Mitochondria & Longevity: Unlocking the Cellular Key to Vitality and Lifespan

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Affiliations & Disclosures

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I am a consultant for Pure Encapsulations. I have no other relevant conflicts of interest to disclose.

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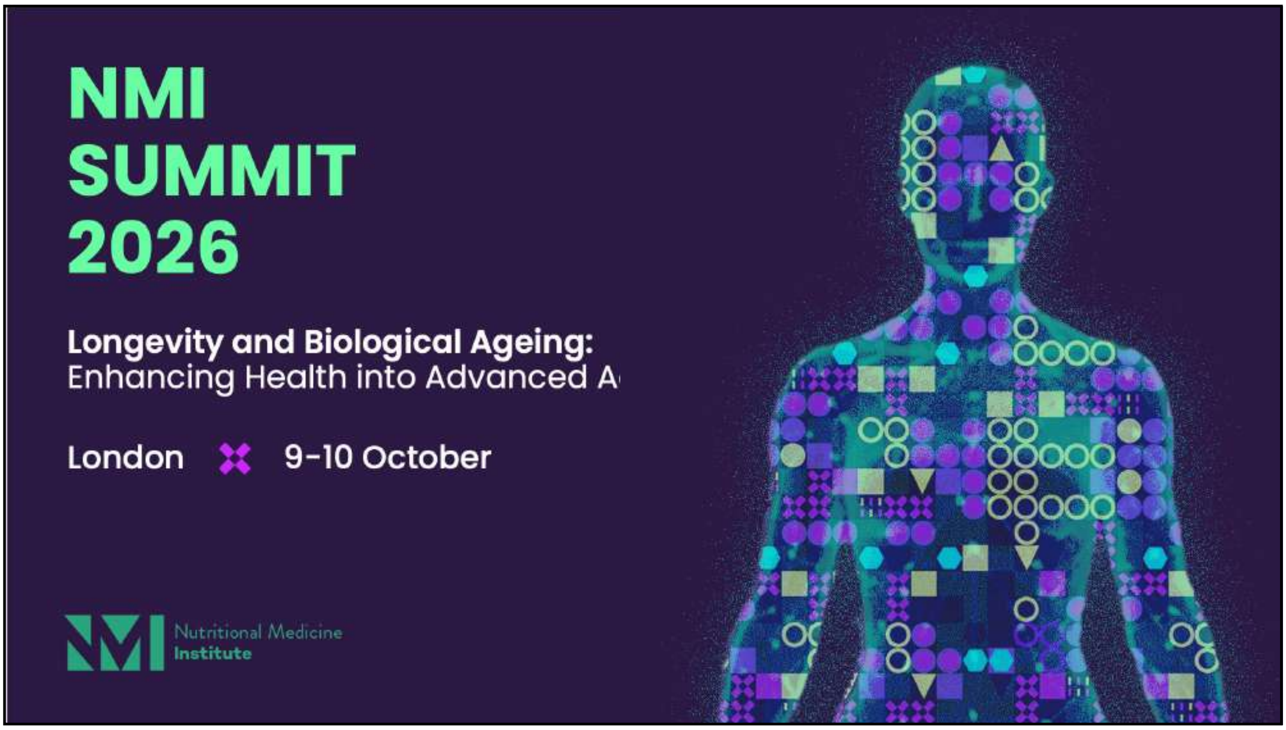

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Learning objectives:

- Review how the (dys)function of mitochondria relates to cellular and physiological health in the context of ageing.
- Explore the strengths and limitations of assessments of mitochondrial in clinical practice.
- Learn how certain dietary patterns and specific nutrients and phytonutrients can be used to optimise mitochondrial function.
- Cover examples of lifestyle medicine-based interventions that have been shown to improve mitochondrial number and/ or function.
- Examine how interventions can be personalised to the individual.

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Yang qi theory and ageing

"From a traditional point of view, Yang Qi represents "material energy" or "energy flow". Yang Qi runs through the meridians and spreads throughout the body to maintain human life activities. It is the root of human growth, development, and reproduction. Coincidentally, mitochondria also represent energy and are closely related to life."

Phenomics. 2022 Jun 16;2(5):336-348.


REVIEW

Mitochondria as the Essence of Yang Qi in the Human Body

Abstract

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Free radical theory and ageing

The initial free radical theory of aging proposed that energy metabolism in the electron transport chain produce intracellular reactive oxygen species that elicit cellular damage and eventually cellular dysfunction.

J Gerontol. 1956 Jul;11(3):298-300.


AGING: A THEORY BASED ON FREE RADICAL AND RADIATION CHEMISTRY

DENHAM HARMAN, M.D., Ph.D.

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Mitochondrial theory and ageing

"The importance of mitochondrial biology as a trait d'union between the basic biology of aging and the pathogenesis of age-related diseases is stronger than ever, although the emphasis has moved from reactive oxygen species production to other aspects of mitochondrial physiology, including mitochondrial biogenesis and turnover, energy sensing, apoptosis, senescence, and calcium dynamics."

J Gerontol A Biol Sci Med Sci. 2015 Nov;70(11):1334-42.


THE GERONTOLOGICAL SOCIETY OF AMERICA

Translational Article

The Mitochondria's Role in the Aging Process

Review

Reconsidering the Role of Mitochondria in Aging

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Triage theory and ageing

"Triage theory posits that when a micronutrient is inadequate, nature selects for a rebalancing of metabolism (e.g., by selection for micronutrient binding constants) that ensures survival of the organism at the expense of metabolism whose lack has only longer-term consequences, which I propose include chronic diseases of aging."

Mech Ageing Dev. 2010 Jul-Aug;131(7-8):473-9.


Mechanisms of Ageing and Development

Review

Optimal micronutrients delay mitochondrial decay and age-associated diseases

Bruce N. Ames

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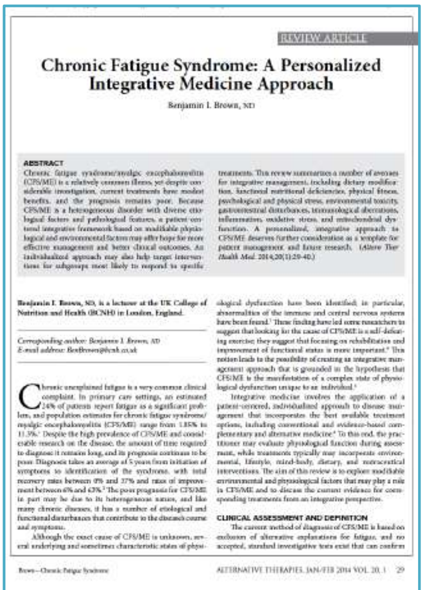
Mitochondrial nutrients

"Mitochondrial nutrients have been defined as nutritional compounds that (1) enter the cells and mitochondria following exogenous administration, (2) protect the mitochondria from oxidative damage, and (3) improve mitochondrial function."

Altern Ther Health Med. 2014 Jan-Feb;20(1):29-40.


REVIEW ARTICLE

Chronic Fatigue Syndrome: A Personalized Integrative Medicine Approach

Benjamin I. Brown, ND

ABSTRACT

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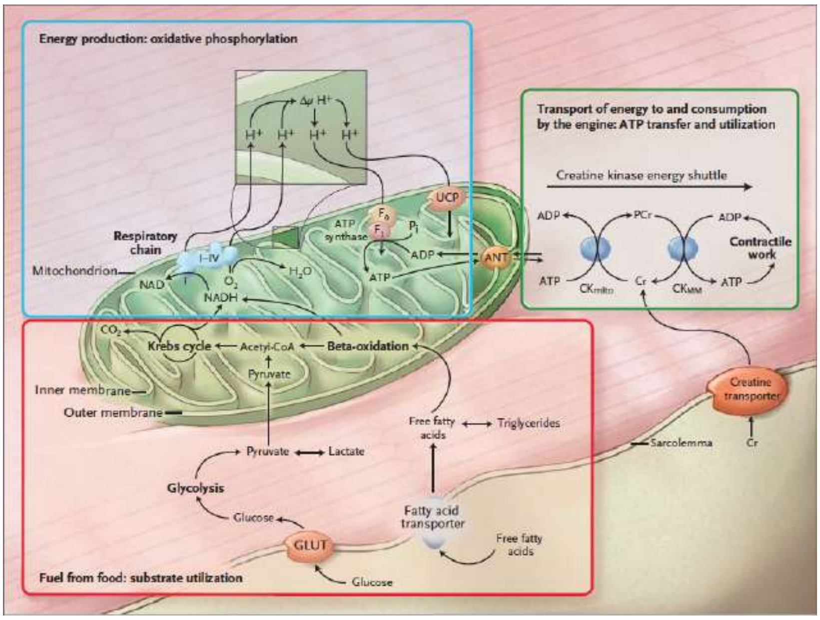

