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WELCOME

Thank you for coming

Today’s talk will
begin soon

Afterwards,
please come to see us at

Stand: B48

Pharma Nord Academy

Influencing sirtuin enzymes

for healthier ageing

Lorraine Nicolle MSc (Nutr.)

Today's Speaker

Lorraine Nicolle

MSc (Nutr.), PGCHE, BA (hons), Dip. CIM, Dip. BCNH

- Registered Nutritionist (MBANT)
- Registered Nutritional Therapist (CNHC)
- Functional Medicine and Healthy Ageing Specialist
- In clinical practice for 20+ years
- Higher education teacher (nutrition science & practice)
- Author/editor of several nutrition books
- Accredited clinical supervisor and mentor for nutrition practitioners

What we're covering today

1. A look at biological age and how it is measured
2. Mechanisms by which sirtuins can slow biological ageing: focus on SIRT1
3. How nutrition may influence SIRT1
4. Evidence from human trial data and how to make use of this in clinical practice

What do we mean by ***biological* age?**

Ageing is a multifactorial process that results in a progressive functional decline of cells, tissues and organs

- *Average* ***chronological*** age has increased significantly over the last few decades
- But how many of those years are spent *in* ***good health?***
- This is more associated with ***biological* age**

How is biological age **measured?**

Not by the number of years of life, but by:

- **Functional tests** like physical ability and strength tests
- **Anthropometric** and body composition data (Muscle mass, BMI, W:H ratio, etc)
- '**Biomarkers**' that reveal the health of your cells, tissues and organs (e.g. HbA1c, eGFR, ApoE, hsCRP…)

Using such data, one person may have a body and brain that is deemed **healthier** (less 'worn out') than another person of the same **chronological** age

‘The 12 Hallmarks of Ageing’

- If your cells and body systems are in better condition than the average for your **chronological** age, you are said to have a **younger biological** age
- To get a healthier quality of life in your later years, you need to aim for a younger biological age
- In the quest to understand and influence the rate of biological ageing, scientists have started focusing on ‘**12 hallmarks of ageing**’

‘The 12 Hallmarks of Ageing’

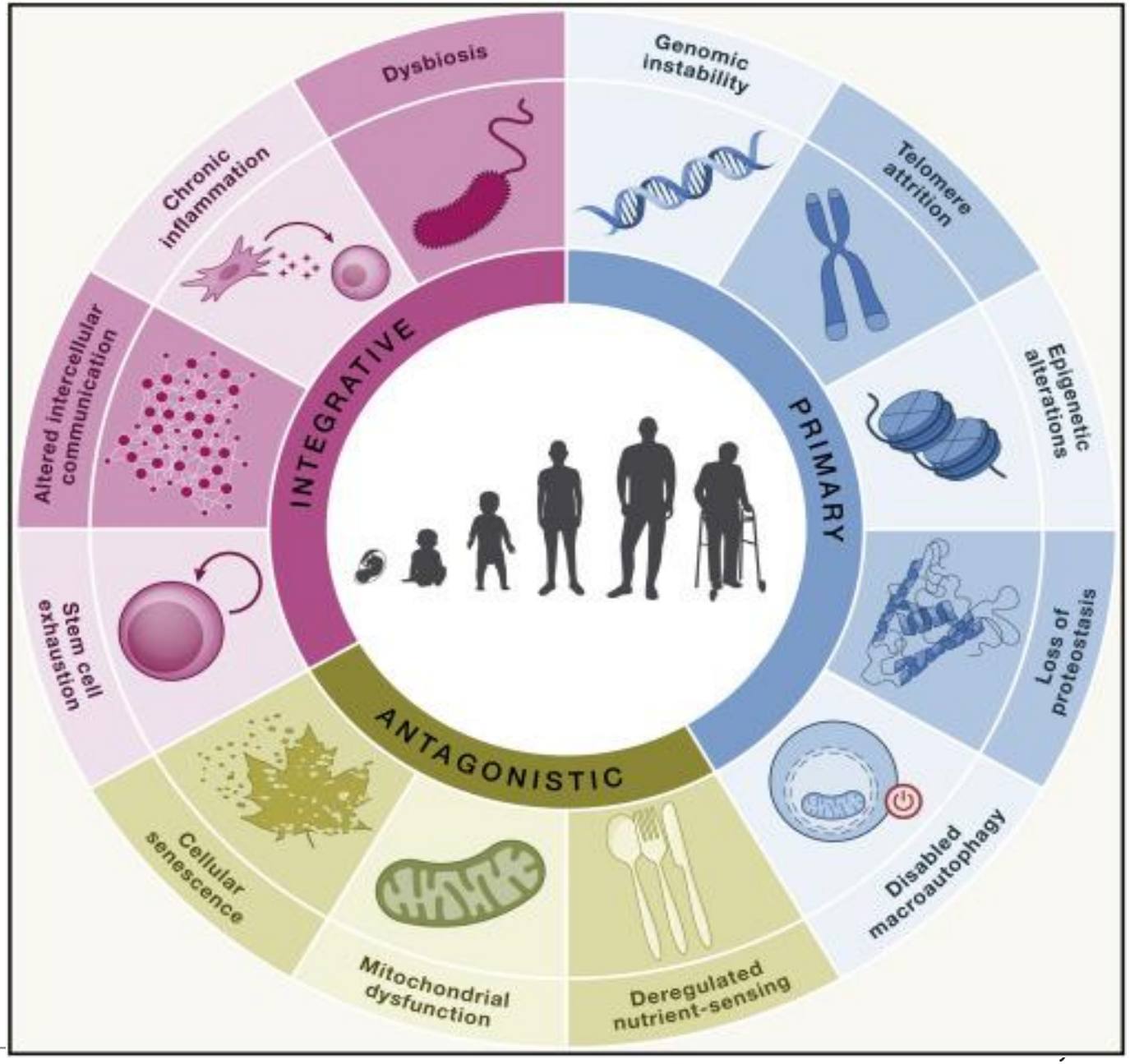
- Described in a paper published last year in the journal *Cell*
- They were identified because they:
  - Tend to increase as we get older
  - Tend to *accelerate* ageing when they are accentuated in experiments
  - Can slow down ageing when therapeutic interventions attenuate them

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of ageing: An expanding universe. Cell. 2023 Jan 19;186(2):243-278.

The primary hallmark (that drives many of the others) is…

Epigenetic alterations

- (We will discuss all these in our full day seminars from September)
- In the meantime…



López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of ageing: An expanding universe. Cell. 2023 Jan 19;186(2):243-278.

Enter the sirtuin enzymes – central to epigenetic alterations

Sirtuins are *'silent information regulator proteins'*

- A group of enzymes known as histone deacetylases (HDACs)
- They remove acetyl groups from histones (and also from other proteins)
- This changes the way DNA (and proteins) work: see next slide

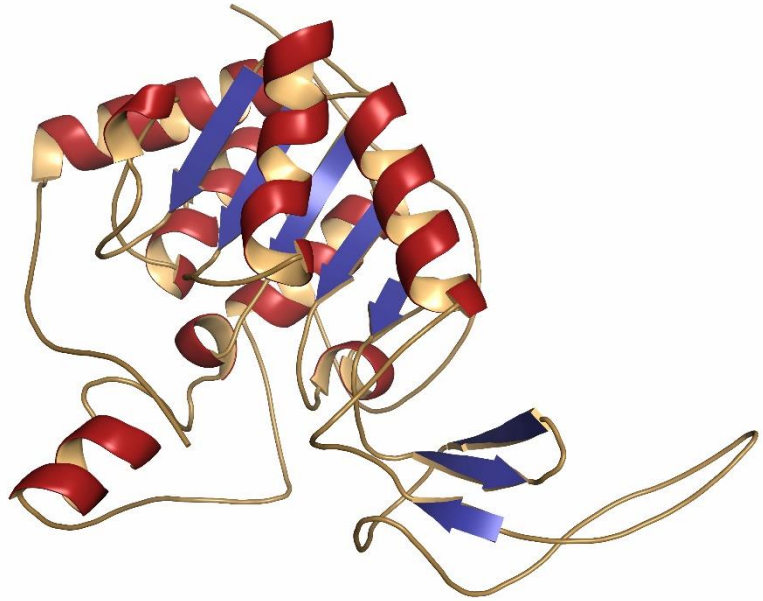


***Image**: Sirtuin 6 (SIRT6)*

Zhao L, Cao J, Hu K, He X, Yun D, Tong T, Han L. Sirtuins and their Biological Relevance in ageing and Age-Related Diseases. ageing Dis. 2020 Jul 23;11(4):927-945. doi: 10.14336/AD.2019.0820. PMID: 32765955; PMCID: PMC7390530.

