14° CONGRESSO NAZIONALE SINut

SINut Società Italiana di Nutraceutica

12-14 settembre 2024

Bologna

Invecchiamento attivo: quali strategie?

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Associazione Italiana di Psicogeriatria

Università degli Studi di Brescia – SS di Geriatria

Il sottoscritto ANGELO BIANCHETTI
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

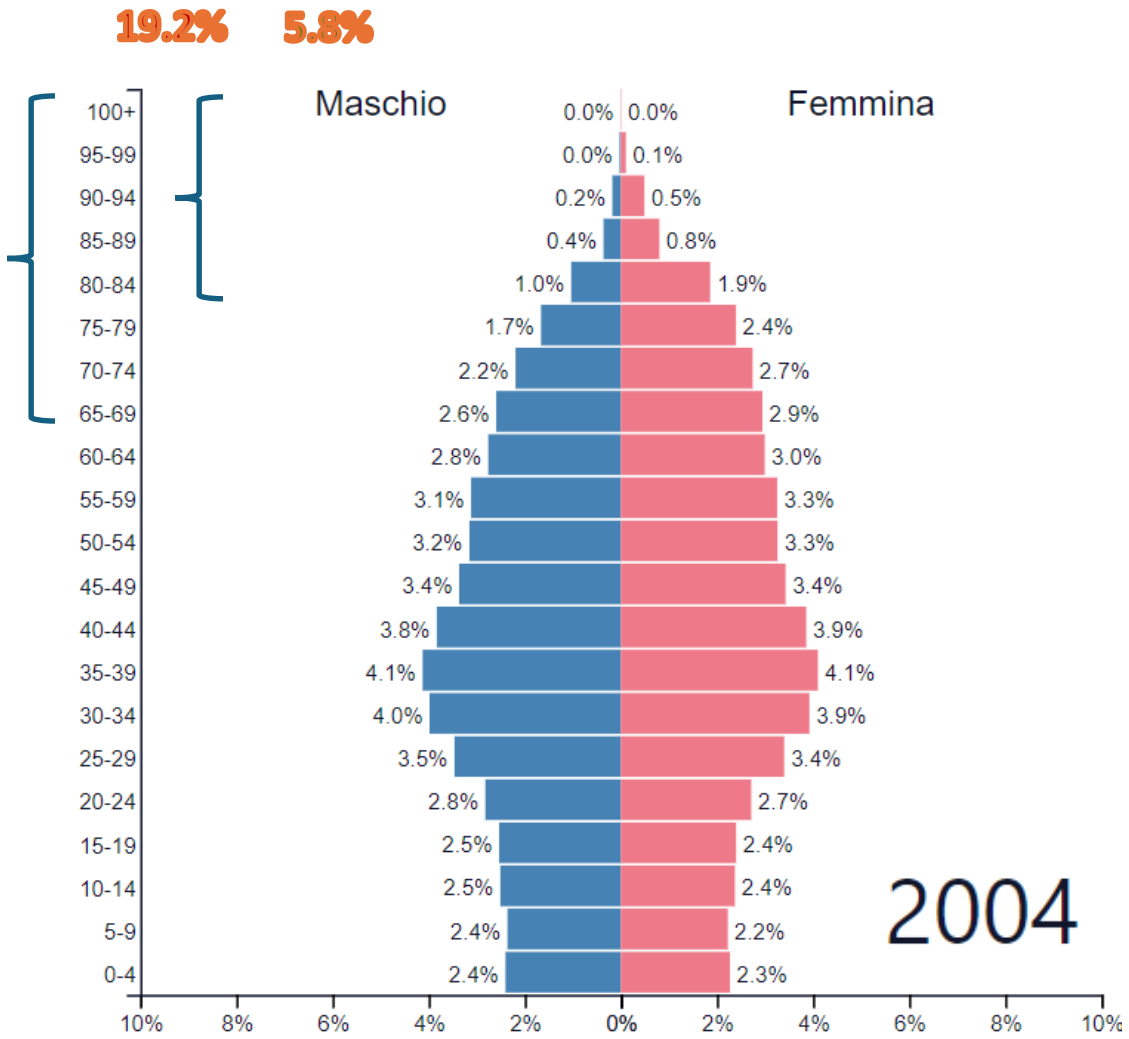
che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

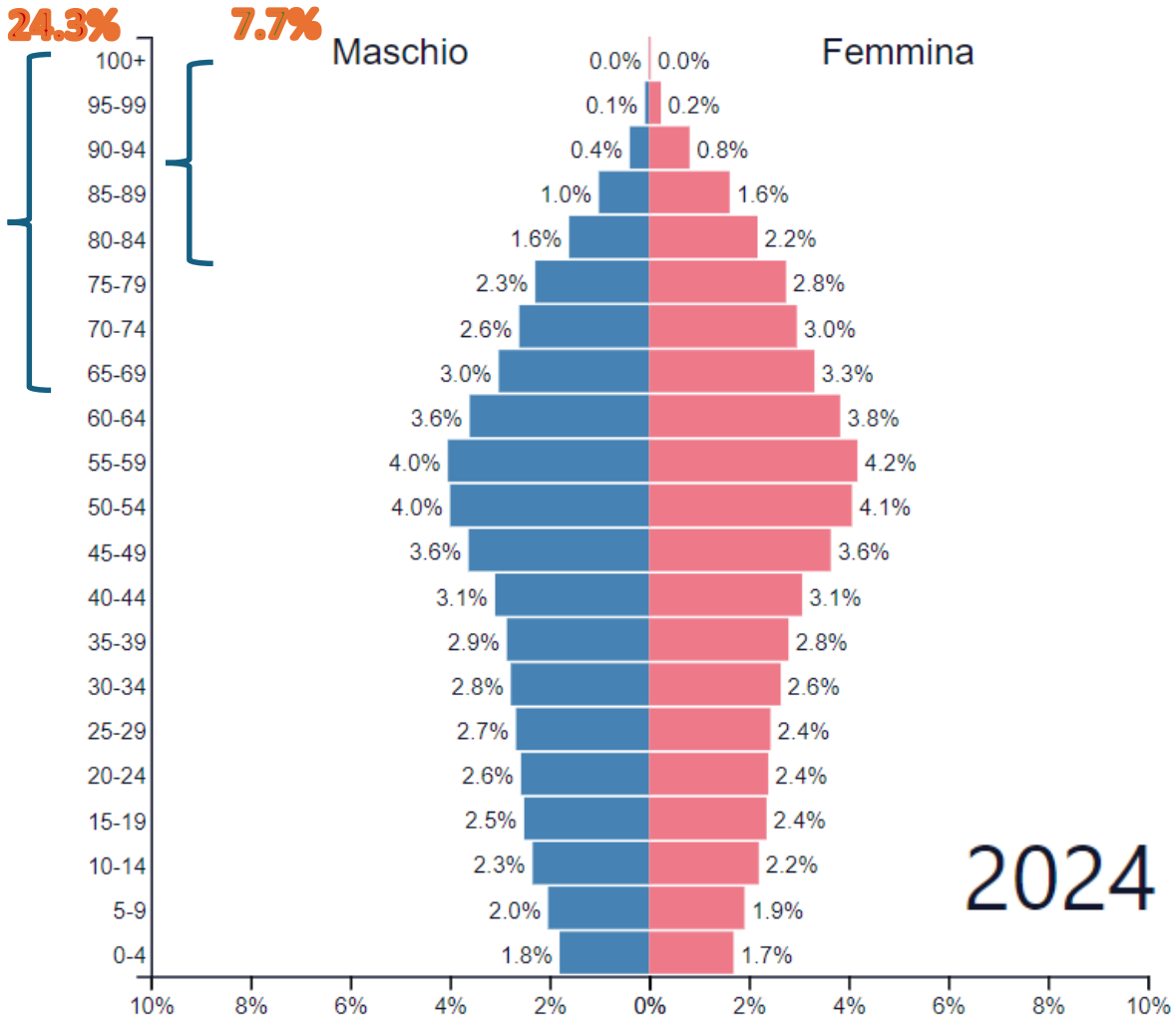
- *Biogen - Named - Valeas - Damor*

Outline

- Invecchiamento
  - definizione
- Salute e malattia nell'anziano
- Determinanti biologici
  - Fragilità, disabilità, capacità intrinseca
- Prevenzione
  - Stili di vita
  - «Trattamenti»