N Engl J Med. 2007 Mar 15;356(11):1140-51

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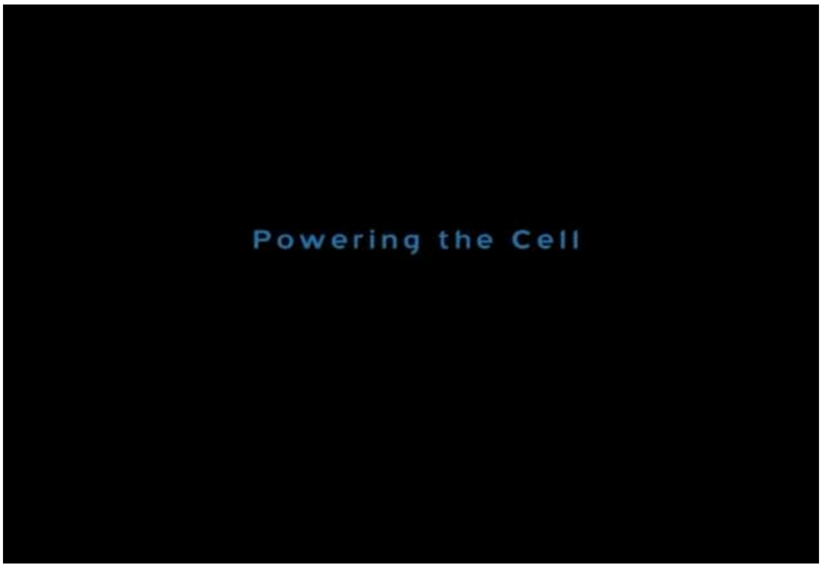

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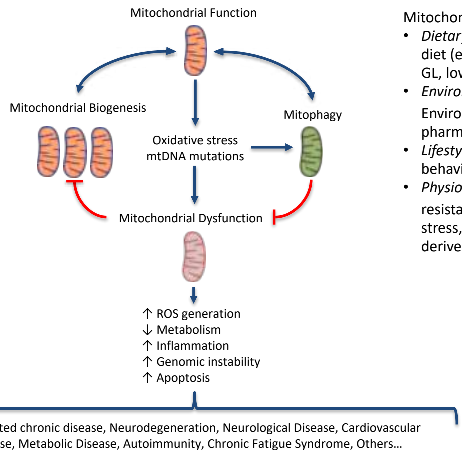
Mitochondrial (dys)function, mitophagy and lifestyle medicine

Mitochondrial function

- *Dietary characteristics:* Caloric balance, intermittent fasting, low-glycemic load (GL), low-saturated fat, high omega-3, high phytonutrient density, organic.
- *Co-factors:* B-group vitamins, ascorbic acid, vitamin D, calcium, iron, magnesium, manganese, iodine, zinc, CoQ10, carnitine, n-acetylcysteine, taurine, ribose, lipoic acid.
- *Trophic-factors:* EPA/ DHA, phospholipids, resveratrol, curcumin, ginkgo, quercetin, spermidine, urolithin A, pyrroloquinoline quinone.
- *Lifestyle factors:* Exercise, relaxation.



Mitochondrial dysfunction

- *Dietary characteristics:* Western diet (energy dense, high-fat, high-GL, low-nutrient density)
- *Environmental factors*: Environmental pollutants, pharmaceutical drugs.
- *Lifestyle factors:* Sedentary behavior, psychological stress.
- *Physiological factors:* insulin resistance, obesity, oxidative stress, inflammation, infection, gut-derived endotoxin exposure.

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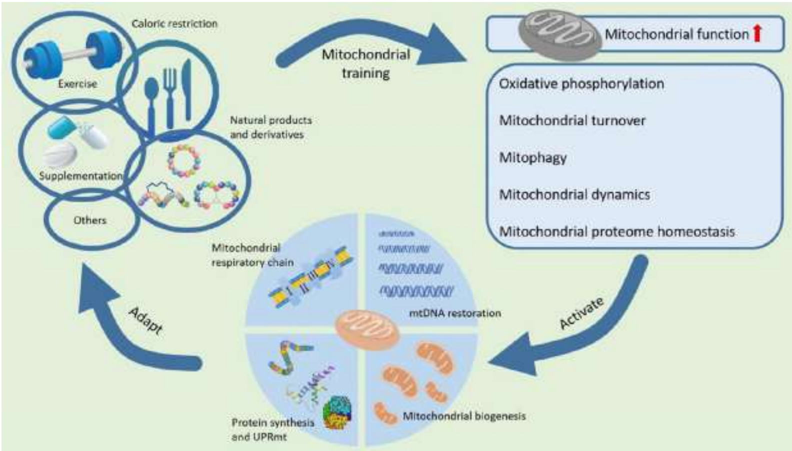
An opportunity for personalised lifestyle medicine



Journal of Holistic Integrative Pharmacy.
Volume 6, Issue 2, June 2025, Pages 159-174.

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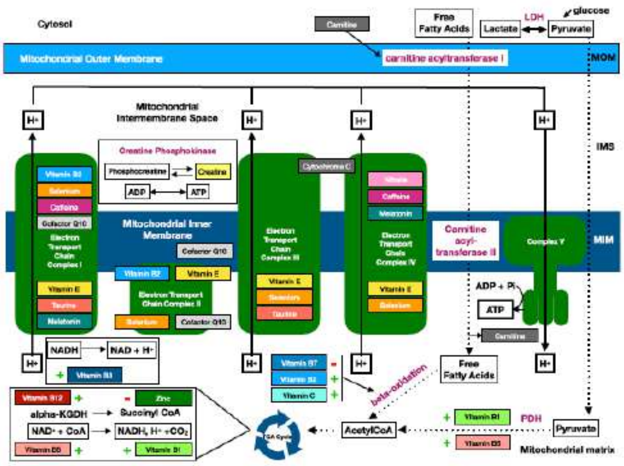
An opportunity for personalised nutrition



Clin Nutr. 2019 Jun;38(3):982-995.

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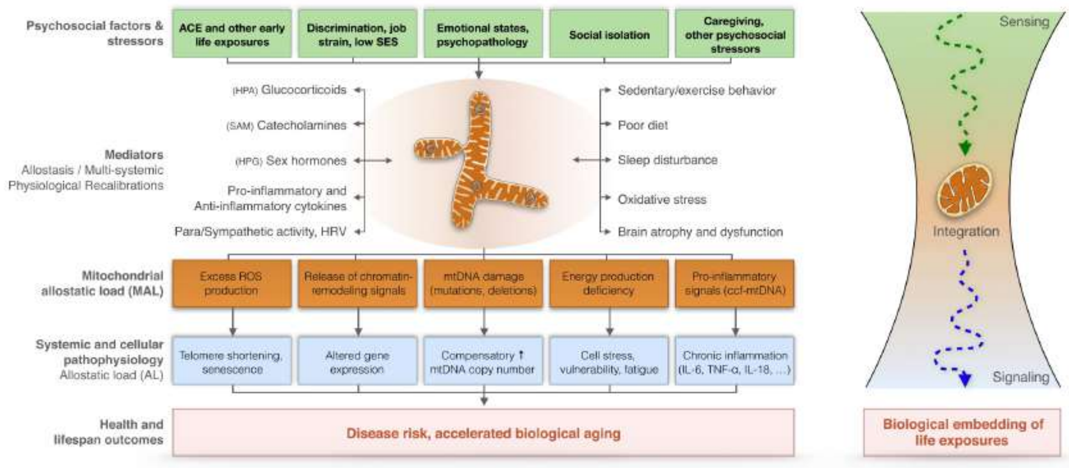
An opportunity for mind-body medicine



Picard and McEwen. Psychosom Med. 2018 Feb/Mar;80(2):126-140.

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Acetyl-l-carnitine

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Carnitine

"L-carnitine is central to mitochondrial processes, fatty acid metabolism, and the production of ATP. L-carnitine also plays a critical role in other important metabolic functions like cellular detoxification, control of ketogenesis and glucogenesis, and stabilization of cell membranes. The protective effects of **micronutrients like L-carnitine that target mitochondria are becoming better understood and hold considerable promise for the management of age and metabolic related diseases."**

Int J Mol Sci. 2022 Feb 28;23(5):2717.