Sirtuins alter **gene expression**

- HDACs allow histones to wrap the DNA more tightly – they condense the DNA, making less of it available for expression – hence **sirtuins can silence genes that can drive cell dysfunction and premature ageing**
- This is an ‘epigenetic’ change to a gene, as it changes the *function* but not the *structure* of the DNA

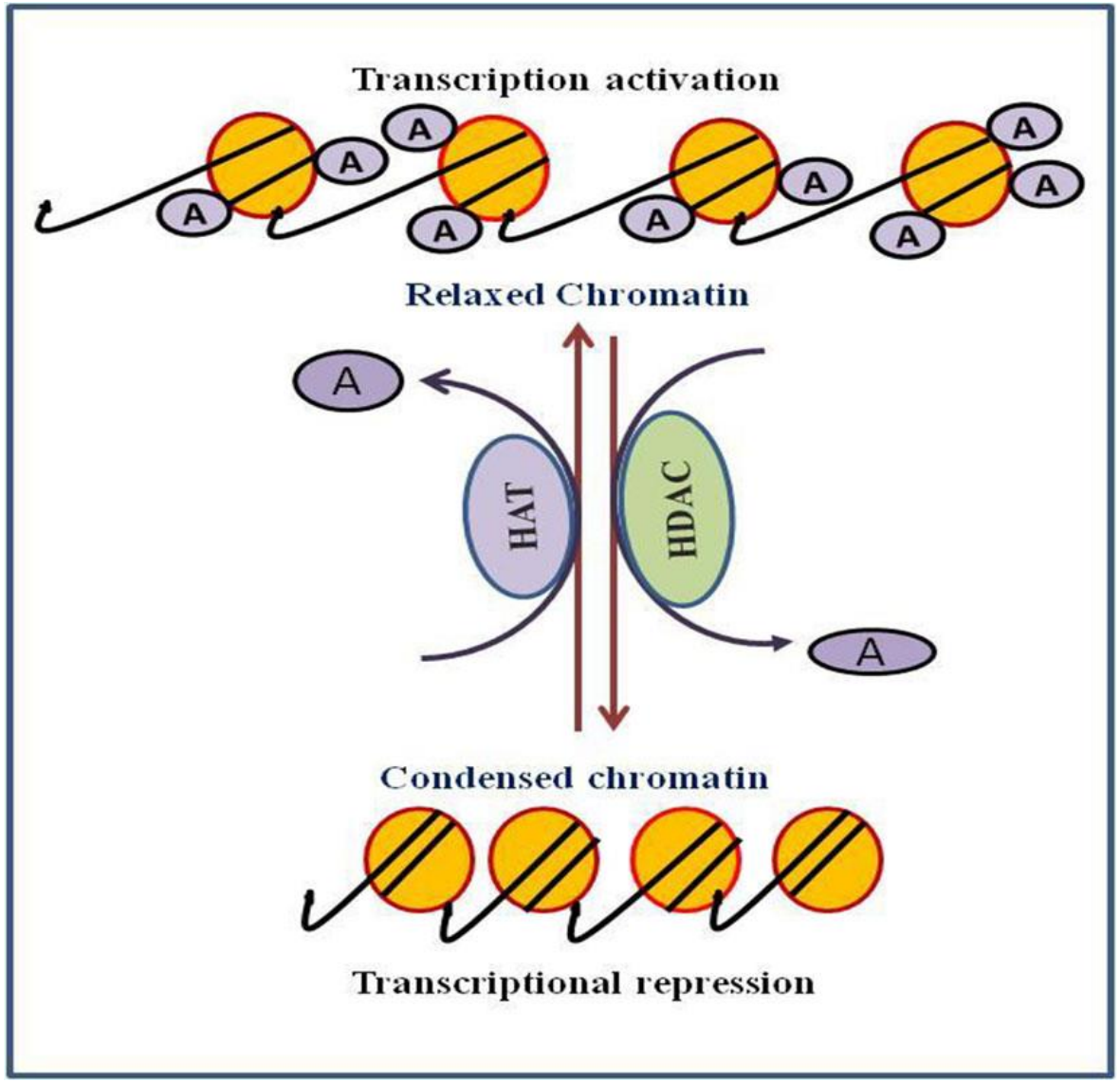


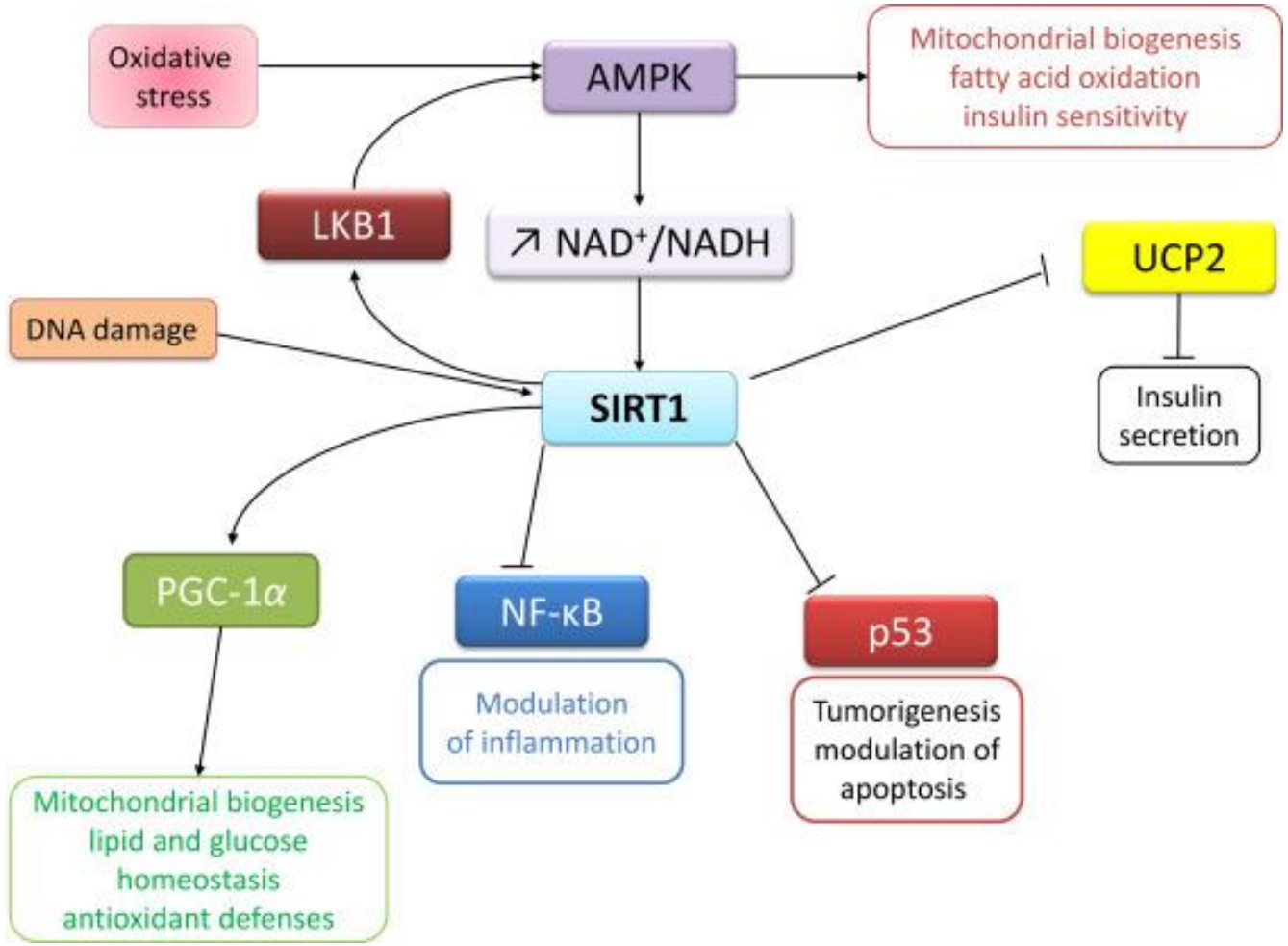
Image: Shukla S, Tekwani BL. Histone Deacetylases Inhibitors in Neurodegenerative Diseases, Neuroprotection and Neuronal Differentiation. Front Pharmacol. 2020 Apr 24;11:537. doi: 10.3389/fphar.2020.00537. PMID: 32390854; PMCID: PMC7194116.