Distribuzione della popolazione residente in Italia





SPERANZA DI VITA: 83,1 anni

DEFINIZIONE DI HEALTHY AGING

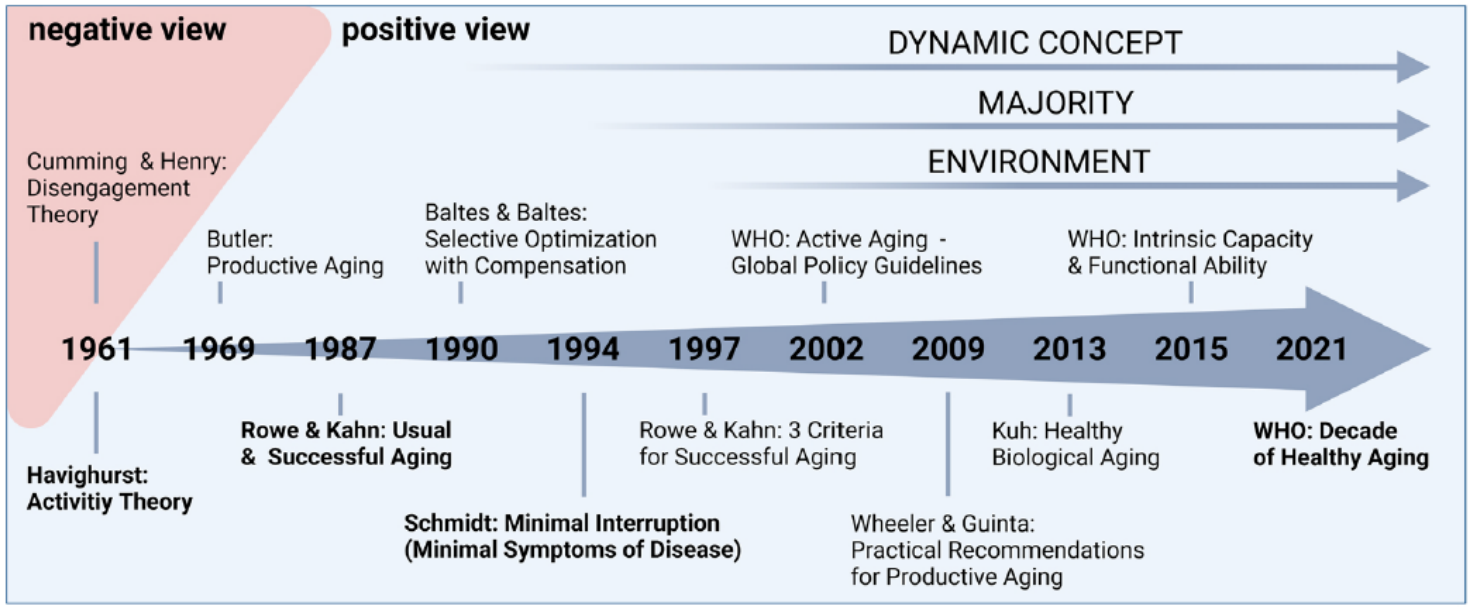


Fig. 1. : Overview of the historical development of the definition of healthy aging. WHO: World Health Organization.

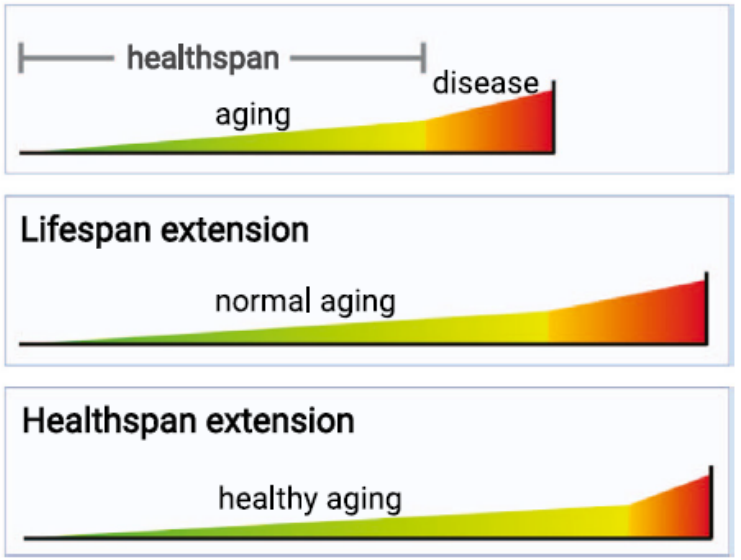


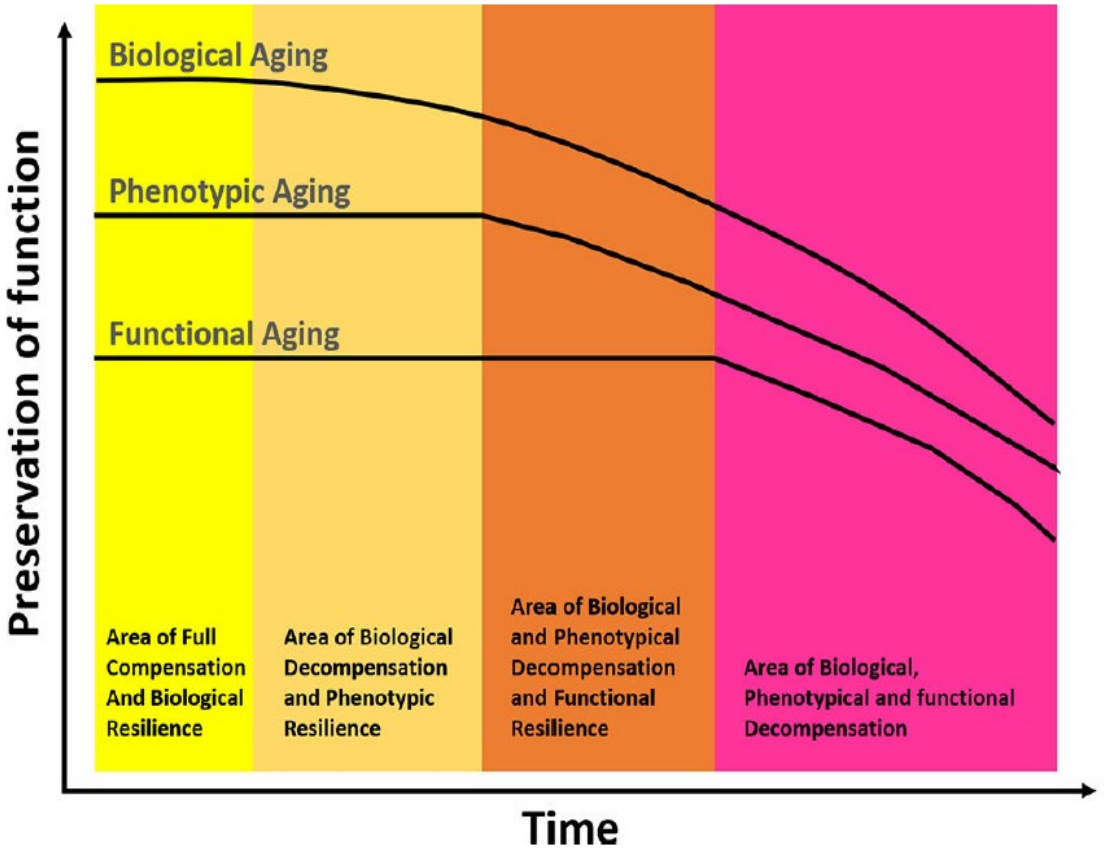
Fig. 2. : Lifespan and healthspan extension in healthy aging.

L'invecchiamento può essere definito come il fenomeno di un declino nei componenti di condizione fisica specifici dell'età di un organismo dovuto a un deterioramento fisiologico interno, con un declino delle funzioni biologiche legato all'età e una progressiva perdita di funzione accompagnata da un aumento della mortalità.

(Kirkwood and Austad 2000; Rose 1991).

L'invecchiamento «in salute» (healthy) è un concetto multidimensionale che si basa su **interazioni dinamiche per tutta la vita tra risorse intrinseche (individuali) ed estrinseche (contestuali)**, implicando processi adattivi attraverso attività di promozione e rafforzamento della salute per i cambiamenti che si verificano con l'invecchiamento per **prolungare l'aspettativa di vita in buona salute e mantenere una qualità di vita e un benessere ottimali a livello personale, familiare e sociale**

eClinicalMedicine
2023;56: 101821



The Metrics of Aging

Functional Aging (impact on daily life)

- Cognitive Function
- Physical Function
- Mood
- Mental Health

Phenotypic Aging (phenotypes that change)

- Body Composition
- Energetics
- Homeostatic Mechanisms
- Brain health

Biological Aging (root mechanisms)

- Molecular damage
- Defective repair
- Energy exhaustion
- Signal/noise reduction

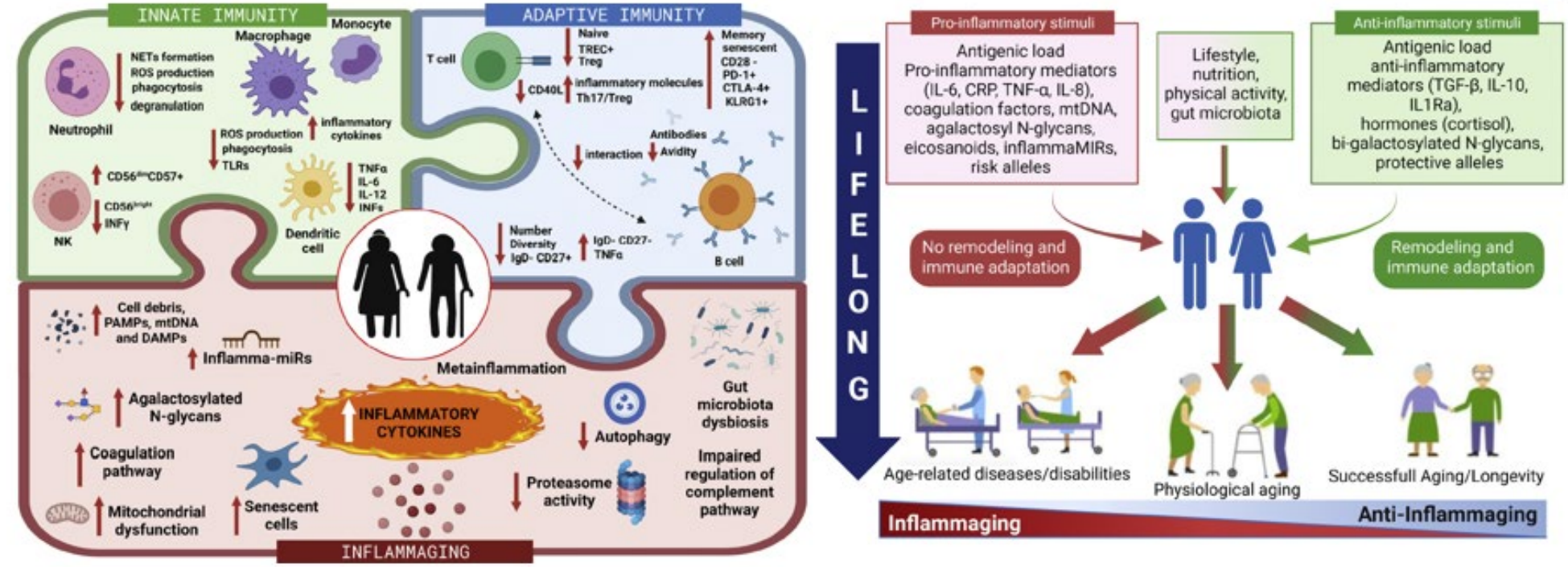
Ferrucci et al, Circ Res. 2018 September 14; 123(7): 740–744.