International Journal of Molecular Sciences

MDPI

Review

The Role of L-Carnitine in Mitochondria, Prevention of Metabolic Inflexibility and Disease Initiation

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Carnitine deficiency and cognitive decline

Serum carnitines decline steadily across the spectrum of healthy subjects, subjective memory complaints, mild cognitive impairment to Alzheimer's disease.

"These findings also suggest that the **serum levels of acetyl-L-carnitine and other acyl-L-carnitines could help to identify the patients before the phenotype conversion to Alzheimer's disease** and the patients who would benefit from the treatment with acetyl-L-carnitine."

PLoS One. 2016 May 19;11(5):e0155694


PLOS ONE

RESEARCH ARTICLE

Serum Levels of Acyl-Carnitines along the Continuum from Normal to Alzheimer's Dementia

Abstract

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Carnitine deficiency and frailty

Frailty status (criteria; involuntary weight loss, exhaustion, muscle weakness, slow gait speed and sedentary behaviour) **is associated with carnitine deficiency**. In frail elderly subjects (3 or more criteria) mean serum concentrations of total and free carnitine were lower compared to both prefrail (1 or 2 criteria) and robust subjects (0 criteria).

Nutrients. 2020 Dec 19;12(12):3887.


nutrients MDPI

Article

Carnitine Serum Levels in Frail Older Subjects

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Delaying mitochondrial aging

"Feeding R-alpha-lipoic acid plus acetyl-L-carnitine (LA/ALC) to old rats partially **restored age-associated mitochondrial dysfunction to the levels of the young rats.** These results indicate that oxidative mitochondrial decay plays an important role in brain aging and that a combination of nutrients targeting mitochondria, such as LA/ALC, could ameliorate mitochondrial decay through preventing mitochondrial oxidative damage**."**

Neurochem Res. 2009 Apr;34(4):755-63.


ORIGINAL PAPER

Mitochondrial Decay in the Brains of Old Rats: Ameliorating Effect of Alpha-Lipoic Acid and Acetyl-L-carnitine

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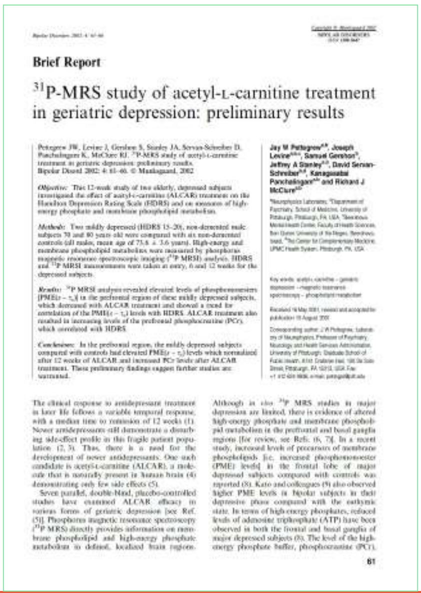
Restoring brain energy in older age

Two mildly depressed, non-demented male subjects 70 and 80 years old were treated with acetyl-L-carnitine at a dose of 3 g daily for 12 weeks. **Acetyl-L-carnitine increased brain prefrontal phosphocreatine levels** which **directly correlated with an improvement in depressive symptoms.**

Bipolar Disord. 2002 Feb;4(1):61-6.



Brief Report

^{31}P-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results

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Restoring brain energy in older age

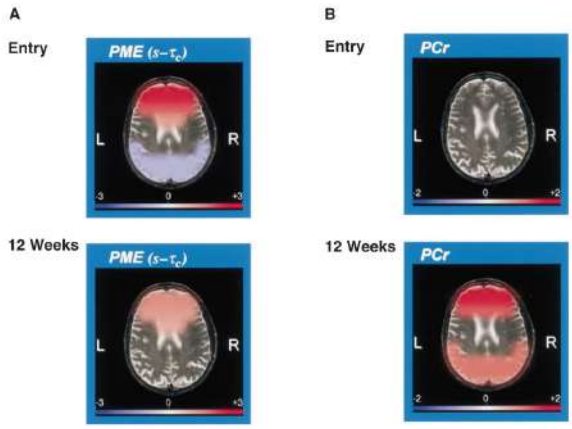

Fig. 3. Z-scores indicated by a color scale of the two mildly depressed subjects compared with controls at entry and 12 weeks for (A) PME($s-\tau_c$) and (B) PCr metabolite levels for those regions with Z-scores greater than 1. The intensity of the colour is scaled to the z-score (mean difference/SD) given on the scale below the image. Z-scores for PME($s-\tau_c$) and PCr levels in the frontal region exceed 3.0 and 2.0, respectively.

Bipolar Disord. 2002 Feb;4(1):61-6.

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Age related depression

"Twelve RCTs (11 of which were ALC monotherapy) with a total of 791 participants were included. Pooled data across nine RCTs (231 treated with ALC versus 216 treated with placebo and 20 no intervention) showed that **ALC significantly reduced depressive symptoms.** In three RCTs comparing ALC versus antidepressants (162 for each group), **ALC demonstrated similar effectiveness compared with established antidepressants** in reducing depressive symptoms. In these latter RCTs, **the incidence of adverse effects was significantly lower in the ALC group** than in the antidepressant group. Subgroup analyses suggested that **ALC was most efficacious in older adults**."

Psychosom Med. 2018 Feb/Mar;80(2):154-159.


SYSTEMATIC REVIEW/META-ANALYSIS

Acetyl-L-Carnitine Supplementation and the Treatment of Depressive Symptoms: A Systematic Review and Meta-Analysis

Nicola Veronese, MD, Brendon Stubbs, PhD, Marco Solmi, MD, Olesya Ajnakina, PhD, Andre F. Carvalho, MD, and Stefania Maggi, MD

ABSTRACT

INTRODUCTION

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Mild cognitive impairment

A meta-analysis of 21 placebo-controlled studies of ALC for mild cognitive impairment (MCI) and mild (early) Alzheimer's disease found **a beneficial effect of ALC on both the clinical scales and the psychometric tests with benefits observed in memory, cognitive function and mood**. Doses were mostly 1500 mg to 2000 mg daily and benefits were noticed within 3 months and increased over time.

Int Clin Psychopharmacol. 2003 Mar;18(2):61-71.


Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease

Stuart A. Montgomery[a], L.J. Thal[b] and R. Amrein[c]

Introduction

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Age related fatigue

In a 6-month randomized controlled trial, centenarians (n=66) with onset of fatigue after even slight physical activity received either 2,000 mg L-carnitine once daily or placebo. Compared to placebo, **L-carnitine-treated centenarians had significant improvements in total fat mass, total muscle mass, plasma concentrations of carnitines** (total carnitine, long-chain acylcarnitine, short-chain acylcarnitine), **physical fatigue, mental fatigue, fatigue severity, and cognitive function.**

Am J Clin Nutr. 2007 Dec;86(6):1738-44

L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial[1–3]

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Age related frailty

In a randomized controlled trial, acetyl-L-carnitine (1,500 mg twice daily) was administered to pre-frail older patient over a 3-month intervention. Compared to placebo, **acetyl-L-carnitine treatment significantly reduced C reactive protein, increased serum-free carnitine and acetyl carnitine, improved cognitive function** (Mini-Mental State Examination) **and improved physical functional** (6-minute walk test).

Curr Pharm Des. 2022;28(38):3158-3166.

Acetyl-L-carnitine Slows the Progression from Prefrailty to Frailty in Older Subjects: A Randomized Interventional Clinical Trial

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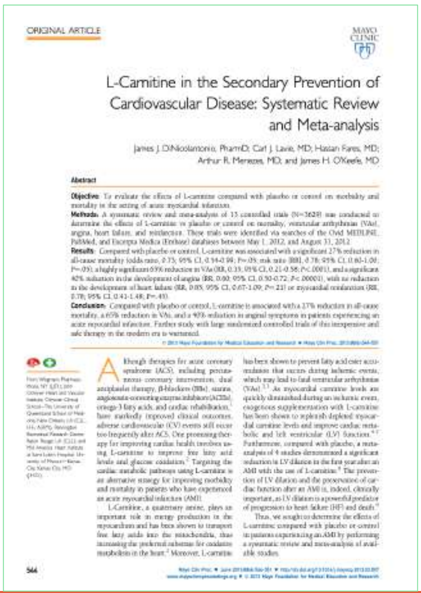
Secondary prevention of CVD

An analysis pooling the collective data from 13 clinical trials including 3629 people in total examined the ability of L-carnitine to reduce cardiovascular disease and death in people who had previously had a heart attack (acute myocardial infarction). Compared with placebo or no carnitine the analysis found that L-carnitine supplementation resulted in a:

- 27% reduction in death from all-causes
- 65% reduction in ventricular arrhythmias
- 40% reduction in anginal symptoms

Mayo Clin Proc. 2013 Jun;88(6):544-51.