SIRT 1

- Because sirtuins can turn off unhelpful / unneeded genes at the right time, they impact many of the hallmarks of ageing in a positive way
- There are seven types of sirtuins in humans (Sirt1-7) and they have a great many functions related to healthy ageing
- We will focus here on SIRT1: Increasing SIRT1 activity in yeast, worms and animals leads to increased lifespan

SIRT1 influences many body functions

- Regulates many age-related signalling pathways (e.g. NF-κB, AMPK, mTOR, P53, PGC1α, and FoxOs), resulting in healthier…
- …mitochondrial biogenesis and mitophagy, redox state, inflammation, apoptosis…



Gagnière J and Bonnet ((2017). Molecular Mechanisms Underlying the Actions of Antioxidant Molecules in Digestive Disorders. In Oxidative Stress and Dietary Antioxidants. Pgs 197-216. Academic Press

Summary so far

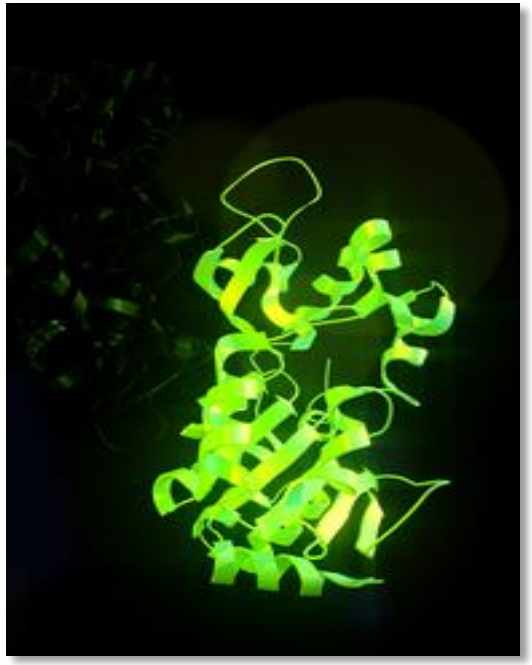
- SIRT1 is a HDAC that reduces expression of certain genes (and proteins)
- It plays an important role in healthy ageing because…
  - … it regulates ageing-related signaling pathways in mitochondrial function, autophagy, inflammation, oxidation, apoptosis, etc
- SIRT1 activation has been shown to extend lifespan and health span in yeast, worms and mice studies
- Sadly, SIRT1 function reduces as we age

Chen C, Zhou M, Ge Y, Wang X. SIRT1 and aging related signaling pathways. Mech Ageing Dev. 2020 Apr;187:111215.

Why should integrative practitioners care about SIRT1?

- *Reduced* sirtuin activity has been shown to increase the risk of age-related diseases in animals and humans
- Clinical trials are starting for pharmaceutical SIRT1 activators
- SIRT1 seems to ***respond to nutrition***

So, if we can use nutrition to influence SIRT1, **could this improve the way we age?**



Zhao L, Cao J, Hu K, He X, Yun D, Tong T, Han L. Sirtuins and their Biological Relevance in ageing and Age-Related Diseases. ageing Dis. 2020 Jul 23;11(4):927-945, Image: AtikaAtikawa - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=86279124, Barbagallo F, La Vignera S, Cannarella R, Mongioì LM, Garofalo V, Leanza C, Marino M, Calogero AE, Condorelli RA. Obesity and Male Reproduction: Do Sirtuins Play a Role? Int J Mol Sci. 2022 Jan 16;23(2):973.

Interventions

What's the evidence?

Interventions

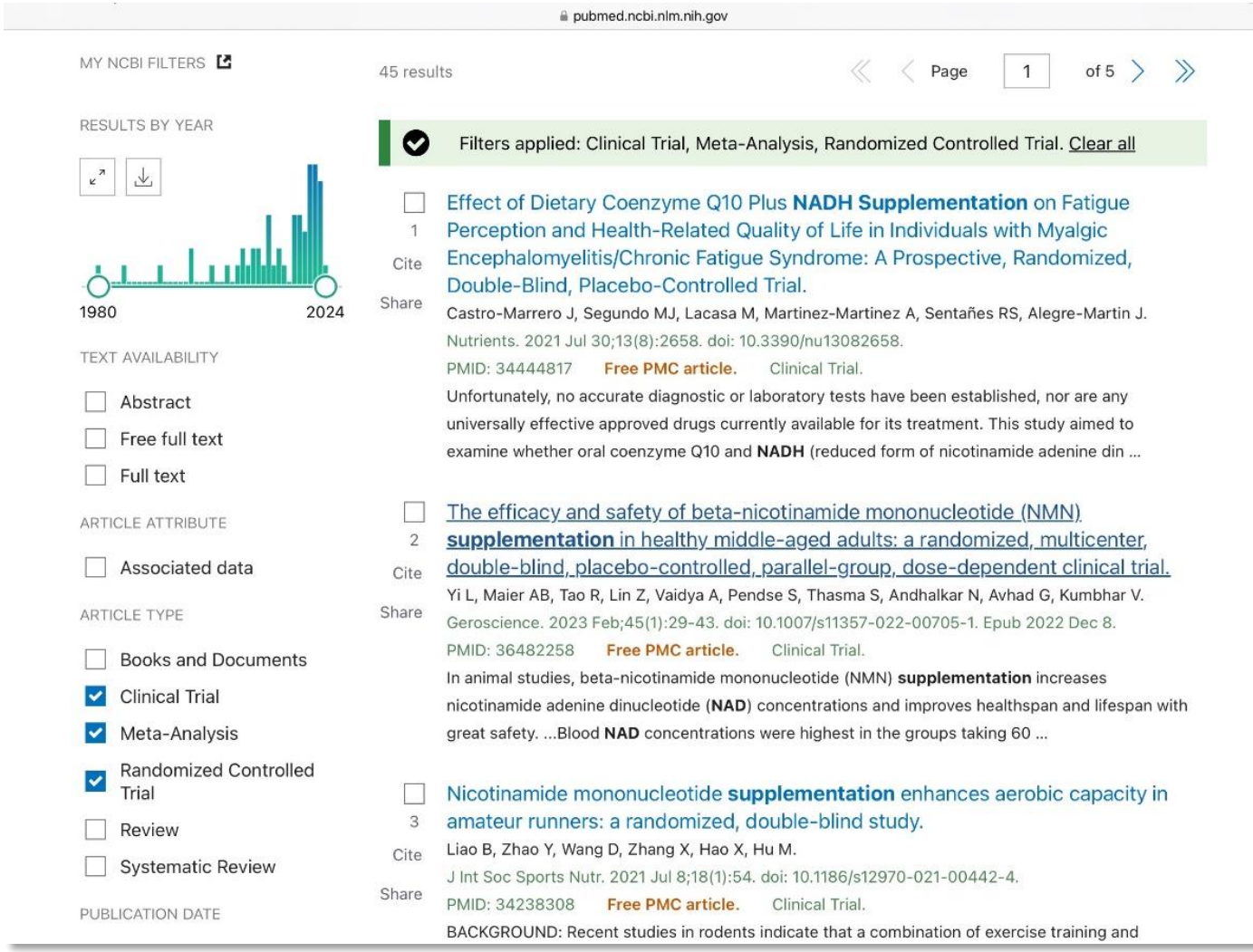
Weight; diet; modulating oxidation

- Obesity reduces SIRT1 activity – so get to work on this
- Exercise, calorie restriction, ketogentic diet and/or fasting can increase SIRT1
  - We will come back to dietary interventions for healthy ageing, including SIRT1 activation, in our full day seminars due to time constraints today
- Oxidative stress reduces SIRT1 activity, hence moderating this and supporting antioxidant functions has been proposed to support SIRT1

DiNicolantonio JJ, McCarty MF, O'Keefe JH. Nutraceutical activation of Sirt1: a review. Open Heart. 2022 Dec;9(2):e002171. Barbagallo F, La Vignera S, Cannarella R, Mongioì LM, Garofalo V, Leanza C, Marino M, Calogero AE, Condorelli RA. Obesity and Male Reproduction: Do Sirtuins Play a Role? Int J Mol Sci. 2022 Jan 16;23(2):973.