ELSEVIER

Immunosenescence and inflammaging in the aging process: age-related diseases or longevity?

Aurelia Santoro [a], Elisa Bientinesi [b], Daniela Monti [b,*]

Ageing Research Reviews 71 (2021) 101422



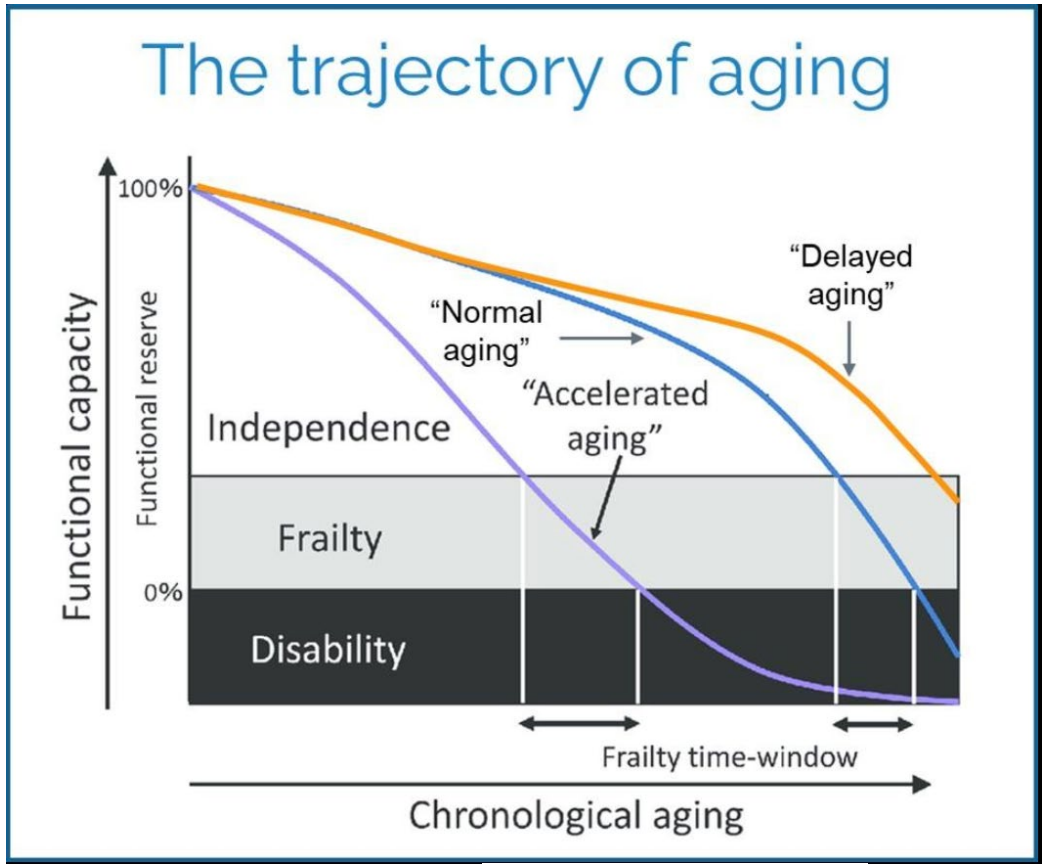
Aging is not uniform among individuals and can be considered **a continuum with the extreme phenotypes represented by diseases and disabilities on one side and healthy aging and longevity on the other side.** Several factors, such as **genetics, nutrition, exercise, previous exposure to microorganisms, sex (biological-related), gender (cultural-related) and human cytomegalovirus status**, can influence immunosenescence. The age-related immune changes may be a mix of **adaptation/resilience and maladaptation**, closely related to the immunobiography. There is an **intricate interrelationship between immunosenescence and inflammaging** able to generate a complex network of adaptive mechanisms that can favor longevity when able to counteract the injuries individuals are exposed lifelong (adaptation) or, on the opposite side, increase the susceptibility to diseases when inadequate (maladaptation). T

Salute e benessere nell'anziano: dal «successo» alla disabilità

Invecchiamento «di successo»

Fragilità

Disabilità



Shinmura K: Cardiac Senescence, Heart Failure, and Frailty. 2016

Il concetto di frailty

"…Una sindrome medica con cause e contributori multipli caratterizzata da una diminuzione della forza, della resistenza e della funzione fisiologica che aumenta la vulnerabilità dell'individuo a sviluppare una maggiore dipendenza e/o morte…"

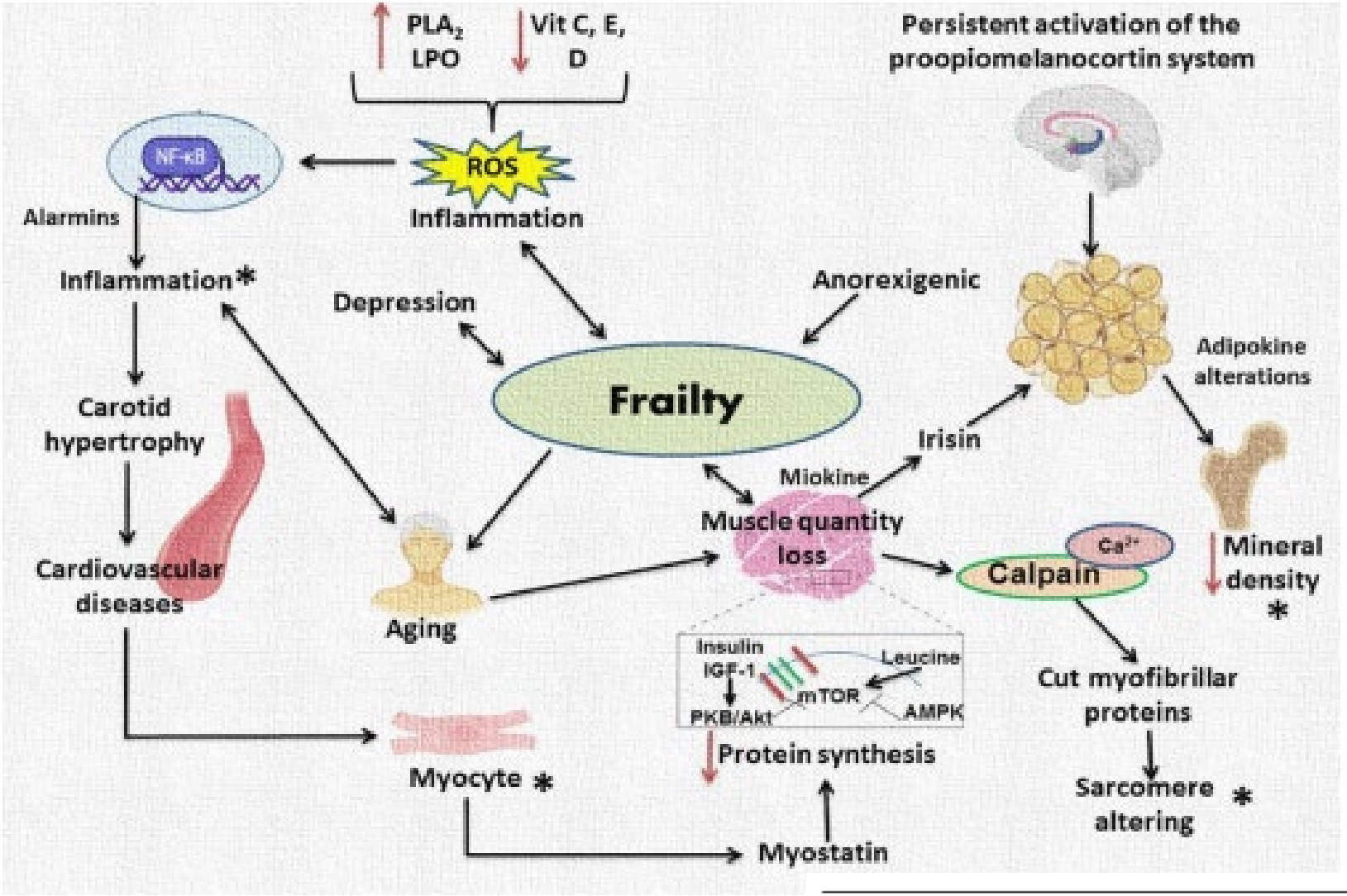
JE Morely et al. Frailty consensus: a call to action. JAMDA 14,382; 2013

Fragilità: condizione di elevata vulnerabilità ovvero di ridotta efficienza omeostatica dopo un evento stressante e conseguenza del declino cumulativo nel corso della vita in molti sistemi fisiologici legato alle patologie, al loro trattamento, agli stili di vita, all'invecchiamento.