ORIGINAL ARTICLE

L-Carnitine in the Secondary Prevention of Cardiovascular Disease: Systematic Review and Meta-analysis

James J. DiNicolantonio, PharmD; Carl J. Lavie, MD; Hassan Fares, MD; Arthur R. Menezes, MD; and James H. O'Keefe, MD

Abstract

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Clinical use of acetyl-l-carnitine

People who may be more likely to respond:

- Symptoms of pain (e.g., diabetic neuropathy, fibromyalgia, migraine).
- Symptoms of fatigue (e.g., age-related fatigue, chronic fatigue syndrome).
- Older age.
- Low serum acetyl-L-carnitine.
- Elevated inflammatory biomarkers.
- Insulin resistance.

Dose and duration:

- 3 grams daily, in divided doses, for at least 8-weeks (onset of action has been reported in as little as 1-week).

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Clinical use of acetyl-l-carnitine

References:

1. Di Stefano G, Di Lionardo A, Galosi E, Truini A, Cruccu G. Acetyl-L-carnitine in painful peripheral neuropathy: a systematic review. J Pain Res. 2019 Apr 26;12:1341-1351.
2. Veronese N, Stubbs B, Solmi M, Ajnakina O, Carvalho AF, Maggi S. Acetyl-L-Carnitine Supplementation and the Treatment of Depressive Symptoms: A Systematic Review and Meta-Analysis. Psychosom Med. 2018 Feb/Mar;80(2):154-159.
3. Bersani G, Meco G, Denaro A, Liberati D, Colletti C, Nicolai R, Bersani FS, Koverech A. L-Acetylcarnitine in dysthymic disorder in elderly patients: a double-blind, multicenter, controlled randomized study vs. fluoxetine. Eur Neuropsychopharmacol. 2013 Oct;23(10):1219-25.
4. Nasca C, Bigio B, Lee FS, Young SP, Kautz MM, Albright A, Beasley J, Millington DS, Mathé AA, Kocsis JH, Murrough JW, McEwen BS, Rasgon N. Acetyl-l-carnitine deficiency in patients with major depressive disorder. Proc Natl Acad Sci U S A. 2018 Aug 21;115(34):8627-8632.
5. Ruggenenti P, Cattaneo D, Loriga G, Ledda F, Motterlini N, Gherardi G, Orisio S, Remuzzi G. Ameliorating hypertension and insulin resistance in subjects at increased cardiovascular risk: effects of acetyl-L-carnitine therapy. Hypertension. 2009 Sep;54(3):567-74.
6. Bigio B, Mathé AA, Sousa VC, Zelli D, Svenningsson P, McEwen BS, Nasca C. Epigenetics and energetics in ventral hippocampus mediate rapid antidepressant action: Implications for treatment resistance. Proc Natl Acad Sci U S A. 2016 Jul 12;113(28):7906-11.

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Creatine

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Creatine deficiency

- Muscle creatine levels are typically lower in vegetarians.[1]
- Elderly people may not consume as much meat or seafood in their diet due to difficulty digesting these food products.[2]
- Older individuals >60 years with low dietary creatine intake (<0.95 grams/day) have poorer cognitive function compared to those consuming more dietary creatine (>0.95 grams/day).[3]
- Around 70% of adults ≥65 years consumed less than the recommended amounts of creatine in their diet (<0.95 grams per day), and low dietary creatine intake was associated with a greater risk of angina pectoris and liver conditions compared to those consuming ≥1.0 grams/day of dietary creatine.[4]
- Higher creatine intake (>1 gram) is inversely associated with all-cause mortality.[5]
- Higher dietary creatine intake is linked to reduced biological age acceleration and mortality risk as estimated by epigenetic biomarkers.[6]

1. Br J Nutr. 2018;119(7):759–770.
2. Nutrients. 2021;13(3):1–18.
3. Aging Clin Exp Res. 2021;33(12):3269–3274.
4. Food Sci Nutr. 2021 Aug 25;9(10):5746-5754.
5. Appl Physiol Nutr Metab. 2025 Jan 1;50:1-6.
6. Lifestyle Genom. 2025 Jul 14;18(1):1-8.

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Brain energy, not just for muscle

Consumption of 20 g creatine-monohydrate a day for 4 weeks resulted in **a statistically significant in brain creatine levels** measured by ^{1}H MRS by, on average, 4.7% in grey matter and 11.5% in cerebral white matter.

Am J Physiol. 1999 Sep;277(3):R698-704.

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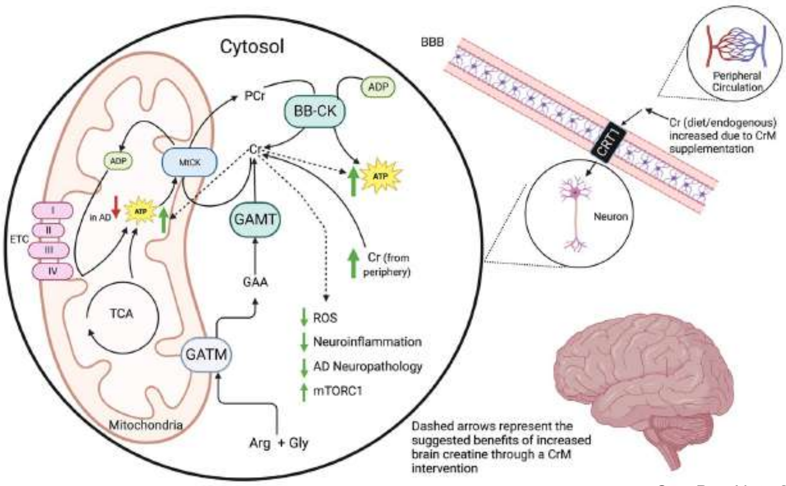
Creatine physiology in the brain and proposed benefits



Curr Dev Nutr. 2023 Sep 29;7(11):102011.

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Creatine for muscle, bone and risk of falls

"Creatine supplementation has shown **potential to enhance bone mineral** in some but not all studies and seems to affect the activation of cells involved in both bone formation and resorption. Creatine has the potential to **decrease the risk of falls** experienced by aging adults which would subsequently reduce the risk of fracture. Finally, preliminary evidence suggests that creatine may have **anti-inflammatory effects** during times of elevated metabolic stress, such as during extended/intense aerobic exercise."

J Clin Med. 2019 Apr 11;8(4):488..


Journal of Clinical Medicine

MDPI

Review

Effectiveness of Creatine Supplementation on Aging Muscle and Bone: Focus on Falls Prevention and Inflammation

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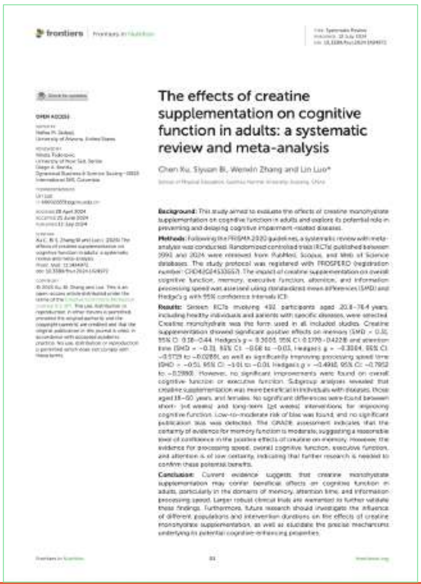
Creatine for cognitive function

A systematic review and meta-analysis of sixteen randomized controlled trials examining the impact of creatine monohydrate found that **creatine supplementation showed significant positive effects on memory, attention time, processing speed time,** however no significant improvements were found on overall cognitive function or executive function. Subgroup analyses revealed that creatine supplementation was more beneficial in individuals with diseases, those aged 18-60 years, and females.

Front Nutr. 2024 Jul 12;11:1424972.


The effects of creatine supplementation on cognitive function in adults: a systematic review and meta-analysis

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Creatine for cognition in older age

A systematic review of creatine and cognition in older adults, including two double-blind interventions and four studies cross-sectional studies suggested benefit with **five of the six (83.3%) studies reporting a positive relationship between creatine and cognition** in older adults, particularly in the domains of memory and attention.