Interventions
NADH

- The reduced form of NAD+ (required by SIRT1 for function)
- 45 human trials and meta-analyses on Pubmed re. NADH supplementation in age-related and degenerative conditions



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Interventions

Plant bioactives

- Many phytochemicals have *in vitro* and animal evidence for increasing SIRT1:
  - curcumin, resveratrol, ellagic acid, quercetin, berberine, ferulic acid, urolithin A, astaxanthin, carnosic acid and neochlorogenic acid
- Some human data emerging, e.g. →

DiNicolantonio JJ, McCarty MF, O'Keefe JH. Nutraceutical activation of Sirt1: a review. Open Heart. 2022 Dec;9(2):e002171. doi: 10.1136/openhrt-2022-002171. PMID: 36522127; PMCID: PMC9756291,

Interventions

Plant bioactives

- In a 12-week RCT of 46 patients with NAFLD…
- ..randomized to take either 3g turmeric powder or placebo daily
  - SIRT1 levels increased significantly vs. controls
  - But no other biomarkers improved

- In an 8-week RCT of 44 adults with T2D (without obesity)…
- …randomized to take either ellagic acid (180 mg) or placebo,
  - SIRT1 increased significantly vs. controls
  - As well as HOMA-IR, fasting blood glucose and insulin

But still ***short-term*** *and* ***small-scale***

Kalhori A, Rafraf M, Navekar R, Ghaffari A, Jafarabadi MA. Effect of Turmeric Supplementation on Blood Pressure and Serum Levels of Sirtuin 1 and Adiponectin in Patients with Nonalcoholic Fatty Liver Disease: A Double-Blind, Randomized, Placebo-Controlled Trial. Prev Nutr Food Sci. 2022 Mar 31;27(1):37-44.

Ghadimi M, Foroughi F, Hashemipour S, et al. Decreased insulin resistance in diabetic patients by influencing Sirtuin1 and Fetuin-A following supplementation with ellagic acid: a randomized controlled trial. Diabetol Metab Syndr. 2021 Feb 5;13(1):16.

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Interventions:

Combination Selenium and Coenzyme Q10

- A much larger and longer study released last year showed that Se + Q10…
- … can increase **SIRT1** levels **in humans**…
- …protecting against **vascular ageing** and atherosclerosis

antioxidants

MDPI

Article

Increased SIRT1 Concentration Following Four Years of Selenium and Q_{10} Intervention Associated with Reduced Cardiovascular Mortality at 10-Year Follow-Up—Sub-Study of a Previous Prospective Double-Blind Placebo-Controlled Randomized Clinical Trial

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check for updates

Citation: Opstad, T.B.; Alexander, J.; Aaseth, J.; Larsson, A.; Seljeflot, I.; Alehagen, U. Increased SIRT1 Concentration Following Four Years of Selenium and Q_{10} Intervention Associated with Reduced Cardiovascular Mortality at 10-Year Follow-Up—Sub-Study of a Previous Prospective Double-Blind Placebo-Controlled Randomized Clinical Trial. *Antioxidants* **2023**, *12*, 759. https://doi.org/10.3390/antiox12030759

Academic Editor: Albino Carrizzo

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Revised: 2 March 2023
Accepted: 16 March 2023
Published: 21 March 2023

Abstract: *Background*: Selenium and coenzyme Q_{10} (SeQ_{10}) possess antioxidant and anti-inflammatory properties, potentially mediated via Sirtuin1 (SIRT1). We aimed to investigate the influence of a SeQ_{10} intervention on SIRT1 concentration, with potential interactions with microRNAs. *Methods*: In this sub-study of a prospective double-blind placebo-controlled clinical trial, healthy subjects (mean age 76 years) were randomized to receive an active treatment ($n = 165$, combined 200 µg/day of Se and 200 mg/day of Q_{10}) or a placebo ($n = 161$). SIRT1 concentration and microRNAs were measured with ELISA and PCR, respectively. *Results*: After four years, SIRT1 concentration was increased in the active treatment group, with mean (SD) ng/mL of 469 (436) vs. 252 (162), $p < 0.001$, and decreased in the placebo group, 190 (186) vs. 269 (172), $p = 0.002$, and the differences between the groups were significant ($p = 0.006$, adjusted). Those who suffered CV death during a 10-year follow-up ($n = 25$ and $n = 52$ in the active treatment and placebo groups, respectively) had significantly lower baseline SIRT1 concentrations compared to the survivors ($p < 0.001$). MiR-130a-3p was significantly downregulated during the intervention and correlated inversely with SIRT1 at baseline ($r = -0.466$, $p = 0.007$). *Conclusion*: The increased SIRT1 concentration after the SeQ_{10} intervention associated with reduced CV mortality, partly mediated via miR-1303a-3p, suggests that SIRT1 is an additional mediator of the intervention, preventing vascular ageing.

Keywords: sirtuin1; selenium; coenzyme Q_{10}; intervention; cardiovascular mortality

1. Introduction

It is now well accepted that an optimal supply of the essential trace element selenium (Se) has multiple health-promoting benefits, and supplementation may be beneficial in subjects with low Se levels [1–4]. With its anti-oxidative and anti-inflammatory effects afforded by a number of selenoproteins, Se has been shown to reduce the harm mediated by reactive oxygen species and to reduce inflammation [2,5,6]. Coenzyme Q_{10} (ubiquonone) is another known regulator of oxidative stress. Coenzyme Q_{10} is primarily present in the mitochondria and is a component of the electron transport chain but also acts as a

Opstad TB, Alexander J, Aaseth J, et al. Increased SIRT1 Concentration Following Four Years of Selenium and Q_{10} Intervention Associated with Reduced Cardiovascular Mortality at 10-Year Follow-Up-Sub-Study of a Previous Prospective Double-Blind Placebo-Controlled Randomized Clinical Trial. Antioxidants (Basel). 2023 Mar 21;12(3):759

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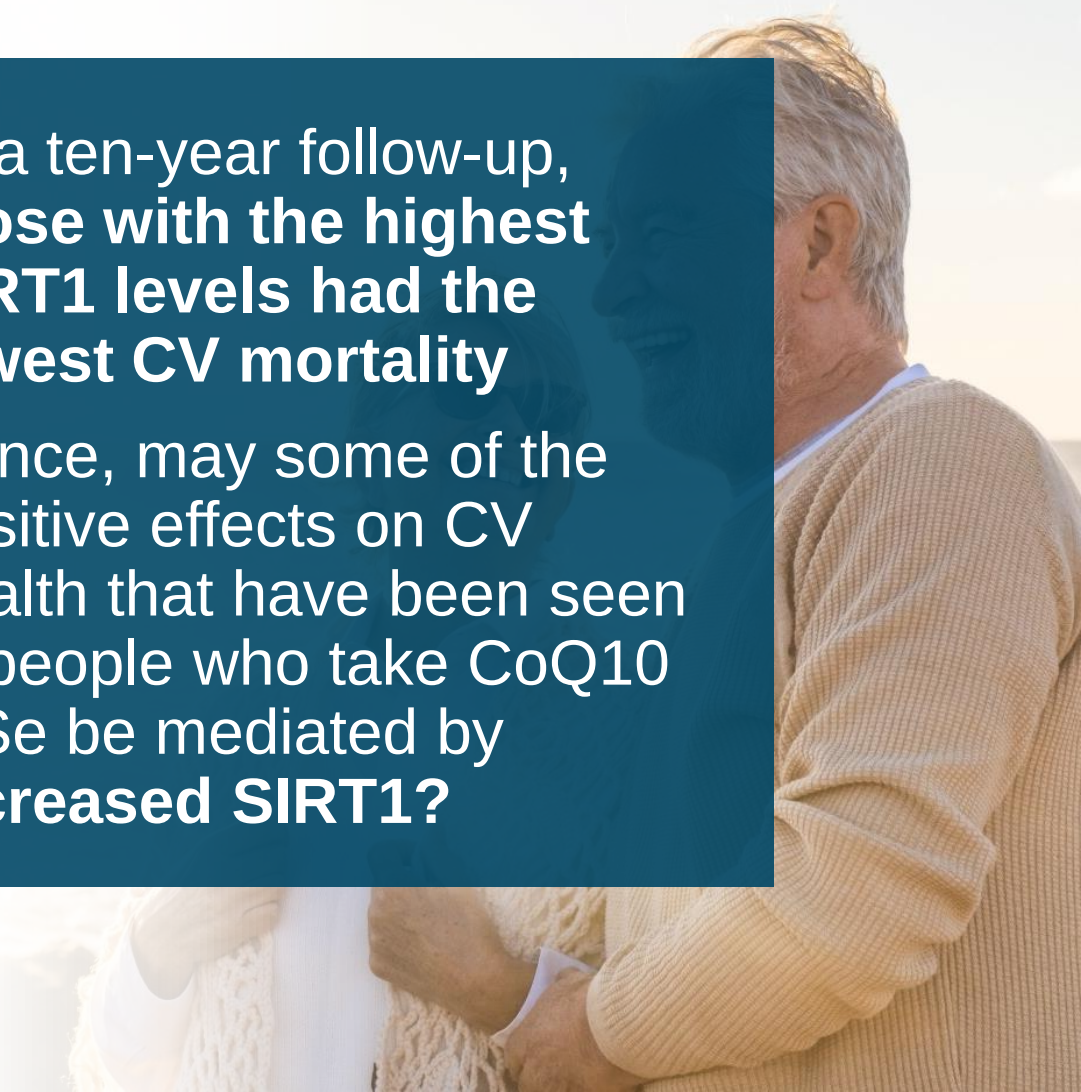
What this study was all about

