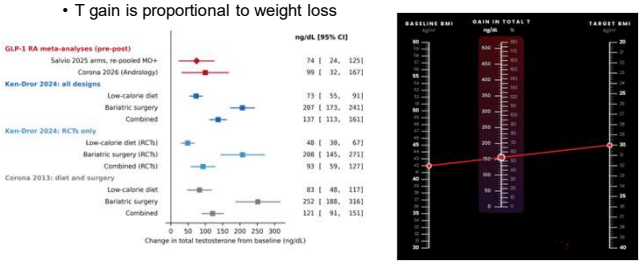


House et al., *Submitted*

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Losing weight increases T

- Aggregation of 5 meta-analyses
  - T gain is proportional to weight loss

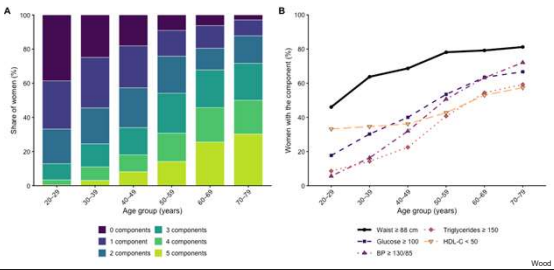


House, Galpin, Wood *Unpublished*

22

All MetS components increase with age in women

- Parallel analysis in 4,789 women form same NHANES cohorts

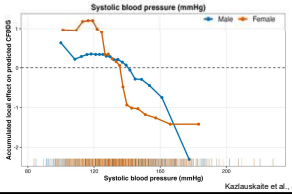


Wood *Unpublished*

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MetS accelerates cognitive changes in menopause

- Women with MetS experience accelerated decrease in processing speed during menopause
  - Primary cognitive risk factor for dementia
- Blood pressure inversely correlated with processing speed

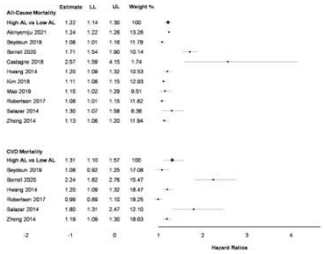


Kaziauskaite et al., J Clin Endocrinol Metab 2020; Abdilahi et al., *In Preparation*

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Chronic stress may accelerate aging

- Meta-analysis of of 17 cohort studies
  - High allostatic load associated with increased all-cause and CVS mortality

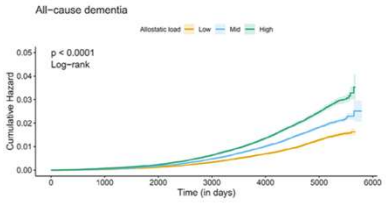


Parker *et al.* Am J Prev Med 2022

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Allostatic load acts through metabolic health

- Metabolic health indicators as proxies of allostatic load
  - Metabolic disease
    - High blood sugar, blood pressure, waist circumference, cholesterol
  - Increased inflammation (CRP)

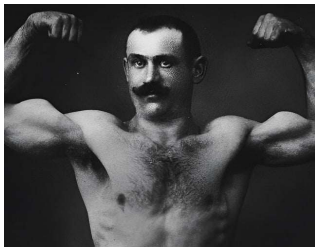


Gou *et al.* Alzheimer's & Dementia 2025

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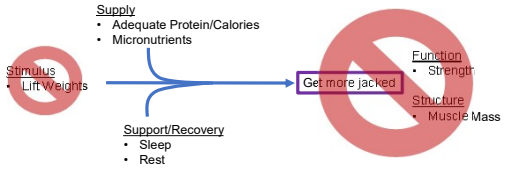
Attempts at some unifying ideas

- Help from the first neuroscientist's hobby



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A simplified model of jackedness

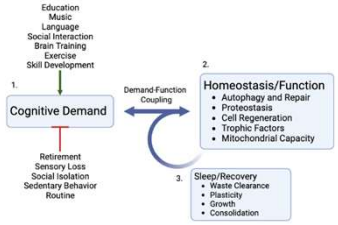


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Demand-function coupling

- The function of a tissue is determined by the stimulus
  - Same as with exercise and fitness/strength
- Similar across all stages of life



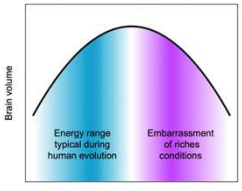


Turknett and Wood, Cells 2022

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The energy continuum as a critical regulator

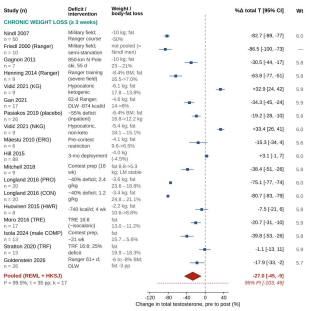
- Maintaining functions requires physiological/biological reserve
  - Aging is a terminal loss of capacity to adapt
  - Reserve predicts later function



Kaplan et al., PNAS 2023

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Weight loss results in low T if not overweight

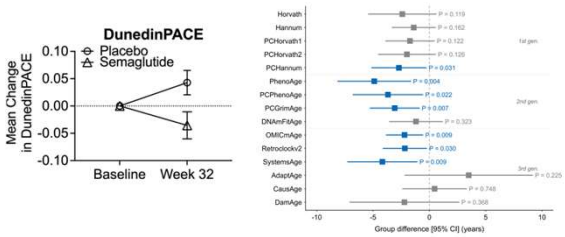


House, Galpin, Wood *Unpublished*

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Very early studies of GLP-1RAs and aging