Nutr Rev. 2025 Sep 13:nuaf135.


Systematic Review

Creatine and Cognition in Aging: A Systematic Review of Evidence in Older Adults

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Creatine for Alzheimer's disease

A single-arm pilot trial investigated the feasibility of creatine (20 g daily) for 8-weeks in patients with Alzheimer's disease (n=19). Supplementation significantly **increased serum creatine and brain creatine** and **improved cognitive function.**

Alzheimers Dement (N Y). 2025 May 19;11(2):e70101.


RESEARCH ARTICLE

Creatine monohydrate pilot in Alzheimer's: Feasibility, brain creatine, and cognition

Aaron N. Smith | In-Young Choi | Phil Lee | Debra K. Sullivan | Jeffrey M. Burns | Russell H. Swerdlow | Emma Kelly | Matthew K. Taylor

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Clinical use of creatine

People who may be more likely to respond:

- Symptoms of poor cognition, poor memory, mental fatigue.
- Poor muscle strength, physical fatigue.
- Vegetarian or vegan diet.

Dose and duration:

- 3-6 grams, once daily, for at least 4-8 weeks.
- A loading phase of 20 g/day (4 x 5 g) for 5 days and a maintenance dose of 3 to 5 g/day is sometimes recommended. However, similar (intramuscular) phosphocreatine levels can be accomplished by taking 3 g/ day over 30 days. After 2 days of loading, maximal accumulation of (intramuscular) creatine occurs and therefore amounts of 20 g/day are unnecessary and will minimise GI side-effects associated with 20 g doses.

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Clinical use of creatine

References:

1. Prokopidis K, Giannos P, Triantafyllidis KK, Kechagias KS, Forbes SC, Candow DG. Effects of creatine supplementation on memory in healthy individuals: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2023 Mar 10;81(4):416-427.
2. Alves CR, Santiago BM, Lima FR, Otaduy MC, Calich AL, Tritto AC, de Sá Pinto AL, Roschel H, Leite CC, Benatti FB, Bonfá E, Gualano B. Creatine supplementation in fibromyalgia: a randomized, double-blind, placebo-controlled trial. Arthritis Care Res (Hoboken). 2013 Sep;65(9):1449-59.
   Brown BI. Nutritional Brain Energy Enhancement for Reducing Mental Fatigue and Improving Mood and Cognition. JOM, 2012; 27(4): 177-186
3. Brosnan JT, Brosnan ME. Creatine: endogenous metabolite, dietary, and therapeutic supplement. Annu Rev Nutr. 2007;27:241-61.
4. Persky AM, Brazeau GA, Hochhaus G. Pharmacokinetics of the dietary supplement creatine. Clin Pharmacokinet. 2003;42(6):557-74.

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CoQ10

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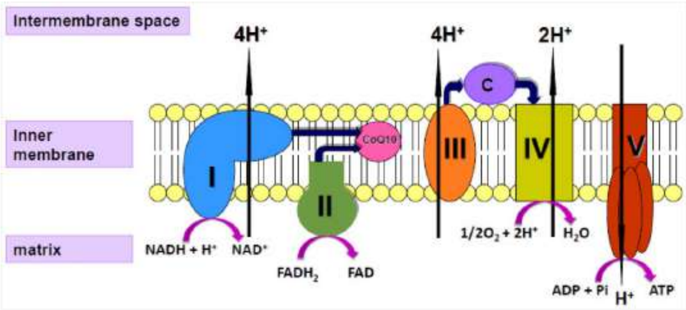
CoQ10



"CoQ10 has a key role in the process of cellular energy supply via oxidative phosphorylation within mitochondria, **shuttling electrons from complexes I and II to complex III** of the mitochondrial respiratory chain; CoQ10 is also a **powerful lipid-soluble antioxidant**, protecting cell membranes from free radical-induced oxidative damage."

Antioxidants (Basel). 2021 Dec 21;11(1):2.

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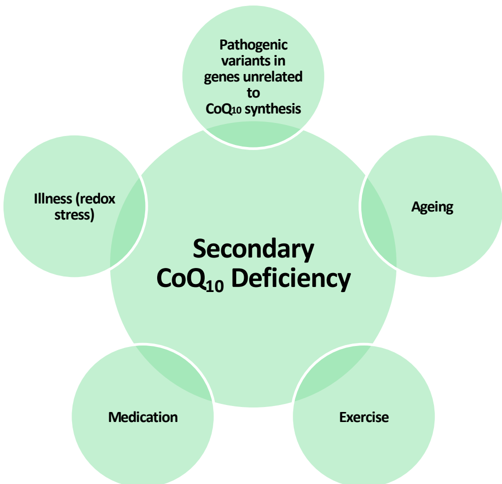
Factors causing secondary CoQ_{10} deficiency



Antioxidants (Basel). 2023 Jul 21;12(7):1469.

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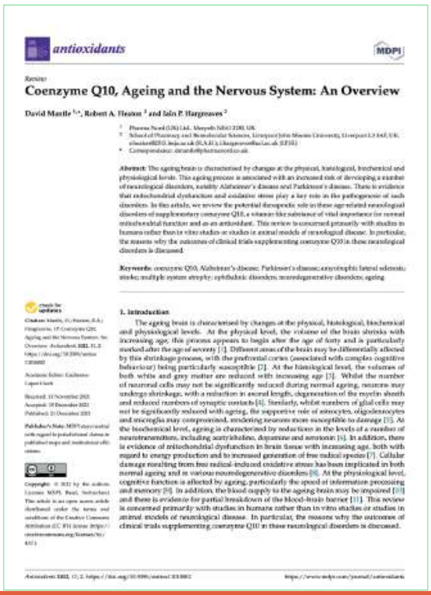
CoQ10 decline with age

"Relatively little data are available in the published literature regarding changes in CoQ10 levels in various human tissues as a function of age. However, in general terms, **optimum CoQ10 production occurs around 25 years of age, with a subsequent age-related decline that may vary in different tissues.** For example, in heart tissue, the production of CoQ10 at age 65 is approximately half of that at age 25 years."

Antioxidants (Basel). 2021 Dec 21;11(1):2


antioxidants MDPI

Review

Coenzyme Q10, Ageing and the Nervous System: An Overview

David Mantle, Robert A. Heaton and Iain P. Hargreaves

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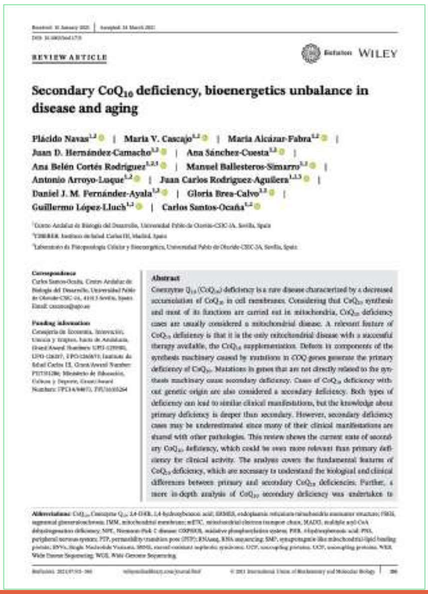
CoQ10 decline and healthspan

"Through its relationship with mitochondrial dysfunction, CoQ10 deficiency has been associated with many age-related diseases, such as type 2 diabetes or insulin resistance, cardiovascular disease, neurodegeneration, chronic kidney disease, liver disease, inflammaging and immunosenescence, or sarcopenia."

Biofactors. 2021 Jul;47(4):551-569


REVIEW ARTICLE WILEY

Secondary CoQ_{10} deficiency, bioenergetics unbalance in disease and aging

Plácido Navas | María V. Cascajo | María Alcázar-Fabra | Juan D. Hernández-Camacho | Ana Sánchez-Cuesta | Ana Belén Cortés Rodríguez | Manuel Ballesteros-Simarro | Antonio Arroyo-Luque | Juan Carlos Rodríguez-Aguilera | Daniel J. M. Fernández-Ayala | Gloria Brea-Calvo | Guillermo López-Lluch | Carlos Santos-Ocaña

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CoQ10 for inflammageing

A meta-analysis of thirty-one double-blind randomized controlled trials (n=1517) of CoQ10 supplementation in the general population, including older age participants, on inflammatory biomarkers demonstrated that **supplementation can significantly reduce the levels of circulating CRP, IL-6 and TNF-α** and increase the concentration of circulating CoQ10. Dose response analysis proposes that daily supplementation of **300-400 mg had a superior anti-inflammatory effect.**

Mol Nutr Food Res. 2023 Jul;67(13):e2200800.