- RCT of 326 men and women, where half took **CoQ10 (200mg) + Se (200mcg)** and the other half took a placebo, over a period of 4 years
- **SIRT1** levels in the active treatment group **increased** significantly, while levels decreased (also significantly) in the placebo group

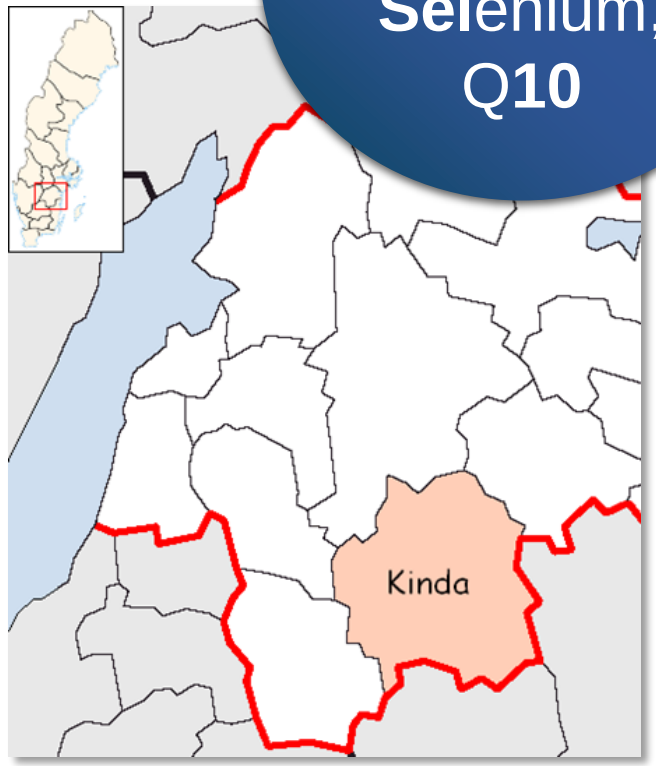
- At a ten-year follow-up, **those with the highest SIRT1 levels had the lowest CV mortality**
- Hence, may some of the positive effects on CV health that have been seen in people who take CoQ10 + Se be mediated by **increased SIRT1?**



Reduced risk of mortality

- This new study was undertaken by analyzing blood samples that the researchers had already taken from their earlier study, known as the KiSel-10 study (2012)
- KiSel-10 studied 443 healthy elderly participants over four years and concluded that the participants taking the Se + CoQ10 had a **54% lower cardiovascular mortality rate** compared with the placebo group

KiSel-10
Kinda
Selenium,
Q**10**

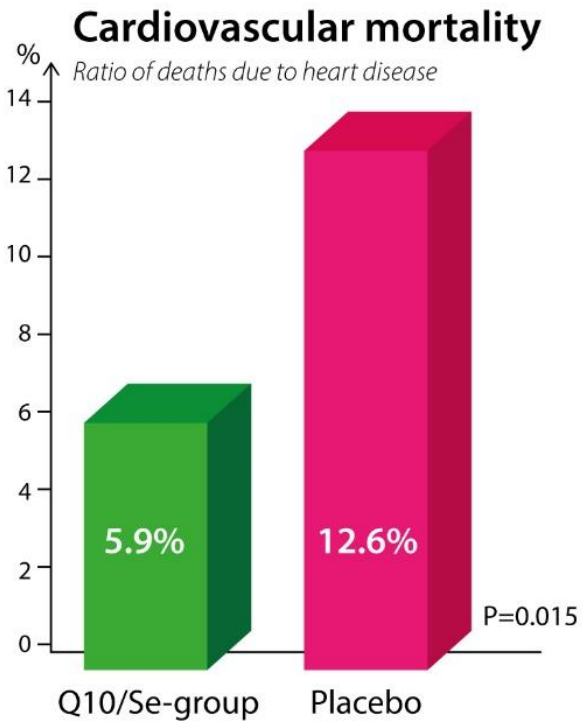


Alehagen U, Peter Johansson et al.:"Cardiocascular mortality and N-Terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: A 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. International Journal of Cardiology, 2012

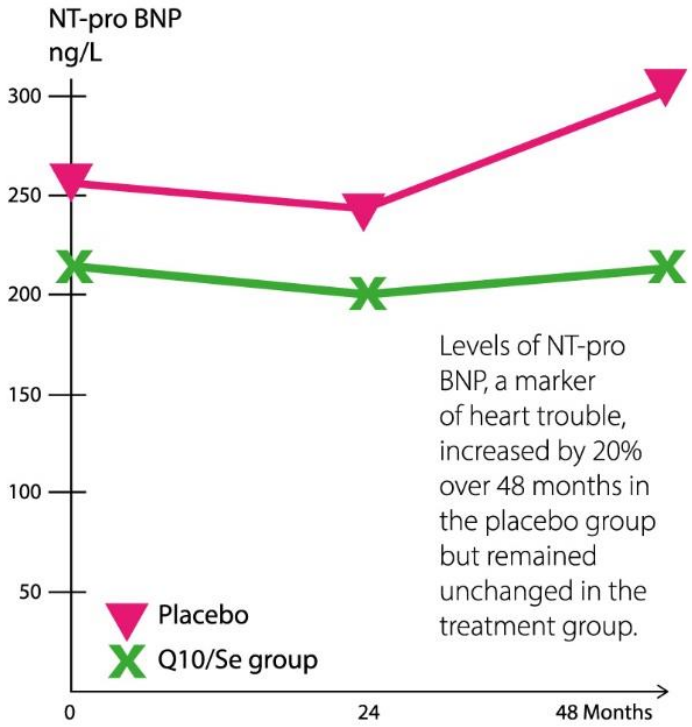
KiSel-10:

Results

- Those taking Q10 & Selenium experienced a 54% risk reduction of mortality
- Levels of the peptide NT-ProBNP remain unchanged over study period (a sign of cardiac wall tension / cardiac stress)



A significant reduction of cardiovascular mortality in the Q10/Se-group (5.9% vs. 12.6%: P=0.015).