- RCT of Semaglutide for HIV-associated lipodystrophy
  - Signal of slowed epigenetic aging across multiple biological clocks

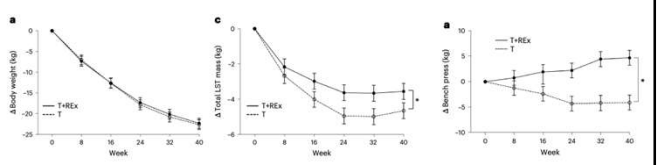


Corley et al., Nature Communications 2026

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"Lean mass" loss with GLP-1s

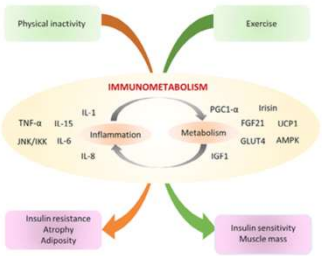
- Lean mass loss includes hepatic and intramuscular triglycerides
- Adding resistance training with tirzepatide
  - Same weight loss, but less muscle loss



Langer et al., Cell Rep Med 2026; Green et al., Nature Medicine 2026

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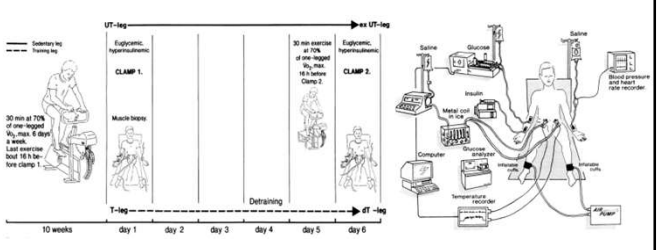
Muscle does all the anti-aging things



Mukund and Subramaniam 2020. PMID: 31407867

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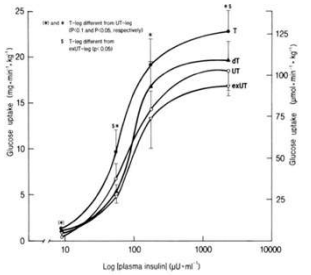
Exercise, muscle, and glucose uptake



Dela et al. 1992. PMID: 1476187

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Exercise, muscle, and glucose uptake

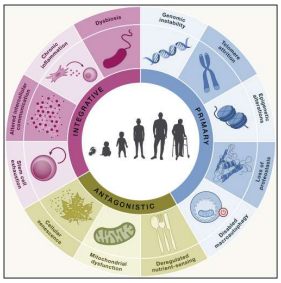


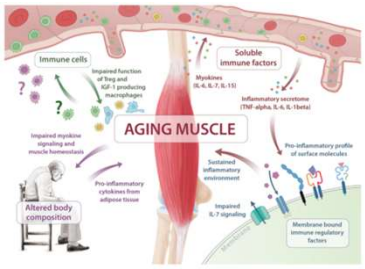
- More muscle + more movement = more glucose uptake

Dela et al. 1992. PMID: 1476187

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Exercise does all the anti-aging things

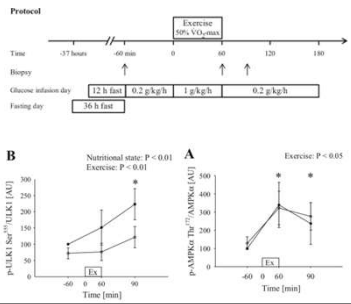




López-Otín et al. 2023; Rebelo-Marques et al. 2018

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Exercise and autophagy



- Exercise increased:
  - AMPK activation
  - Autophagy
- Not augmented by 36h of fasting
- Similar autophagy increase to 72h of fasting

Møller et al. 2015. PMID: 25678702
Vendelbo et al. 2014. PMID: 25020061

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Exercise and autophagy

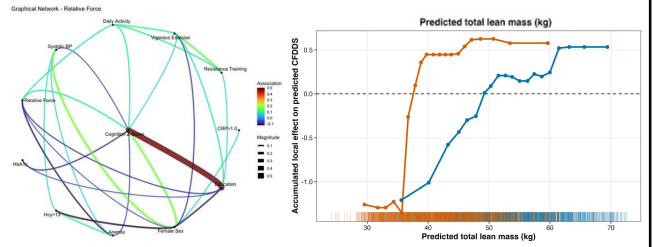
- Human studies show exercise >> fasting for autophagy
  - Largely in muscle tissue
  - Increases with increasing intensity
- Animal studies show exercise -> autophagy in peripheral tissue
  - Brain
  - Liver
  - Cardiac muscle

Schwalm et al. 2015. PMID: 25957282
Brandt et al. 2018. PMID: 29626392
He et al. 2012. PMID: 22258505
He et al. 2012. PMID: 22892563
Chun et al. 2018. 28419000

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Activity and muscle predict processing speed

- Adults >65 y/o NHANES 1999-2023



Storopschuk et al., Lifestyle Medicine 2023; Abdilahi et al., *In Preparation*

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Summary

- Aging and metabolic disease are intricately linked
  - Cause and consequence?
- Tissue function is stimulus-driven
  - Stimulus counteracts many of the “hallmarks” of aging
  - Energetic state as a critical regulator
- Many predictors and risk factors act through metabolic health
- Aging-related risk factors are increasingly modifiable
  - Not life-extension, more prevention of life shortening

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Metabolic Health and Longevity in an Aging Population

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