REVIEW

Molecular Nutrition Food Research

Efficacy and Optimal Dose of Coenzyme Q10 Supplementation on Inflammation-Related Biomarkers: A GRADE-Assessed Systematic Review and Updated Meta-Analysis of Randomized Controlled Trials

Shanshan Hou, Zezhong Tian, Dan Zhao, Ying Liang, Suming Dai, Qiuhua Ji, Zhiying Fan, Zhihao Liu, Meitong Liu, and Yan Yang*

1. Introduction

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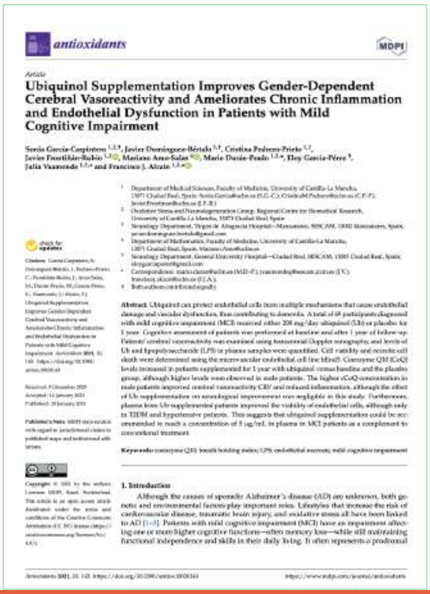
CoQ10 for cognitive impairment

In a randomized controlled trial, participants diagnosed with mild cognitive impairment (n=69) received either ubiquinol (200 mg once daily) or placebo for 1 year. Supplementation increased plasma CoQ10 and **a subgroup with higher plasma levels (5 µg/mL) exhibited improved cerebral vasoreactivity and reduced inflammation,** although the effect supplementation on neurological improvement was negligible.

Antioxidants (Basel). 2021 Jan 20;10(2):143.


antioxidants

MDPI

Article

Ubiquinol Supplementation Improves Gender-Dependent Cerebral Vasoreactivity and Ameliorates Chronic Inflammation and Endothelial Dysfunction in Patients with Mild Cognitive Impairment

Sonia García-Carpintero, Javier Domínguez-Bértalo, Cristina Pedrero-Prieto, Javier Frontiñán-Rubio, Mariano Amo-Salas, Mario Durán-Prado, Eloy García-Pérez, Julia Vaamonde and Francisco J. Alcain

1. Introduction

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CoQ10 and Alzheimer's disease

- Low levels of CoQ10 in blood are associated with an increased risk of developing Alzheimer's disease.[1]
- A 16-week randomized controlled trial in subjects with mild to moderate Alzheimer disease found no benefit of 1200 mg CoQ10 daily. Changes in blood CoQ10 levels following supplementation were not measured.[2]
- Potential reasons for treatment failure include[3]
  - Low bioavailability supplement formulation (supplement absorption should always be quantified via plasma CoQ10).
  - It is unknown if supplementary CoQ10 can penetrate the blood–brain barrier.
  - Co-administration of a high dose of vitamin E may inhibit access to the brain for CoQ10, via competition for shared lipoprotein or other carrier types.
  - Alzheimer's disease is etiologically heterogeneous, and it is unknown what patient characteristics might influence response to CoQ10.

1. Atherosclerosis. 2014 Dec;237(2):400-3.
2. Arch Neurol. 2012 Jul;69(7):836-41.
3. Antioxidants (Basel).2021 Dec 21;11(1):2.PMID:35052506

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CoQ10 for cardiovascular ageing

"CoQ10 deficiency has been observed in patients with congestive heart failure, angina pectoris, coronary artery disease, cardiomyopathy, and hypertension. The clinical benefits of CoQ10 supplementation in prevention and treatment of cardiovascular diseases have been observed in many trials. CoQ10 may be recommended to patients at risk for or diagnosed with cardiovascular disease as an adjunct to conventional treatment."

Clin Chim Acta. 2015 Oct 23;450:83-9.


Clinica Chimica Acta

Invited critical review

Coenzyme Q10 treatment of cardiovascular disorders of ageing including heart failure, hypertension and endothelial dysfunction

Yan-Kun Yang, Lin-Ping Wang, Lei Chen, Xiu-Ping Yan, Kun-Qi Yang, Ling-Gen Gao, Xian-Liang Zhou

ARTICLE INFO

ABSTRACT

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CoQ10 in heart failure, hypertension and endothelial dysfunction

Reference number	Author	Study design	No. of patients	Diagnosis	CoQ10 daily oral dose	Significant finding
CHF						
[63]	Langsjoen (1985)	Crossover	19	CHF	100 mg	Increased EF
[64]	Judy (1986)	Parallel	14	CHF	100 mg	Improved CO and EF
[65]	Poggesi (1991)	Crossover	20	ICM	100 mg	Improved EF
[66]	Permanetter (1992)	Parallel	25	IDCM	100 mg	No benefit
[67]	Rengo (1993)	–	60	CHF	100 mg	Improved EF
[23]	Morisco (1993)	Randomised double-blind placebo-controlled	641	CHF	100 mg	Fewer hospitalizations for CHF at 1 year
[68]	Morisco (1994)	Crossover	6	CHF	2 mg/kg	Improved EF, VS, CO
[69]	Hofman-Bang (1995)	Crossover	79	CHF	150 mg	Improved EF
[70]	Watson (1999)	Crossover	30	CHF	100 mg	EF and VS unaltered, left ventricular systolic and diastolic volume ↓
[71]	Munkholm (1999)	RandomizedRandomised double-blind placebo-controlled	22	CHF	200 mg	Improved SV and exercise tolerance
[72]	Khatta (2000)	Two parallel groups	55	CHF	200 mg	Improved Exercise tolerance, EF unaltered, oxygen consumption ↑
[73]	Keogh (2003)	Randomised double-blind, placebo-controlled	39	CHF	150 mg	Improved exercise tolerance
[51]	Belardinelli (2006)	Double-blind, placebo-controlled crossover design	23	CHF	150 mg	Improved exercise tolerance
[26]	Hosseini (2008)	Randomised placebo-controlled	50	CHF	150 mg	Improved EF
[74]	Langsjoen (2008)	–	7	CHF	450–900 mg	Improved EF and NYHA class
[20]	Mortensen (2014)	Randomised, placebo-controlled, trial	420	CHF	300 mg	Improved symptoms and survival
Hypertension						
[75]	Yamagami (1986)	Randomised, placebo-controlled, double-blind trial	52	EH	100 mg	Reduction in SBP (6.6 ± 7.09 mm Hg) and DBP (2.2 ± 4.1 mm Hg)
[76]	Digiesi (1990)	Randomised, placebo-controlled, crossover trial	18	EH	100 mg	Reduction in SBP (10.3 ± 2.31 mm Hg) and DBP (8.1 ± 1 mm Hg)
[77]	Singh (1999)	Randomised, double-blind trial	59	EH, CAD	120 mg	Reduction in SBP (11.5 ± 2.2 mm Hg) and DBP (5 ± 1.17 mm Hg)
[40]	Burke (2001)	Randomised, double-blind, placebo-controlled trial	83	Isolated systolic hypertension	120 mg	Reduction in SBP of the CoQ-treated group (17.8 ± 7.3 mm Hg)
ED						
[57]	Raitakari (2000)	Double-blind crossover study	12	Moderate hypercholesterolemia	150 mg	Not associated with improvement in arterial ED
[55]	Watts (2002)	Case-control study	40	Type 2 diabetes	200 mg	Improvement in arterial ED
[54]	Kuettner (2005)	Prospective, randomised, cross-over study	25	ED	150 mg	Improvement in arterial ED
[50]	Tiano (2007)	Randomised controlled study	19	CAD	300 mg/d	Improvements in ED and endothelium-bound ecSOD activity
[45]	Hamilton (2009)	Double-blind crossover study	23	Type 2 diabetes, ED	200 mg/d	Improvement in arterial ED
[56]	Dai (2011)	Randomised, double-blind, placebo-controlled study	28	CAD	300 mg/d	Improvement in arterial ED

Clin Chim Acta. 2015 Oct 23;450:83-9.