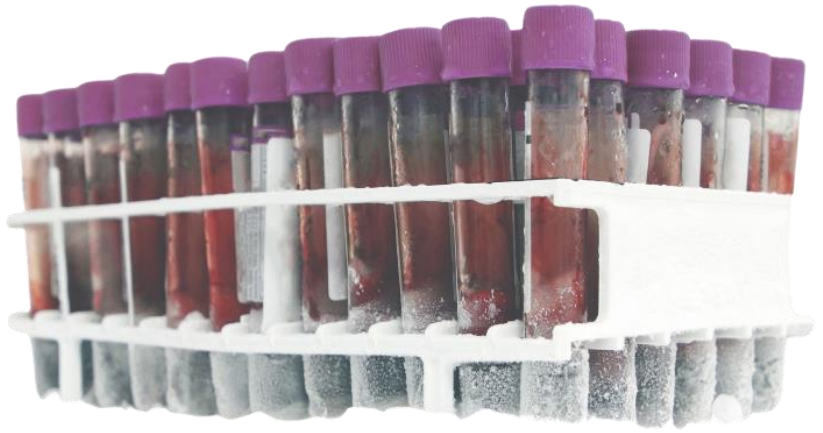


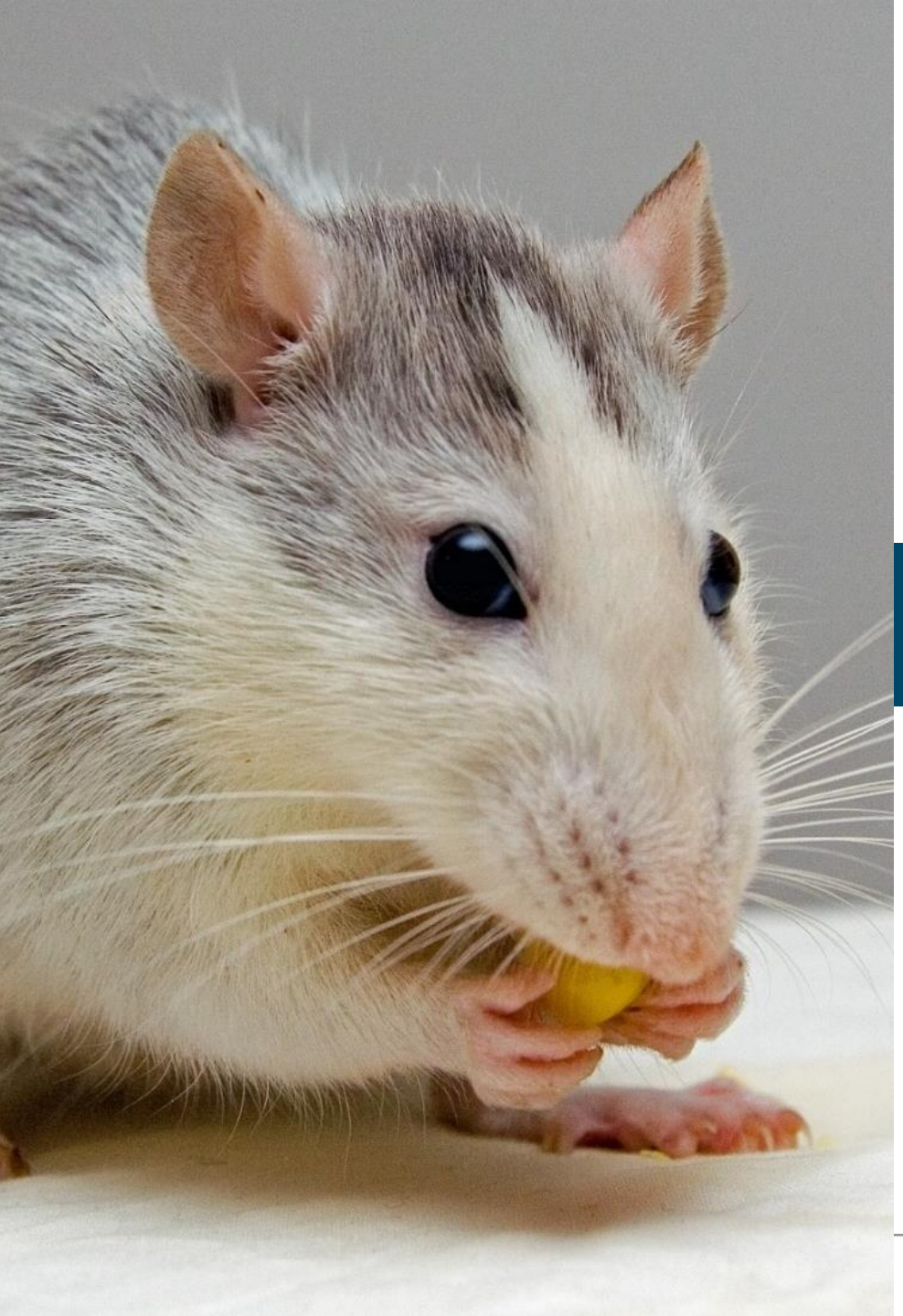
Alehagen U, Peter Johansson et al.:"Cardiocascular mortality and N-Terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: A 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. International Journal of Cardiology, 2012

The new (2023) study looked at *why* this happened

What were the *biological mechanisms?*

- The researchers analysed the huge number of blood samples they'd collected and were in deep freeze storage
- Found that that the participants who were more likely to have survived ten years after the original KiSel-10 trial, had **higher levels of SIRT1** at the end of the 4 years of supplementing the Se and CoQ10





Why is this study so important?

Many dietary supplements have plenty of animal data – But…

'A running joke among health researchers is that everything has been cured — in mice'

This study showed, *for the first time*, a benefit of Q10 + Se on SIRT1 to ageing humans living in the real world.

- And that the supplements were well-tolerated and were absorbed from the human gut in order to exert their positive action

Check Hayden, E. Misleading mouse studies waste medical resources. *Nature* (2014). https://doi.org/10.1038/nature.2014.14938

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SIRT1's relevance to cardiovascular health

- SIRT1 is highly active in endothelial cells
- But is very much reduced in the arteries of older people
- And tends to be lower in patients with more CVD and cerebrovascular dxs
- Lack of SIRT1 has been proposed as a *mediator* of CVD

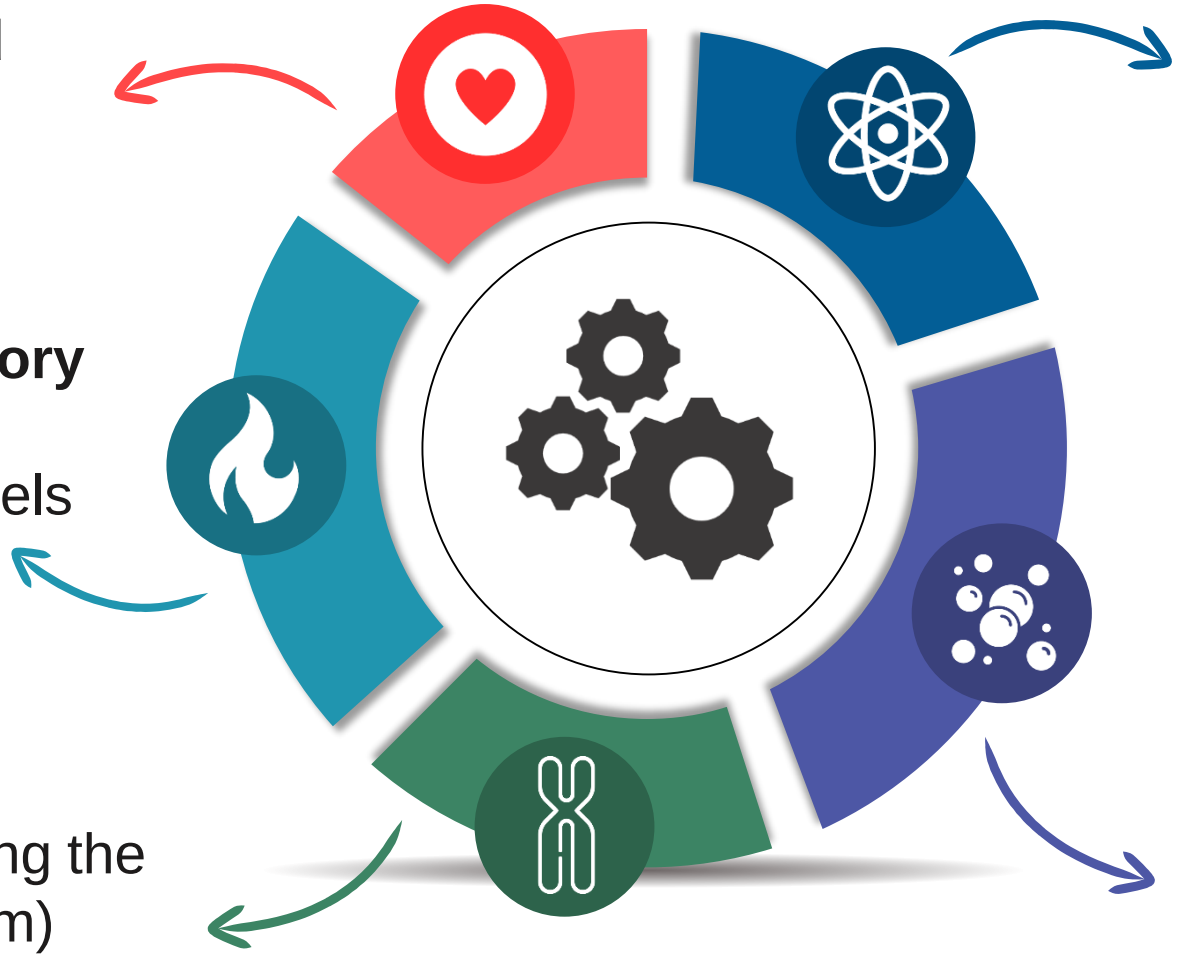
In this latest study:

- SIRT1 increased in the group taking CoQ10 + Se but decreased in the placebo group
- Those who suffered CV death during the 10-year follow-up had **significantly lower baseline SIRT1 levels compared to the survivors** (no matter whether they were in the treatment or placebo group)