Lancet 2013; 381: 752-62

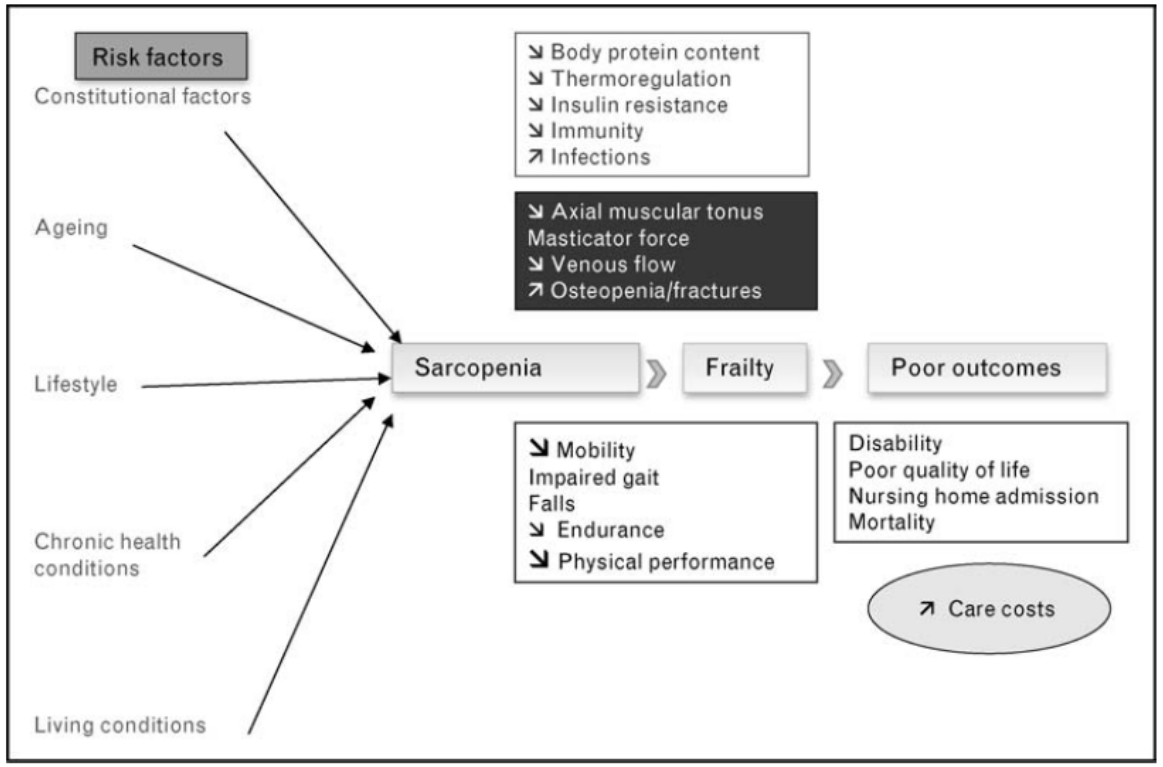
Oxidative stress activates several transcription factors that enhance the expression of more than 500 genes, including those encoding growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules, and anti-inflammatory molecules. **There are increased oxidative stress levels in aged muscles. Inflammation and oxidative stress mediators are biomarkers for frailty.** There is a link between C-reactive protein, IL-6, fibrinogen, and white blood cell count and frailty. **Markers of oxidative stress have been associated with frailty** in small cross-sectional studies and the participation of inflammation and oxidative stress in the frailty process has also been tested in experimental models.

Frailty and the Interactions between Skeletal Muscle, Bone, and Adipose Tissue



International Journal of Molecular Sciences

Int. J. Mol. Sci. **2023**, *24*, 4534. https://doi.org/10.3390/ijms24054534



Current Opinion in Clinical Nutrition and Metabolic Care 2010, 13:1–7

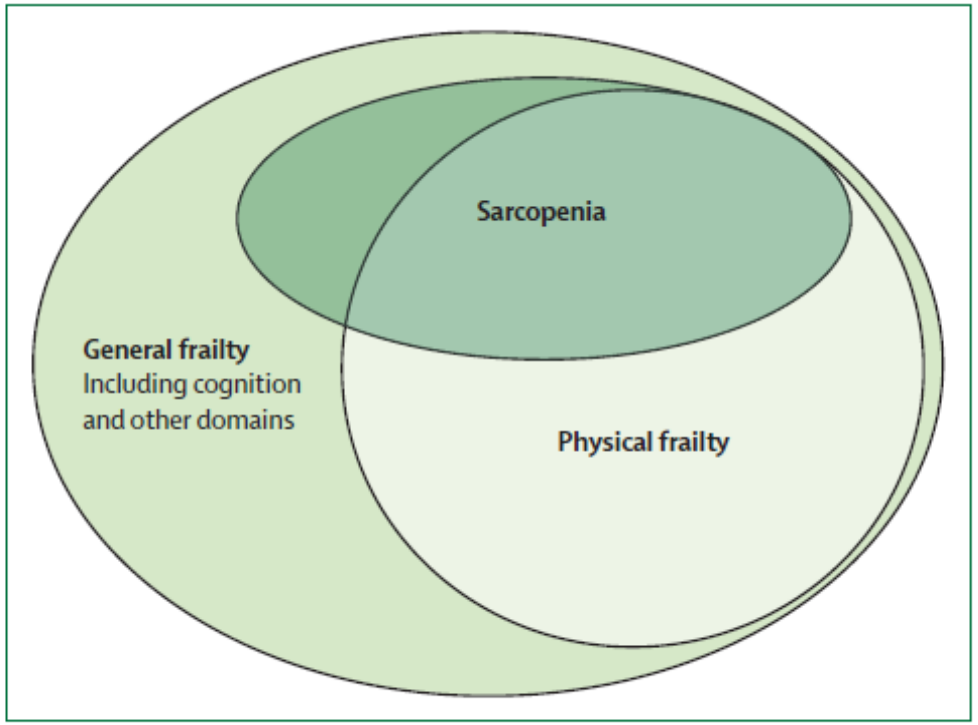


Figure 3: Schematic diagram showing the diagnostic overlap between sarcopenia and physical or general frailty

Lancet 2019; 393: 2636–46

Sarcopenia e frailty sindromi geriatriche correlate

CAPACITA' INTRINSECA (INTRINSIC CAPACITY)

La capacità intrinseca (CI) è definita come l'insieme di tutte le capacità fisiche e mentali su cui un individuo può fare affidamento durante la sua vita. La fragilità e la CI sono due concetti che derivano dalla stessa necessità di superare i paradigmi medici tradizionali che influenzano negativamente il modo corretto in cui la pratica clinica e la ricerca dovrebbero essere condotte nelle persone anziane.

Global Strategy and Action Plan on Ageing and Health. Geneva:World Health Organization, (2017).

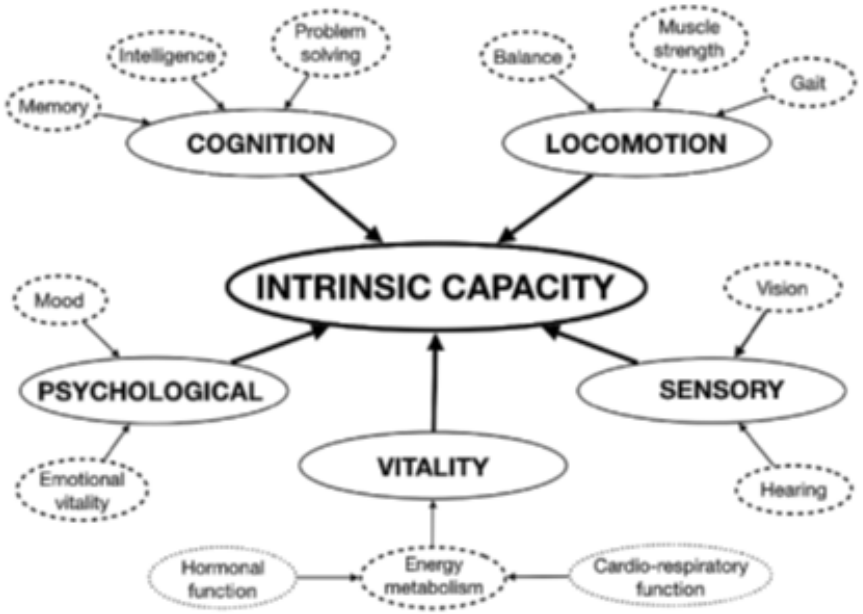


Figure 2. The five domains (i.e., locomotion, sensory, cognition, psychological, vitality) constituting the intrinsic capacity construct. Examples of possible subdomains are also provided.

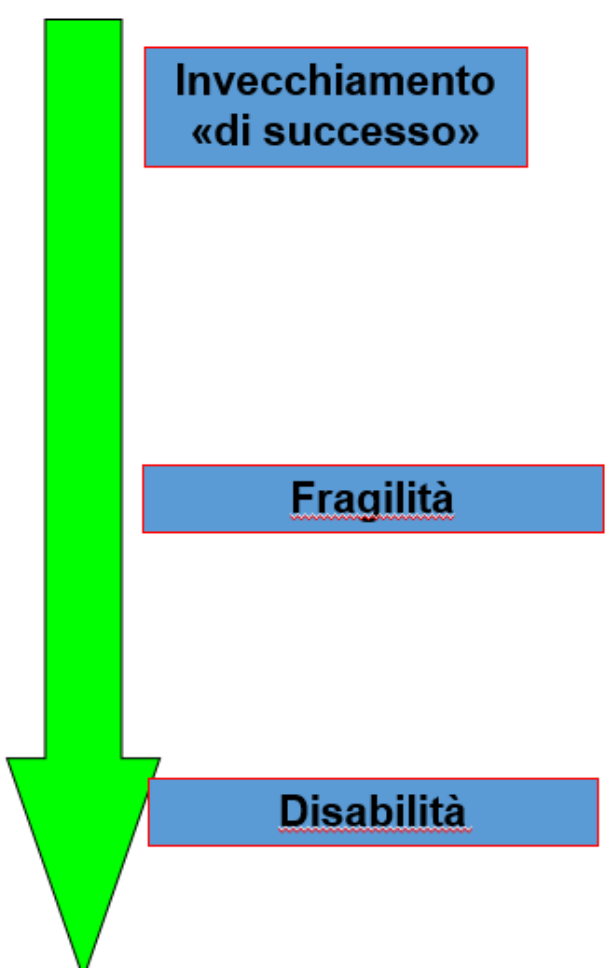
Cesari M, et al. J Gerontol A Biol Sci Med Sci 2018;73(12):1653–60