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Prevention of cardiovascular death

An intervention trial of selenium (200 µg daily) and coenzyme Q10 (200 mg daily) in older age adults (aged 70 to 88) (n=443) for 4-years reported a significantly reduced risk of cardiovascular mortality at a follow up time of 5.2 years with cardiovascular mortality 5.9% vs. 12.6% for placebo. **At 12-years follow-up, a significantly reduced risk of mortality could be seen,** with a cardiovascular mortality of 28.1% in the active treatment group, and 38.7% in the placebo group.

PLoS One. 2018 Apr 11;13(4):e0193120.

PLOS | ONE

RESEARCH ARTICLE

Still reduced cardiovascular mortality 12 years after supplementation with selenium and coenzyme Q10 for four years: A validation of previous 10-year follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly

Abstract

Background

Selenium and coenzyme Q10 are both necessary for optimal cell function in the body. The intake of selenium is low in Europe, and the endogenous production of coenzyme Q10 decreases as age increases. Therefore, an intervention trial using selenium and coenzyme Q10 for four years as a dietary supplement was performed. The main publication reported reduced cardiovascular mortality as a result of the intervention. In the present sub-study the objective was to determine whether reduced cardiovascular (CV) mortality persisted after 12 years, in the supplemented population or in subgroups with diabetes, hypertension, ischemic heart disease or reduced functional capacity due to impaired cardiac function.

Methods

From a rural municipality in Sweden, four hundred forty-three healthy elderly individuals were included. All cardiovascular mortality was registered, and no participant was lost to the follow-up. Based on death certificates and autopsy results, mortality was registered.

Findings

After 12 years a significantly reduced CV mortality could be seen in those supplemented with selenium and coenzyme Q10, with a CV mortality of 28.1% in the active treatment group, and 38.7% in the placebo group. A multivariate Cox regression analysis demonstrated a reduced CV mortality risk in the active treatment group (HR: 0.58; 95%CI 0.42–

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Clinical use of CoQ10

People who may be more likely to respond:

- Plasma CoQ10 <1µmol/l (does not reflect tissue levels).
- Elevated inflammatory biomarkers (CRP, IL-6, TNF-α).
- Elevated oxidative stress (malondialdehyde, total antioxidant capacity, SOD activity).
- Nutrient-drug interactions (statins, beta blockers, propranolol and metoprolol, phenothiazines and tricyclic antidepressants).

Dose and duration:

- 100-300 mg daily, in divided doses, for at least 8-12 weeks.

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Clinical use of CoQ10

References:

1. Moreno-Fernández AM, Cordero MD, Garrido-Maraver J, Alcocer-Gómez E, Casas-Barquero N, Carmona-López MI, Sánchez-Alcázar JA, de Miguel M. Oral treatment with amitriptyline induces coenzyme Q deficiency and oxidative stress in psychiatric patients. J Psychiatr Res. 2012 Mar;46(3):341-5.
2. Hou S, Tian Z, Zhao D, Liang Y, Dai S, Ji Q, Fan Z, Liu Z, Liu M, Yang Y. Efficacy and Optimal Dose of Coenzyme Q10 Supplementation on Inflammation-Related Biomarkers: A GRADE-Assessed Systematic Review and Updated Meta-Analysis of Randomized Controlled Trials. Mol Nutr Food Res. 2023 Jul;67(13):e2200800.
3. Talebi S, Pourgharib Shahi MH, Zeraattalab-Motlagh S, Asoudeh F, Ranjbar M, Hemmati A, Talebi A, Wong A, Mohammadi H. The effects of coenzyme Q10 supplementation on biomarkers of exercise-induced muscle damage, physical performance, and oxidative stress: A GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials. Clin Nutr ESPEN. 2024 Apr;60:122-134.
4. Akbari A, Mobini GR, Agah S, Morvaridzadeh M, Omidi A, Potter E, Fazelian S, Ardehali SH, Daneshzad E, Dehghani S. Coenzyme Q10 supplementation and oxidative stress parameters: a systematic review and meta-analysis of clinical trials. Eur J Clin Pharmacol. 2020 Nov;76(11):1483-1499.
5. Garrido-Maraver J, Cordero MD, Oropesa-Avila M, Vega AF, de la Mata M, Pavon AD, Alcocer-Gomez E, Calero CP, Paz MV, Alanis M, de Lavera I, Cotan D, Sanchez-Alcazar JA. Clinical applications of coenzyme Q10. Front Biosci (Landmark Ed). 2014 Jan 1;19(4):619-33.

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Dietary patterns

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Less sugar

Ten healthy normal weight adults were submitted to a high fructose diet (+3.5 g fructose/kg fat-free mass per day) for 7 days. There was a marked impact on a large cluster of genes related to energy metabolism, mitochondrial function, and lipid oxidation, thus supporting the concept that overconsumption of fructose-containing foods could contribute to metabolic deterioration in humans.

Mol Nutr Food Res. 2016 Dec;60(12):2691-2699.

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Lower unhealthy fat

Insulin-sensitive subjects were fed an isoenergetic high-fat diet (HFD) (50%) for 3-days with muscle biopsies before and after intervention. Oligonucleotide microarray analysis revealed 297 genes were differentially regulated by the HFD. Six genes involved in oxidative phosphorylation (OXPHOS) decreased.

Diabetes. 2005 Jul;54(7):1926-33.


A High-Fat Diet Coordinately Downregulates Genes Required for Mitochondrial Oxidative Phosphorylation in Skeletal Muscle

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More phytochemicals

"Curcumin, resveratrol, and flavonoids (quercetin EGCG, genistein) most markedly activate the mTOR-regulated gene expression and the posttranscriptional modification of mitophagy-related factors, in addition to promoting the mitogenesis, mitochondrial dynamics, and mitophagy, suggesting that they might be the most promising neuroprotective phytochemicals **at least in vitro**."

Int J Mol Sci. 2019 May 17;20(10).


Mitochondria in Neuroprotection by Phytochemicals: Bioactive Polyphenols Modulate Mitochondrial Apoptosis System, Function and Structure

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Glucoraphanin-rich broccoli

Subjects were randomly assigned to consume 400 g standard broccoli, 400 g high-glucoraphanin (HG) broccoli, or 400 g peas each week for 12 wk, with no other dietary restrictions. The metabolic changes observed with the HG broccoli diet are consistent with a rebalancing of anaplerotic and cataplerotic reactions and enhanced integration of fatty acid β-oxidation with TCA cycle activity.

Am J Clin Nutr. 2013 Sep;98(3):712-22.

A diet rich in high-glucoraphanin broccoli interacts with genotype to reduce discordance in plasma metabolite profiles by modulating mitochondrial function[1–3]

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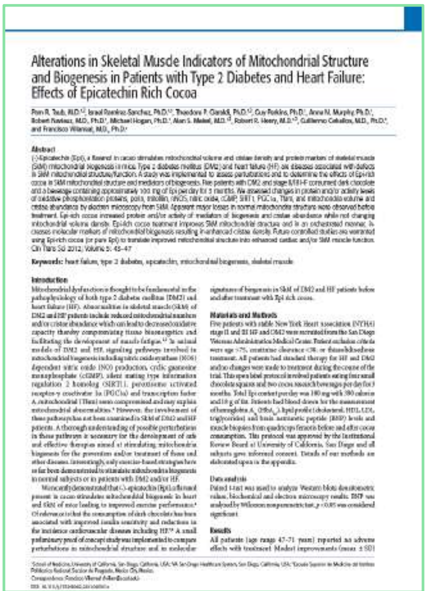
Epicatechin-rich cocoa

Patients with type 2 diabetes mellitus and stage II/III heart failure consumed dark chocolate and a beverage containing approximately 100 mg of epicatechin per day for 3 months. Epicatechin-rich cocoa treatment improved skeletal muscle mitochondrial structure and in an orchestrated manner, increases molecular markers of mitochondrial biogenesis resulting in enhanced cristae density.

Clin Transl Sci. 2012 Feb;5(1):43-7.



Alterations in Skeletal Muscle Indicators of Mitochondrial Structure and Biogenesis in Patients with Type 2 Diabetes and Heart Failure: Effects of Epicatechin Rich Cocoa

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Lower energy density

Six months of 25% caloric restriction in healthy humans increased the expression of genes involved in mitochondrial biogenesis and mitochondrial DNA copy number. The activity of key mitochondrial enzymes of the tricarboxylic acid cycle, *β*-oxidation, and the electron transport system, conversely, were unchanged.

PLoS Med. 2007;4(3):e76.