Mechanisms of SIRT1 proposed by the researchers

Improved endothelial health via increased NO production

Increased antioxidant enzymes such as GPX1



Reduced inflammatory NF-kB in cells of the heart and blood vessels

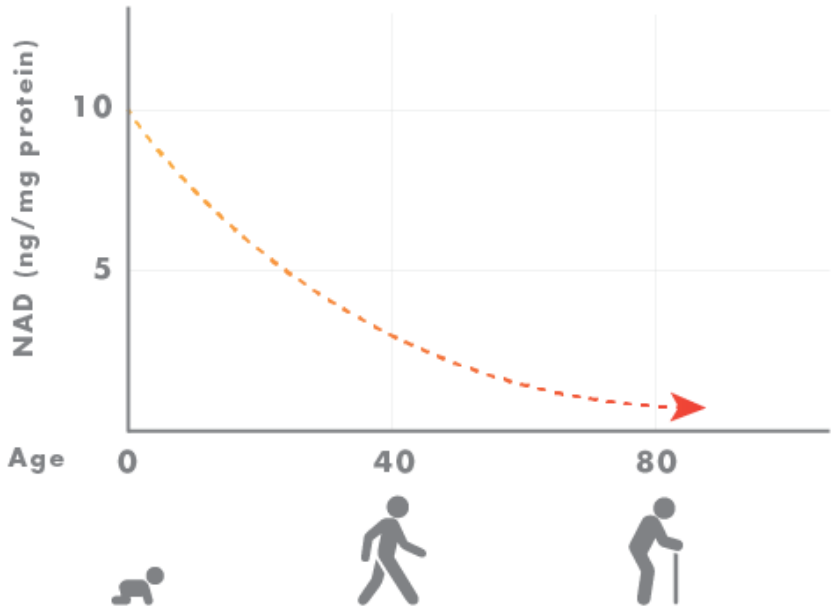
Suppressed formation of foam cells that cause arterial plaque

Prevented telomere shortening (stabilizing the DNA in the CV system)

(SIRT1 has been shown to reduce the uptake of oxidised LDL-c)

Exactly *how* do CoQ10 + Se increase SIRT1?

- SIRT1 requires **NAD+**
- Sadly, NAD+ synthesis reduces with age (see graph)
  - probably due to less efficient NAD+ salvaging enzymes
- However, Se-methylselenocysteine has been found to restore NAD+ levels
  - This is a selenoprotein found in food form Se including selenised yeast

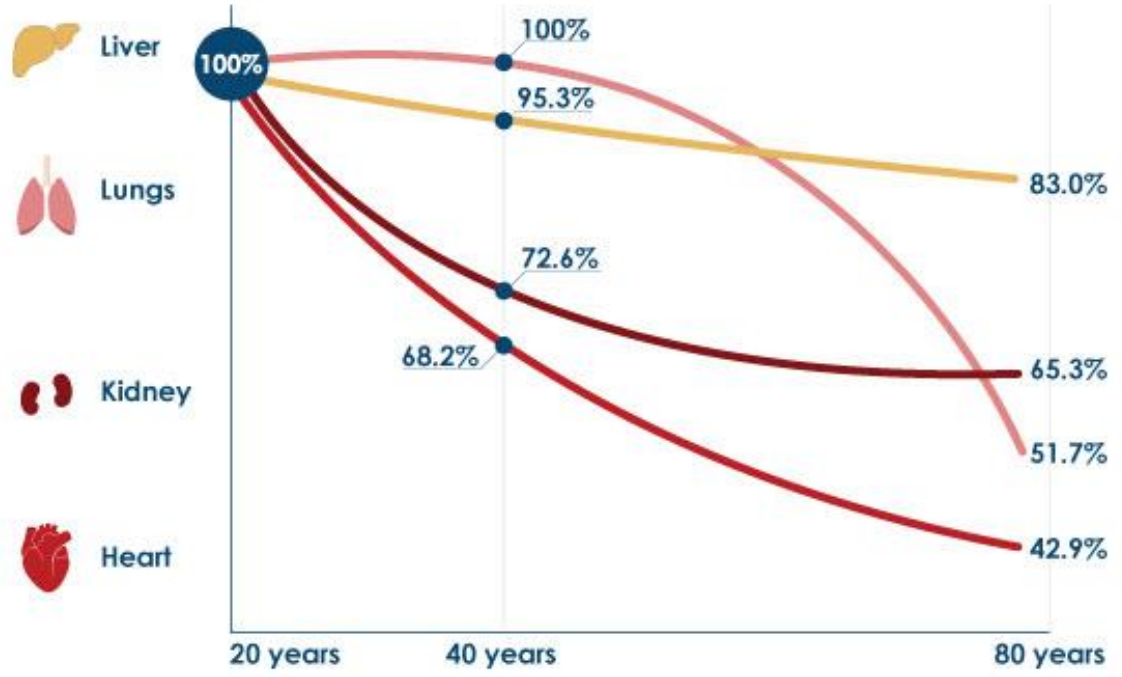


Massudi, et al., 2012

† Based on one analysis of human skin tissue

Exactly *how* do CoQ10 + Se increase SIRT1?

- **CoQ10 deficiency** has been found to reduce the NAD+/NADH ratio
  - Sadly, CoQ10 synthesis *also* reduces with age
- Therefore, increasing **CoQ10 + Se may have increased NAD+** in the study participants…
  - …which in turn may be responsible for **increasing SIRT1**



Graph: *Q10 synthesis reduces with age*

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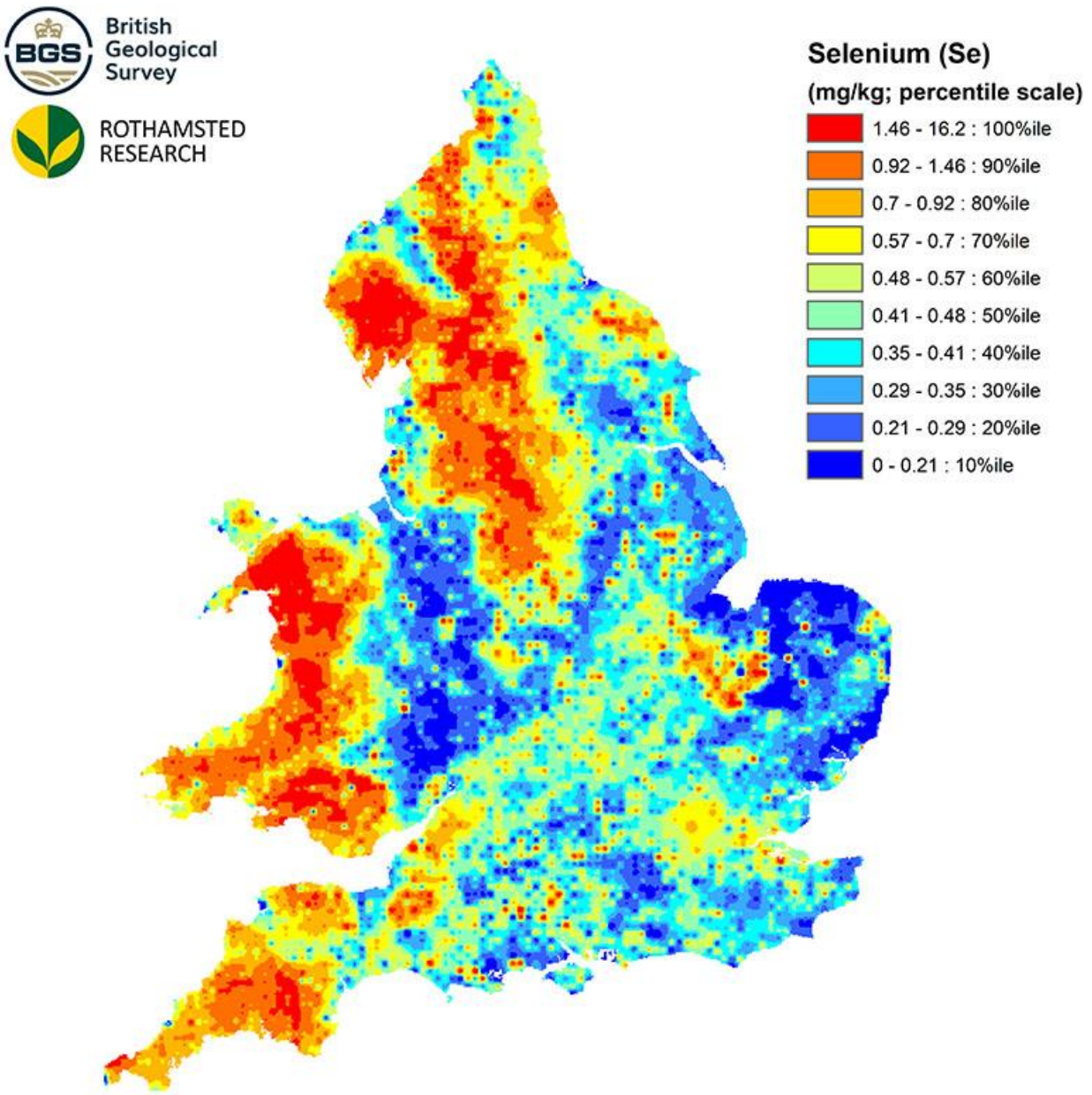
Are your clients sufficient in Selenium?