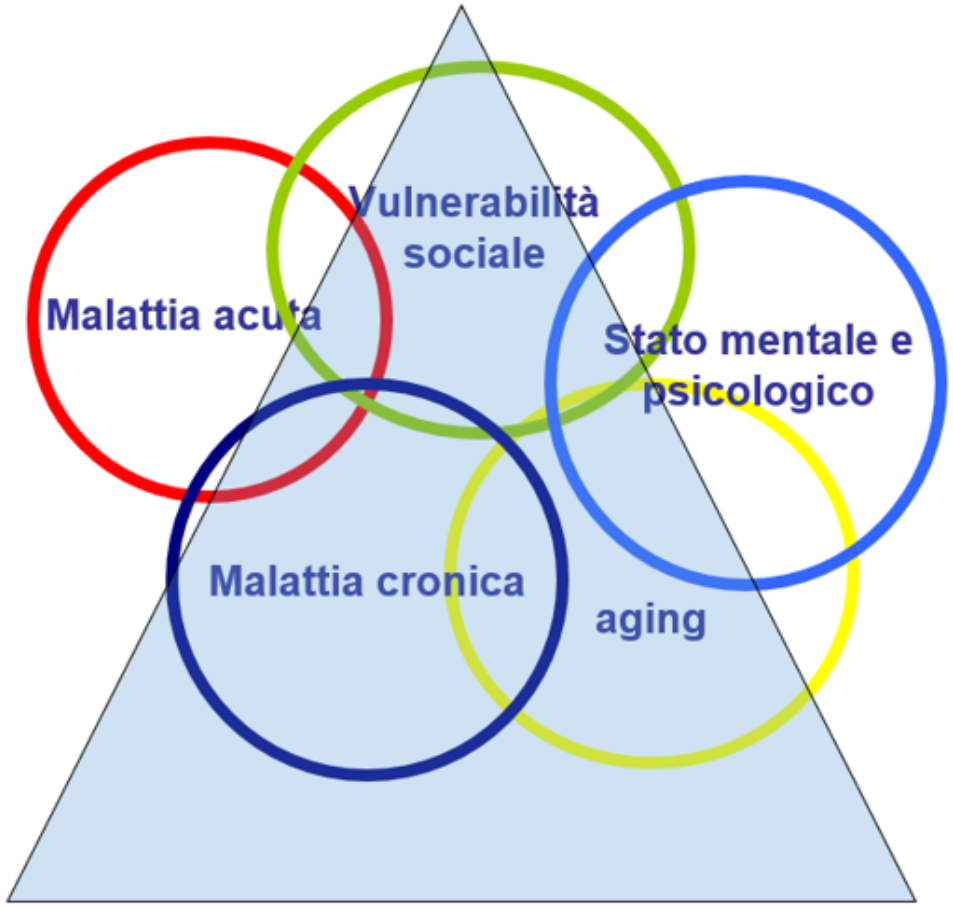
Fragilità e Capacità Intrinseca

Caratteristica	Fragilità	Capacità Intrinseca (CI)
Definizione	Condizione di vulnerabilità aumentata con ridotta riserva fisiologica e capacità di resistenza agli stress.	Insieme delle capacità fisiche e mentali che una persona può sfruttare nel corso della sua vita.
Origine del concetto	Medico, con focus sulla vulnerabilità agli esiti negativi di salute.	Introduzione dall'Organizzazione Mondiale della Sanità (OMS) per valutare il potenziale complessivo di salute e benessere.
Sintomi/Caratteristiche	Debolezza muscolare, perdita di peso, affaticamento, lentezza, ridotta attività fisica.	Include domini come forza fisica, mobilità, cognizione, vista, udito, stato psicologico.
Focus	Identificazione e gestione del rischio di esiti negativi di salute (cadute, ospedalizzazioni, mortalità).	Mantenimento e promozione della salute e del benessere generale, indipendentemente dalle malattie croniche.
Obiettivo	Ridurre la vulnerabilità e prevenire gli esiti negativi di salute.	Prolungare l'aspettativa di vita in buona salute e mantenere una qualità di vita ottimale.
Approccio terapeutico	Interventi mirati per migliorare la resistenza agli stress e la capacità di recupero.	Promozione della salute attraverso attività di empowerment e adattamento ai cambiamenti legati all'invecchiamento.
Impatto	Maggiore suscettibilità a esiti negativi di salute.	Potenziale per una vita più lunga e sana con una migliore qualità di vita.
Valutazione	Spesso basata su test e indici specifici (es. Fried Frailty Index).	Valutazione olistica delle capacità fisiche e mentali, tenendo conto di vari domini.

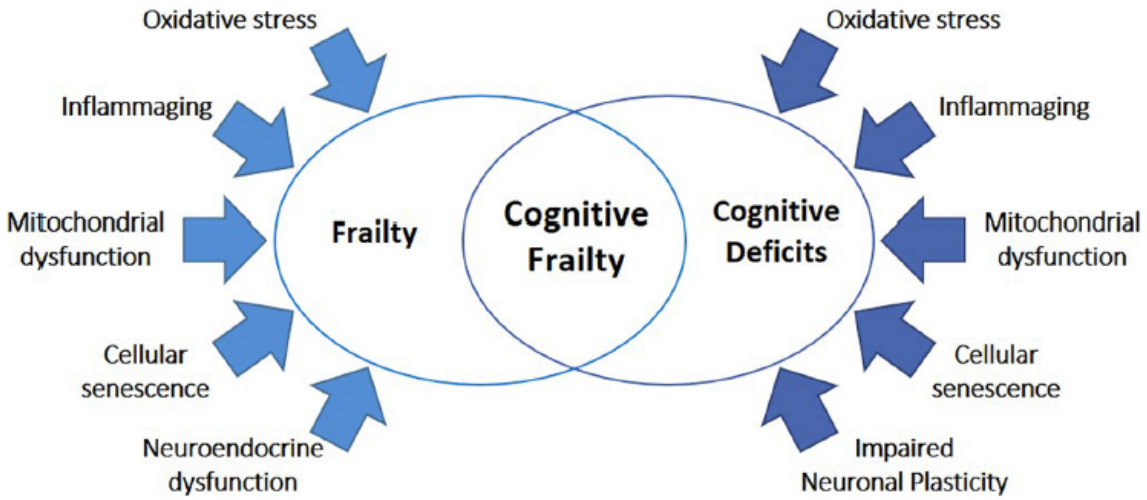
World Health Organization. (2015). World report on ageing and health. Geneva: World Health Organization. Available at: WHO World Report on Ageing and Health

Salute e benessere nell'anziano: dal «successo» alla disabilità





frontiers in Aging Neuroscience
REVIEW
published: 12 November 2021
doi: 10.3389/fnagi.2021.763110



Oxidative stress, inflammaging, mitochondrial dysfunction, cellular senescence, neuroendocrine dysfunctions, and impaired neuronal plasticity are all key factors in the development of frailty.

Oxidative stress, which results from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them, can lead to cellular damage and dysfunction.

Inflammaging, a chronic low-grade inflammation associated with aging, contributes to the development of frailty and age-related diseases.

Mitochondrial dysfunction, characterized by impaired energy production and increased ROS levels, is also implicated in frailty, as it can lead to cellular damage and senescence.

Cellular senescence, is associated with frailty due to its impact on tissue homeostasis and regeneration.

Neuroendocrine dysfunctions, including alterations in hormone secretion and signaling, can impair the body's ability to respond to stress and maintain homeostasis, contributing to frailty.

I**mpaired neuronal plasticity**, can lead to cognitive deficits and physical frailty.