PLoS MEDICINE

Calorie Restriction Increases Muscle Mitochondrial Biogenesis in Healthy Humans

ABSTRACT

Background

Methods and Findings

Conclusions

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Dietary ketosis

"…the **dramatic shift in energy metabolism** and subsequent increase in circulating ketones induced by a ketogenic diet **can enhance mitochondrial function and endogenous antioxidant defence.** The primary mechanism behind these adaptations appears to be the increased demand for fat oxidation resulting from carbohydrate restriction. However, **ketones themselves have important metabolic and signalling effects that enhance mitochondrial function and endogenous antioxidant defence…**"

J Nutr Metab. 2018 Feb 11;2018:5157645.

Hindawi

Review Article

Nutritional Ketosis and Mitohormesis: Potential Implications for Mitochondrial Function and Human Health

Vincent J. Miller, Frederick A. Villamena, and Jeff S. Volek

1. Introduction

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Ketosis, fasting and calorie restriction

A study evaluating the effects of 1-month of calorie restriction (CR), intermittent fasting (IF), a ketogenic diet (KD), and an ad libitum habitual diet (AL) on mitochondrial function in monocytes and its modulation by the gut microbiota (n=44) found that **CR, IF and KD interventions had an increase in the maximal respiration oxygen consumption rate in monocytes compared to that in the AL group.** The improvement in mitochondrial function was associated with a decrease in monocyte dependence on glycolysis after the IF and KD interventions. **Serum lipopolysaccharide and intracellular signalling in monocytes decreased** with the three interventions to those in the AL group.

Clin Nutr. 2024 Aug;43(8):1914-1928.


Clinical Nutrition

Randomized Control Trials

Intermittent fasting, calorie restriction, and a ketogenic diet improve mitochondrial function by reducing lipopolysaccharide signaling in monocytes during obesity: A randomized clinical trial

Martha Guevara-Cruz, Karla G. Hernández-Gómez, Citlally Condado-Huerta, Luis E. González-Salazar, Ana Karen Peña-Flores, Edgar Pichardo-Ontiveros, Aurora E. Serralde-Zúñiga, Mónica Sánchez-Tapia, Otoniel Maya, Isabel Medina-Vera, Lilia G. Noriega, Adriana López-Barradas, Oscar Rodríguez-Lima, Irma Mata, Viridiana Olin-Sandoval, Nimbe Torres, Armando R. Tovar, Laura A. Velázquez-Villegas

ARTICLE INFO

SUMMARY

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Lifestyle medicine

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Relaxation

Relaxation practice for 8-weeks (yoga, meditation, repetitive prayer) **enhanced expression of genes associated with energy metabolism, mitochondrial function, insulin secretion and telomere maintenance**, and reduced expression of genes linked to inflammatory response and stress-related pathways.

PLoS One. 2013 May 1;8(5):e62817.


Relaxation Response Induces Temporal Transcriptome Changes in Energy Metabolism, Insulin Secretion and Inflammatory Pathways

Manoj K. Bhasin, Jeffery A. Dusek, Bei-Hung Chang, Marie G. Joseph, John W. Denninger, Gregory L. Fricchione, Herbert Benson, Towia A. Libermann

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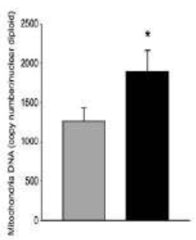
Exercise

In healthy, older (average age 67 years) men and women 30 minutes of moderate exercise 4-6 days a week for 12-weeks increased cell mitochondria number by 53%.



J Gerontol A Biol Sci Med Sci. 2006 Jun;61(6):534-40


Effects of Exercise on Mitochondrial Content and Function in Aging Human Skeletal Muscle

Elizabeth V. Menshikova, Vladimir B. Ritov, Liane Fairfull, Robert E. Ferrell, David E. Kelley, and Bret H. Goodpaster

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Assessment of mitochondrial function

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Assessing function

"At this time, there are no clinically available tests to directly measure mitochondrial ATP production. […] there are several indirect measures of mitochondrial dysfunction. Most readily available are blood levels of lactate and pyruvate."

Integr Med (Encinitas). 2014 Apr; 13(2): 8–15.

THE PATH AHEAD

Mitochondria—Fundamental to Life and Health

Joseph Pizzorno, ND, Editor in Chief

In the past few years, I have become progressively more aware of the foundational importance of optimal mitochondrial function for health and the growing body of research showing that dysfunction is surprisingly common and associated with most chronic disease. In my IMCJ 12.5 editorial, Lara and I presented helpful clinical pearls on mitochondrial health from the Institute of Functional Medicine conference in Dallas last spring. In my IMCJ 13.1 editorial, I stated that glutathione is "… vital to mitochondrial function and maintenance of mitochondrial DNA (mtDNA)." I have found the mitochondrial connection to health so interesting and important that I have now developed a 90-minute lecture on the topic and think the time has come for an editorial.

As illustrated in Table 1, with such a long list of common diseases now caused by or aggravated by mitochondrial dysfunction, it is difficult to overstate its importance.

How Much ATP Does the Body Produce Every Day?

I wish there were some way to cover up the answer—before you, dear reader, answer this question

Table 1. Partial List of Diseases Caused or Aggravated by Mitochondrial Dysfunction

- Early aging
- Amyotrophic lateral sclerosis
- Alzheimer's disease
- Autism
- Cardiovascular disease
- Chronic fatigue syndrome
- Dementia
- Diabetes

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Blood Molecules to Assess Mitochondrial Function

Molecule	Specificity	Sensitivity	Notes
mtDNA copy #/cell	74% in MDDs	100% in MDDs	
Lactate	34–62%	83–100%	Post prandial best
Pyruvate	50–75%	87%	
Lactate:Pyruvate	69-100%	11-82%	
GDF-15	High	78%	

All are measures of patients with primary mitochondrial disorders.

Hubens WHG, et al. Blood biomarkers for assessment of mitochondrial dysfunction: An expert review. Mitochondrion. 2022 Jan;62:187-204.
Shayota BJ. Biomarkers of mitochondrial disorders. Neurotherapeutics. 2024 Jan;21(1):e00325.

Credit: Pizzorno, J. [Presentation]. NMI Summit 2024.

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Clinical assessment of CoQ10

CoQ10 is an actionable biomarker of mitochondrial function. Assessments include:

- Plasma reference levels are typically in the range of 0.5–1.7 mM, however plasma CoQ10 status, which is the result of dietary intake and hepatic synthesis, does not reflect that of other tissues.
- Skeletal muscle and skin fibroblasts reference ranges are 140–580 pmol/mg and 39–75 pmol/mg, respectively, and reflect tissue CoQ10 levels.
- Cerebral spinal fluid is considered the appropriate surrogate to evaluate cerebral CoQ10 status, and a tentative reference range of 5.7–9.0 nM has been established.

Hargreaves I, Heaton RA, Mantle D. Disorders of Human Coenzyme Q10 Metabolism: An Overview. Int J Mol Sci. 2020 Sep 13;21(18):6695.

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8-OHdG (indirect of redox stress)

"Reactive oxygen species and reactive nitrogen species generate a large number of **oxidative modifications in DNA** including nucleotide oxidation, strand breakage, loss of bases, and adduct formation. The •OH radical can react with all purine and pyrimidine bases, as well as deoxyribose backbone, generating various products, **the most common one being 7,8-dihydroxy-8-oxo-2-deoxyguanosine (8-OHdG),** which can be assessed **noninvasively in the urine."**

Oxid Med Cell Longev. 2019 May 5;2019:8267234


Hindawi

Review Article

Biomarkers of Oxidative Stress in Metabolic Syndrome and Associated Diseases

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Urinary organic acids

"Urinary organic acids were generally unremarkable. […] there were no clinically or pathologically important variations in the metabolism of pyruvate (lactate), the tricarboxylic acid cycle, ketone body production (3-hydroxy-n-butyric acid) or b-oxidation of fatty acids (adipic and suberic acids), in the c-glutamyl cycle (pyroglutamic acid) or neurotransmitter metabolism."

Clin Chim Acta. 2005 Nov;361(1-2):150-8.


Available online at www.sciencedirect.com

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Urinary and plasma organic acids and amino acids in chronic fatigue syndrome

Mark G. Jones, Elizabeth Cooper, Saira Amjad, C. Stewart Goodwin, Jeffrey L. Barron, Ronald A. Chalmers

Abstract

1. Introduction

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"The science behind chronic illness calls for a focus **not on the average** but on **the individual.** Precisely because everyone of us in, in fact, unique, an operating model that treats us as average can't possibly be effective."

- Jeffery Bland PhD.

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