Selenium is an essential mineral and is needed for selenoproteins that have antioxidant and other crucial roles in the human body.

- Studies show that we need more than 100mcg of selenium daily, but the average intake is less than half of that.
- The average selenium intake in the UK and large parts of Europe is relatively low because there is little selenium in the agricultural soil compared with other parts of the world (see next →)

(Front Nutr. 2018 Jul 19;5:55).

British Geological survey data shows that much of the UK has Se-depleted soil



Examples of Selenoproteins and their roles:

Glutathione Peroxidases

Antioxidant substances which **help protect cells** from damage

Deiodinases

Needed for the essential functioning of **thyroid** hormones

Thioredoxin Reductases

Substances which **regenerate** certain antioxidants, including **coenzyme Q10**

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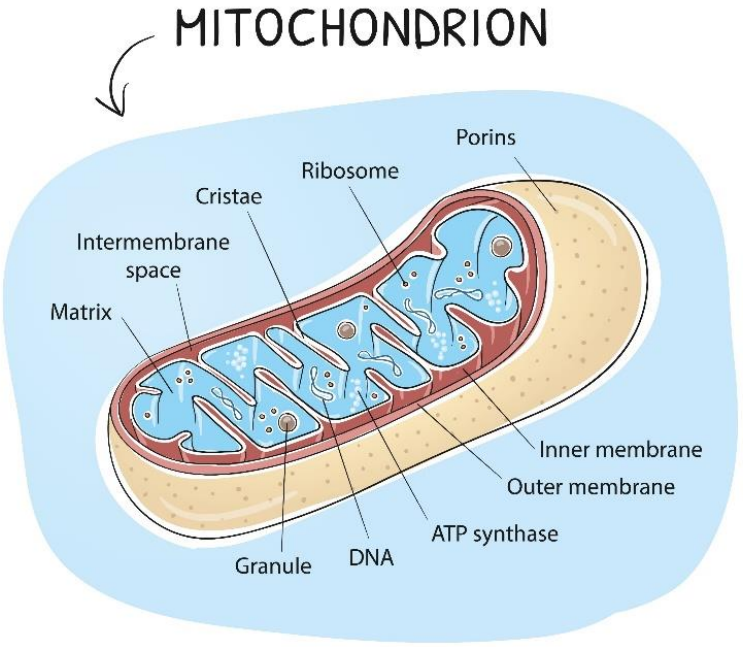
Are your clients **sufficient in CoQ10?**

Coenzyme Q10 is a vitamin-like substance that is used in the mitochondria for energy production and to protect against oxidative stress.

- Most of the body's CoQ10 requirements are met by endogenous synthesis
- But the capacity for **CoQ10 production decreases with increasing age** (we saw earlier; & see next →)
- This means organs can suffer unless we look to supporting healthy levels.



Adv Exp Med Biol. 2019;1178:103-112

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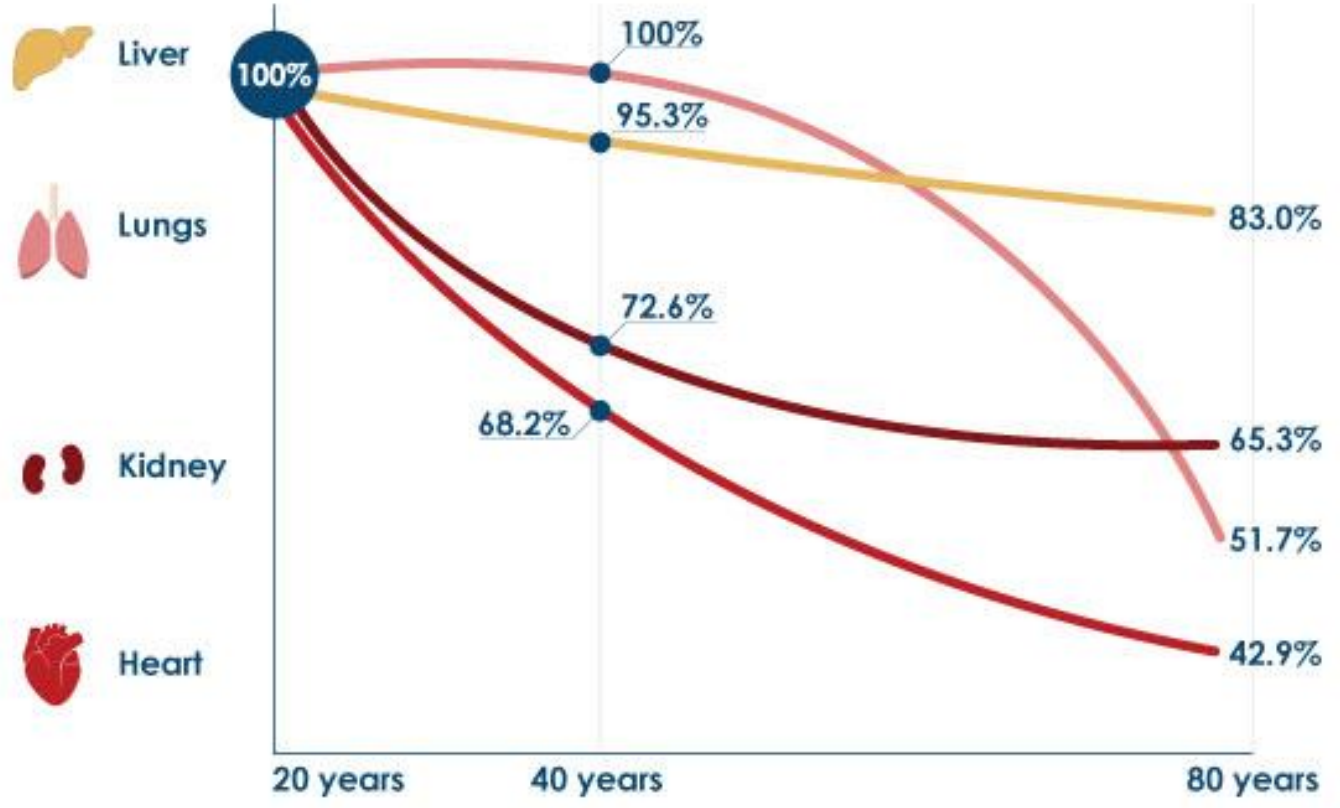
Remember:

Endogenous CoQ10 synthesis reduces with age



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102 clinical studies of Bio-Quinone

(More than any other Q10 product)

27 are gold standard studies: randomized, double-blind, placebo-controlled studies enrolling 30 or more subjects:

- Heart failure
- Diabetes
- Longevity
- Statins
- Infertility
- Acute coronary syndrome
- Prostate cancer
- HIV Infections
- Oxidative stress

Fig. 3 **A double-blind placebo-controlled clinical trial for CAM therapies.**

To sum up

1. **SIRT1** alters gene expression in a way that supports healthy ageing
2. Increased SIRT1 activity extends life in yeast and mice; and is associated with **lower risk of degenerative diseases** in humans
3. SIRT1 activity tends to **reduce as we age**
4. **Fasting, CR, keto diets and exercise** can increase SIRT1 and there is preliminary data on supplements of **NADH (or its precursors) and plant bioactives**
5. One of the largest and longest human trials has shown that **Q10 + Se** significantly increases SIRT1 and reduces CV mortality

Coenzyme Q10

Bio-Quinone Q10 ®

- Used in 100+ clinical trials for 30+ years
- Reference product of the International Coenzyme Q10 Association
- Patented superior bioavailability
- Documented bioavailability, proven in human clinical trials
- Manufactured under pharmaceutical control

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Selenium-yeast

SelenoPrecise

A selenium formulation with high documented absorption

- EFSA approved for bioavailability & safety
- Contains more than 30 organically bound selenium compounds
- Used in more than 40 published scientific trials
- Manufactured under pharmaceutical control

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Any Questions?

Come and see us at stand:

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