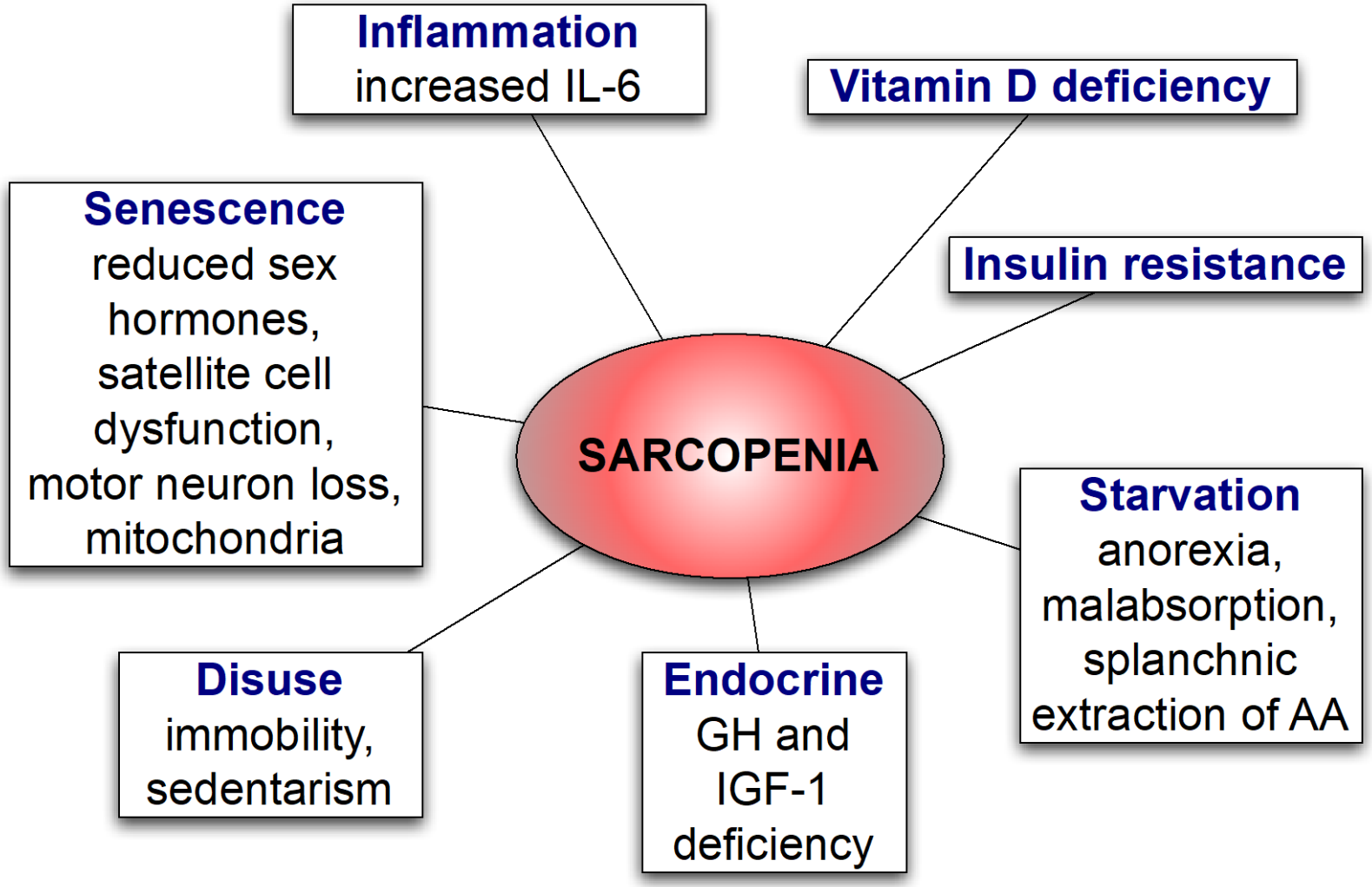
These mechanisms are interconnected and contribute to the development of frailty by affecting various physiological systems, including the **immune system, skeletal muscle function, and tissue regeneration**.

Prevention of Frailty

1. **Regular Physical Activity**: Engaging in regular exercise, such as strength training, walking, and balance exercises, can improve muscle strength and mobility.
2. **Balanced Diet**: Eating a nutritious diet that includes a variety of fruits, vegetables, lean proteins, and whole grains can help maintain a healthy weight and provide essential nutrients.
3. **Social Engagement**: Staying socially active can improve mental health and prevent feelings of loneliness and depression.
4. **Cognitive Training**: Activities that stimulate the brain, such as reading, puzzles, or learning new skills, can help maintain cognitive function.
5. **Regular Health Check-ups**: Keeping up with medical appointments can help detect and treat health issues before they contribute to frailty.
6. **Adequate Sleep**: Ensuring sufficient and good quality sleep supports overall health and can prevent physical and cognitive decline.
7. **Fall Prevention Measures**: Implementing safety modifications in the home and practicing balance exercises can reduce the risk of falls.
8. **Management of Chronic Conditions**: Proper management of conditions like diabetes, heart disease, infections, or arthritis can minimize their impact on physical health.

Puts et al, Age Ageing. 2017; Pilotto et al, Ageing Res Rev. 2020; Dent E et al, Lancet 2019; 394: 1376–86

Therapeutic approaches to sarcopenia



Cederholm *et al.* Clin Geriatr Med 2011

Nutraceuticals for aging brain, frailty, inflammaging

- Polyphenols
  - Flavonoids, Ginkgo biloba
  - Blueberry and soy flavonoids
  - Resveratrol
  - Curcumin
- Vitamins and oligoelements
  - Vitamin C, vitamin E, vitamin D
  - Folic ac and vitamin B
  - Zinc
- Ω-3 fatty acids
- Antioxidants (Lipoic ac, Glutathione supplements, PEA)
- Acetyl-L-carnitine
- Homotaurine
- CDP-choline, Choline alfoscerate, Phosphatidylserine, Fortasyn Connect

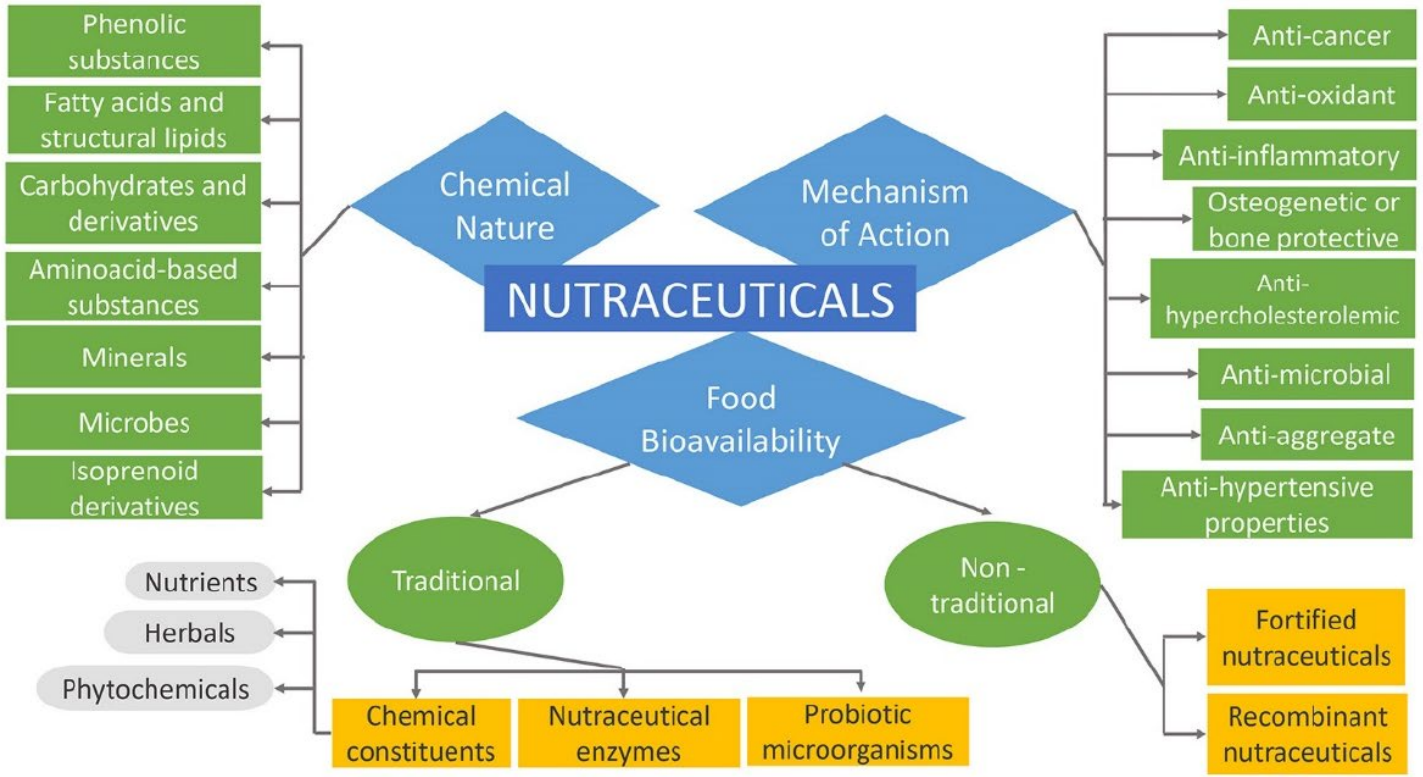


Figure 4. Classification of Nutraceuticals.

International Journal of Molecular Sciences
Int. J. Mol. Sci. **2022**, *23*, 4102. https://doi.org/10.3390/ijms23084102

SERIES: NUTRITION ISSUES IN LONG-TERM CARE
The Role of Nutrition in Modifiable Geriatric Syndromes
Annals of Long-Term Care

Mary Litchford, PhD, RD, LDN [1] **Series Editor:** Liz Friedrich, MPH, RD, CSG, LDN [2]

Mecocci P et al, *FPHAR* 2014; De Domenico S et al, *JGG*, 2017; Vaclos GS et al, *Dialogues Clin Neurosci* 2019; Maccioni RB et al, *Biomolecules*, 2022

materials

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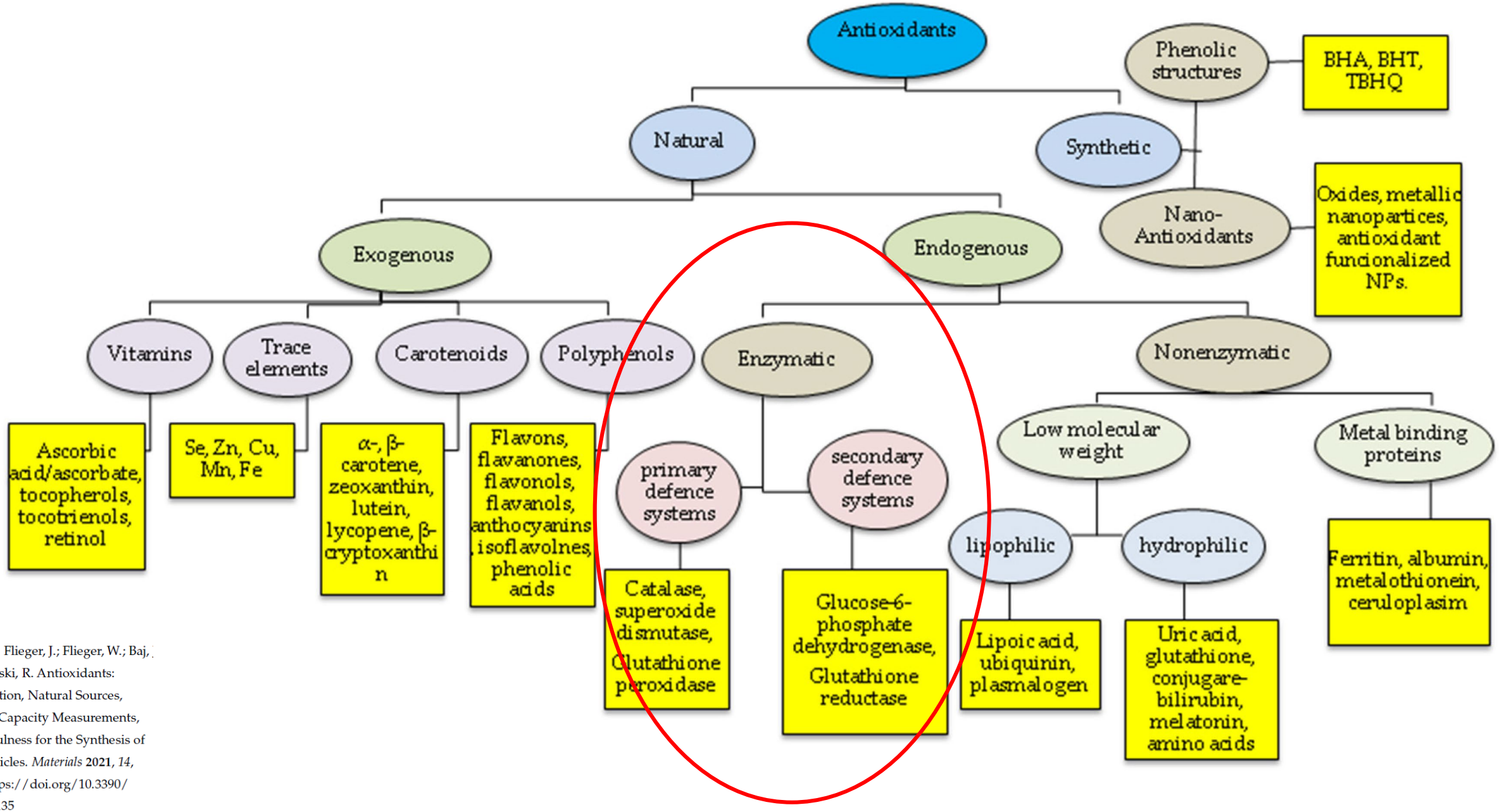


Citation: Flieger, J.; Flieger, W.; Baj, Maciejewski, R. Antioxidants: Classification, Natural Sources, Activity/Capacity Measurements, and Usefulness for the Synthesis of Nanoparticles. *Materials* **2021**, *14*, 4135. https://doi.org/10.3390/ma14154135

Role of GSH in clinical conditions and disease

- Aging and related disorders
- Brain disorders (autism, Alzheimer's disease, Parkinson's disease, bipolar disorders and schizophrenia, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis)
- Cancer
- Chronic liver disease
- Cystic fibrosis
- Diabetes, especially uncontrolled diabetes
- Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS)
- Infertility in both men and women
- Blood hypertension

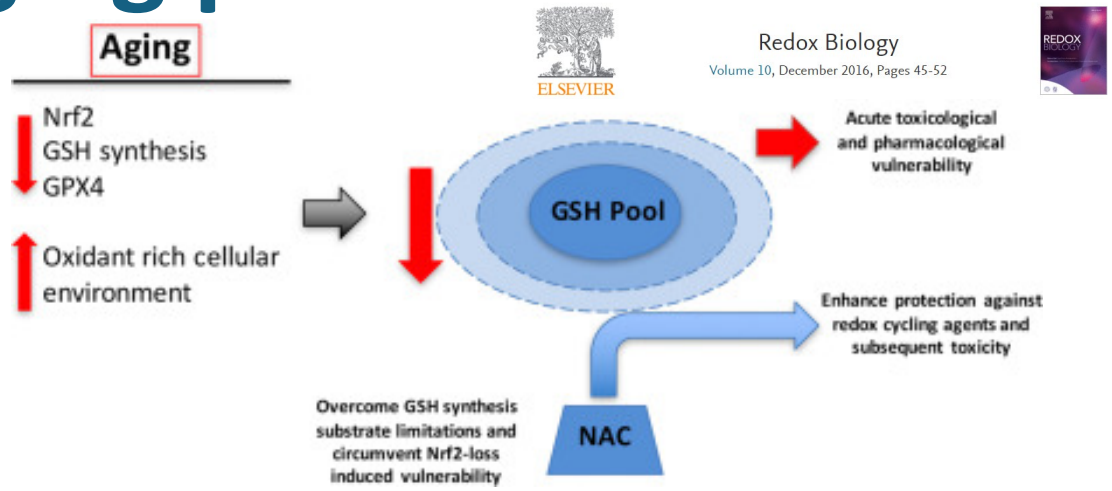
Glutathione: pharmacological aspects and implications for clinical use

Andrea Novelli,[1] Angelo Bianchetti[2]

Geriatric Care 2022; volume 8:10390

Glutathione and aging process.

- Given the **multiple biological mechanisms of glutathione** (antioxidant activity, detoxification of endogenous compounds and xenobiotics; modulation of immune function, DNA synthesis, repair, and expression) it is hypothesized that **glutathione plays a role in the aging process itself.**
- **Geriatric syndromes, such as frailty, sarcopenia and multimorbidity,** are characterized by physical vulnerability to stress and a lack of physiological reserve.
- **GSH depletion is also manifested by progressive loss of mitochondrial function** due to the accumulation of damage to mtDNA and GSH status has been found in parallel with **telomerase activity**, an important indicator of lifespan.
- The best indicator of the importance of glutathione is that its **cellular and mitochondrial levels directly are highly associated with health and longevity** and the ability of animal species to protect their mtDNA is directly proportional to longevity.
- GSH also plays a central role in **cell death, including apoptotic cell death.**



Redox Biology
Volume 10, December 2016, Pages 45-52
ELSEVIER

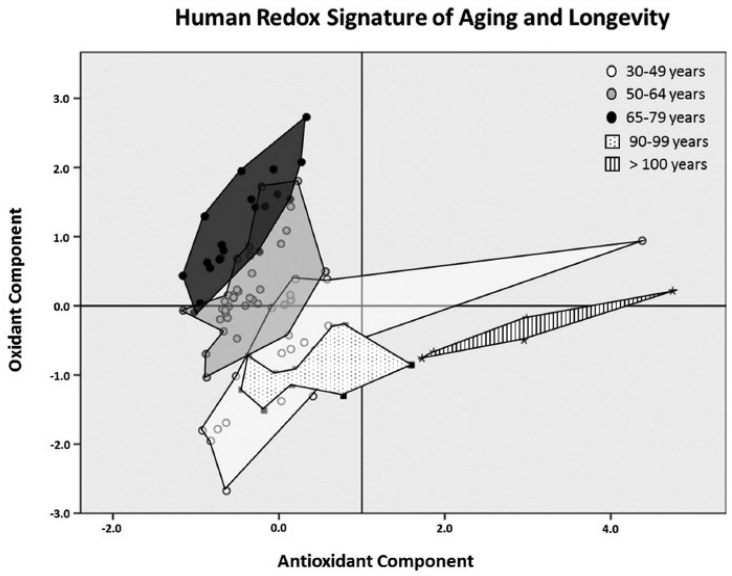


Figure 4. Human redox signature of aging and longevity. Principal component

Journals of Gerontology: BIOLOGICAL SCIENCES, 2020, Vol. 75, No. 4

Geriatric Care 2022; volume 8:10390

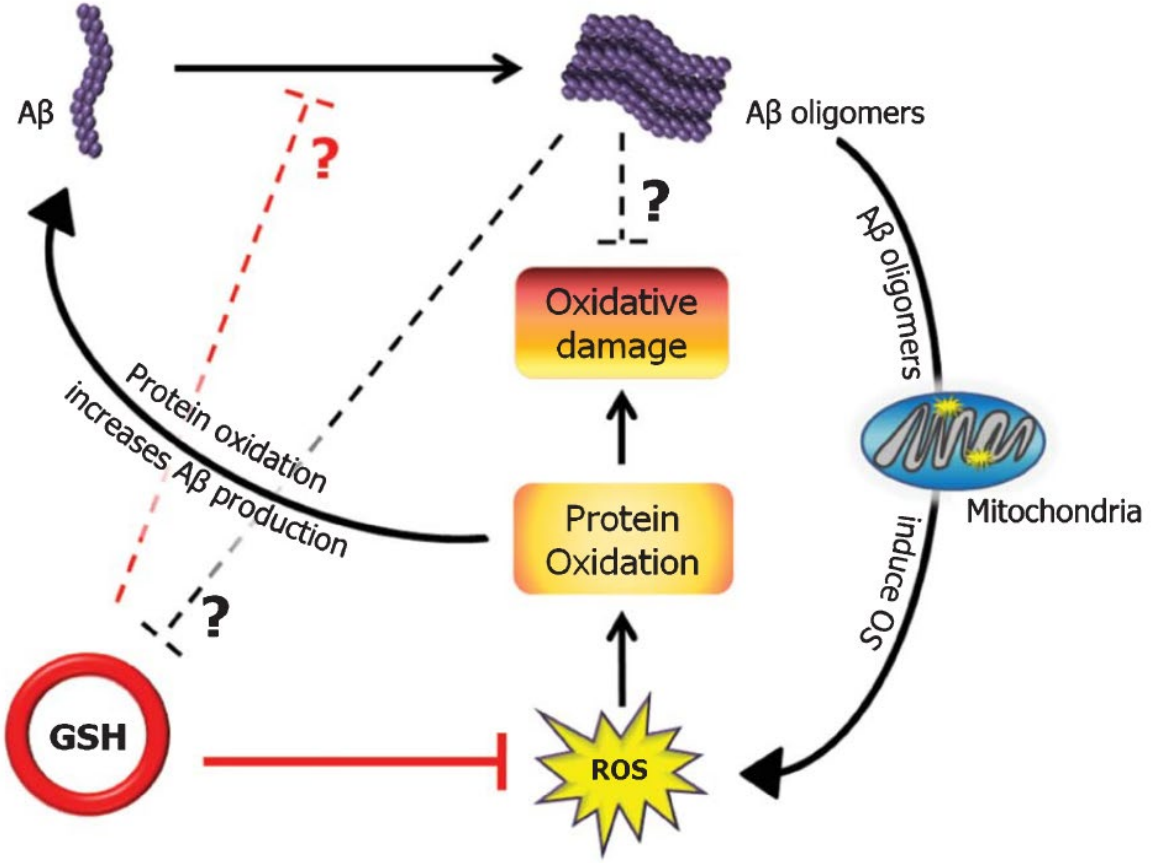
Glutatione e neurodegenerazione

- Schematic depicting the **complex interplay between oxidative stress (OS) and amyloid-B (AB) peptides and the potential role of glutathione (GSH) in regulating Alzheimer's disease (AD) pathology.**
- Studies have shown that AB oligomers induce mitochondrial reactive oxygen species (ROS) formation. ROS formation leads to oxidative modification of various cellular proteins, thereby affecting their function.
- Recent studies suggest that. **oxidation of proteins involved in AB peptide formation can, in turn, increase Ab production.**
- **GSH is a potent antioxidant that has been shown to attenuate Ab-induced oxidative damage**. Preliminary in vitro evidence also suggests that **GSH may be directly involved in attenuating AD pathogenesis**.
- In vitro studies have provided evidence that **AB may directly disrupt GSH cycle homeostasis and lead to GSH depletion**.
- Arrows ends indicate a positive/stimulatory effect, whereas flat ends are indicative of a negative/inhibitory effect. Dashed lines with question mark are indicative of preliminary evidence that remains to be corroborated.

The Emerging Role of Glutathione in Alzheimer's Disease

Sumiti Saharan[a] and Pravat K. Mandal[a,b,*]

Journal of Alzheimer's Disease 40 (2014) 519–529



Neurochemistry International
Volume 144, March 2021, 104931

Supplementation with γ-glutamylcysteine (γ-GC) lessens oxidative stress, brain inflammation and amyloid pathology and improves spatial memory in a murine model of AD

12-14 settembre 2024
Bologna

- The accumulation of oxidative stress, neuroinflammation and abnormal aggregation of amyloid β-peptide (Aβ) have been shown to induce synaptic dysfunction and memory deficits in Alzheimer's disease (AD). **Cellular depletion of the major endogenous antioxidant Glutathione (GSH) has been linked to cognitive decline and the development of AD pathology**.
- **Supplementation with γ-glutamylcysteine (γ-GC), the immediate precursor and the limiting substrate for GSH biosynthesis, can transiently augment cellular GSH levels by bypassing the regulation of GSH homeostasis.**
- Our study has demonstrated that **γ-GC can lessen oxidative stress, inflammation and Aβ burden in an AD mouse model**.
- The beneficial effects in AD of increasing cellular GSH through the administration of γ-GC may not only result in protection against neurodegeneration but also improvement in cognitive function, which is currently not possible in the clinic.

Strategies for increasing gluthatione cellular levels

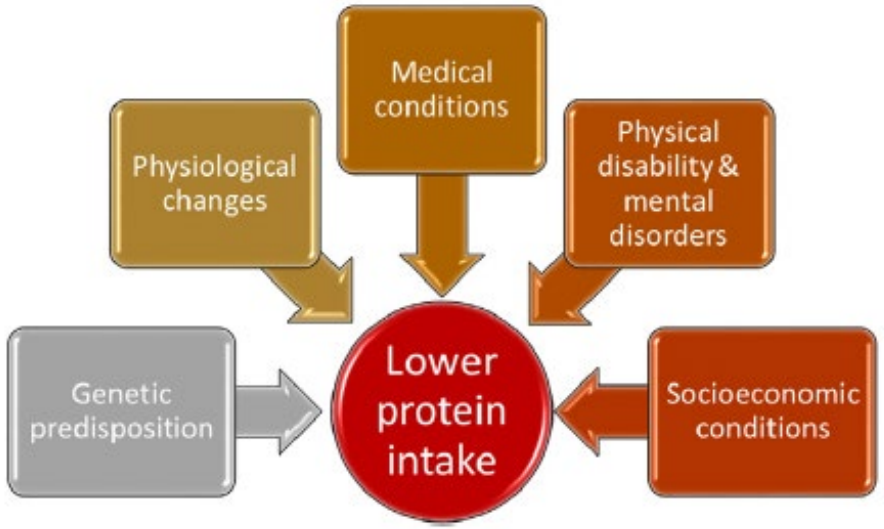
- There is an average of 30 g of glutathione in the body, which has a half-life of about 48 hours
- On average, the human body consumes 3 g of glutathione per day
- In conditions of deficiency or increased need**, it is necessary to increase blood and cellular levels**
  - **Dietary Protein or omega-3 fatty acids** supplementation are the most popular among the different strategies to improve glutathione levels.
  - **Cysteine** availability is the rate-limiting step in the de novo production of glutathione
  - On the other hand, the obvious strategy to increase gluthatione levels is to **directly administer** it. This can be done *orally, intravenously, intranasal, or in nebulized form.*
  - Oral administration is controversial; unmodified oral glutathione is unlikely to consistently elevate cellular levels, since it would be degraded by digestive peptidases.
  - Recent research suggests that when **glutathione is administered in liposomal or sublingual forms it may be made more bioavailable and favorably impact systemic glutathione levels**.

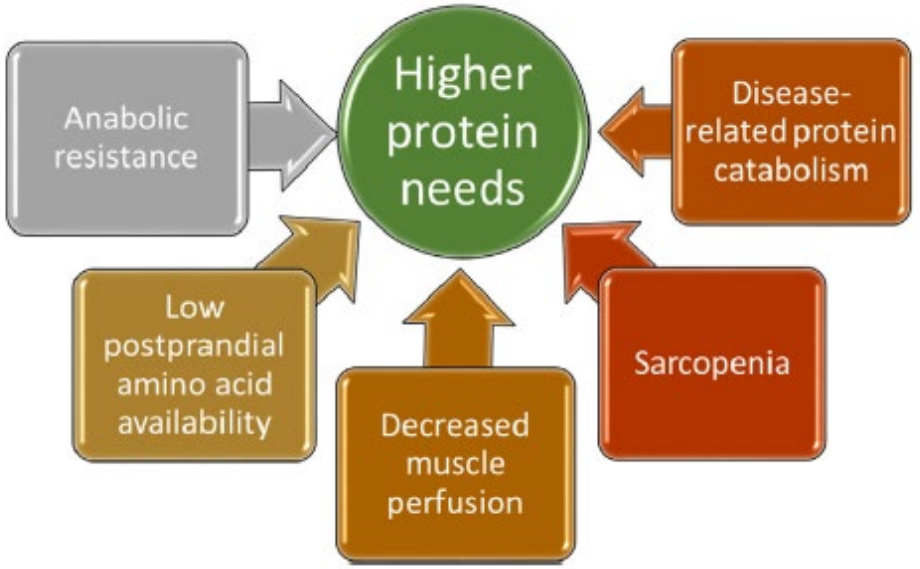
Glutathione: pharmacological aspects and implications for clinical use

Andrea Novelli,[1] Angelo Bianchetti[2]

Geriatric Care 2022; volume 8:10390

Quando utilizzare gli integratori nella sarcopenia?





Conclusioni

- L'invecchiamento è un processo dinamico, influenzato dagli stili di vita, dalla storia personale, dalle relazioni e dalle patologie.
- La fragilità (fisica e cognitiva) è la condizione clinico-biologica di transizione fra invecchiamento di successo e patologia, condizione dinamica e potenzialmente «reversibile»
- La sarcopenia è una sindrome geriatrica che è fortemente collegata ai meccanismi ed ai fattori di rischio della fragilità
- Fattori genetici ed epigenetici sono coinvolti nello sviluppo dei meccanismi che portano alla sarcopenia e alla fragilità
- Infiammazione cronica, sbilanciamento dei meccanismi ossidativi/riduttivi, disfunzione mitocondriale, alterazioni neuroendocrine sono alla base dei processi di invecchiamento e influenzano lo sviluppo delle fragilità.
- Gli stili di vita, la nutrizione, l'adeguata attività fisica e mentale, una vita ricca di contatti sociale significativi e l'uso di specifici supplementi può modificare i processi di invecchiamento, di fragilità e di neurodegenerazione e la sarcopenia.

The Harvard Gazette

HEALTH & MEDICINE

Good genes are nice, but joy is better

BY Liz Mineo
Harvard Staff Writer

DATE April 11, 2017

Harvard study, almost 80 years old, has proved that embracing community helps us live longer, and be happier

PNAS

Optimism is associated with exceptional longevity in 2 epidemiologic cohorts of men and women

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Significance

Optimism is a psychological attribute characterized as the general expectation that good things will happen, or the belief that the future will be favorable because one can control important outcomes. Previous studies reported that more optimistic individuals are less likely to suffer from chronic diseases and die prematurely. Our results further suggest that optimism is specifically related to 11 to 15% longer life span, on average, and to greater odds of achieving "exceptional longevity," that is, living to the age of 85 or beyond. These relations were independent of socioeconomic status, health conditions, depression, social integration, and health behaviors (e.g., smoking, diet, and alcohol use). Overall, findings suggest optimism may be an important psychosocial resource for extending life span in older adults.