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# ICE-BREAKING

## Who is Who?

September 19, 2022

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# Transgenerational Ageing (1)

**Rossella E. Nappi**
(UNIPV-ITALY)

GLADE – VIRTUAL INSTITUTE FOR GOOD HEALTH AND WELL-BEING,
18 – 25 September, 2022

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# Ageing & Geroscience

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# Medico-sociological problems of an ageing population

## AGE COMPOSITION OF A POPULATION

It is established that the age composition of a population is among the best yardsticks that can be used for the assessment of the biological healthiness of a people. It is a true record of the reactions of an organised group of living human beings, generation by generation, to those agencies, catastrophic and gentle, which affect the biological variables of natality, mortality, and migration. It shows how, for example, industrialisation, urbanisation, the spread of education, and changes in systems of land tenure, in the status of women, in standards of living, and in standards of value affect the birth-rate, death-rate, and migration-rate, and in so doing disturb the relative proportions of the young, the mature, and the old in the population concerned. It is the record of the social history of the people and furnishes a measure of the quality of social legislation. It therefore must attract the attention of all who are concerned with plans for the amelioration of man and of the social institutions that he has invented.

*Crew, 1946*

# Biopsychosocial approach to human health

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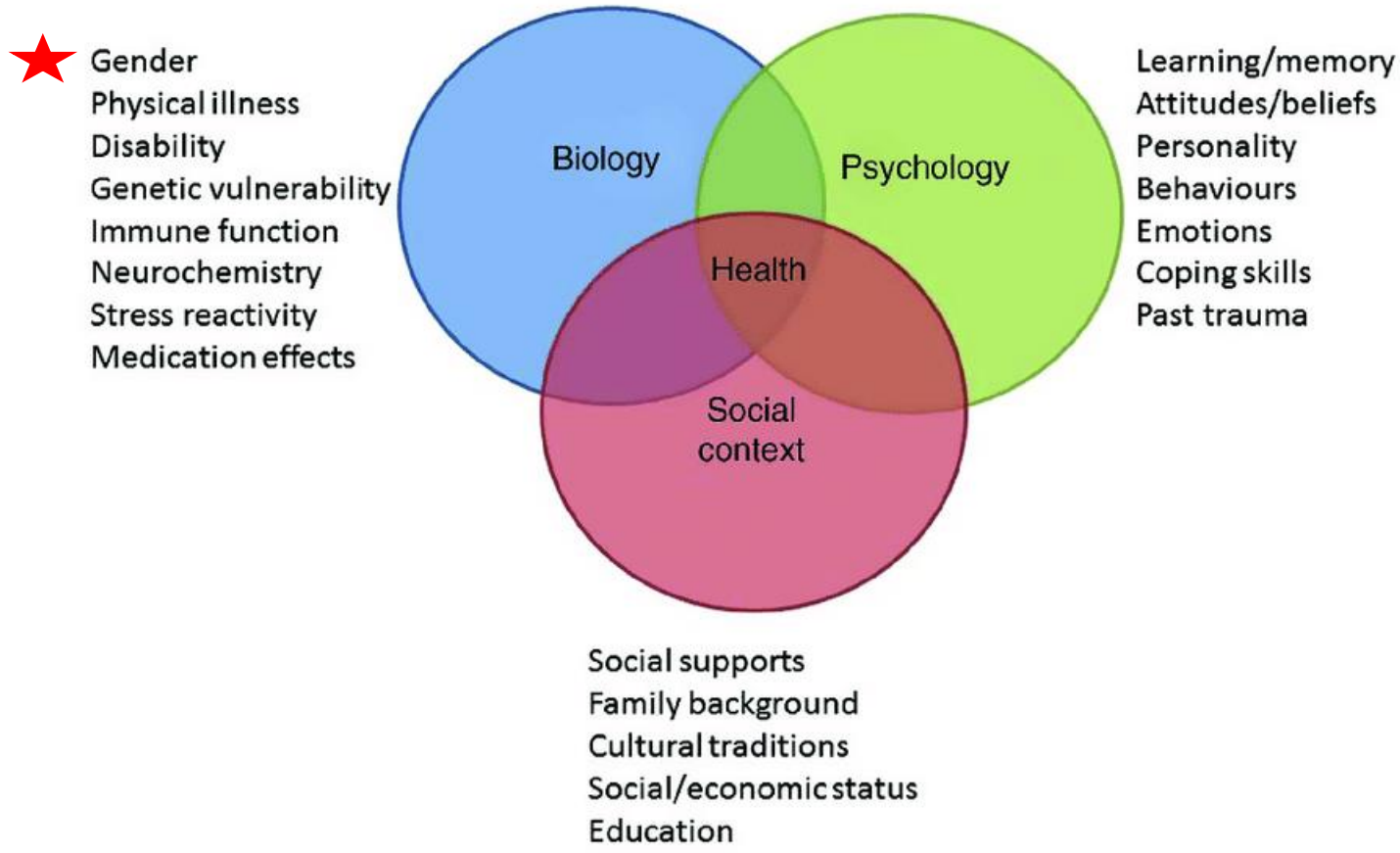


*Storms, 2017*

# Life expectancy of women across the globe

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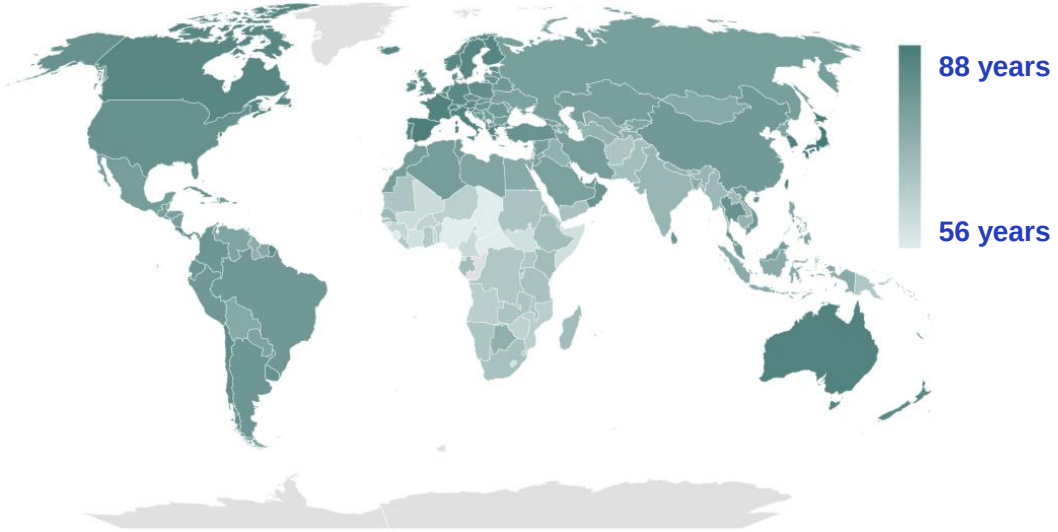
It has reached 73.8 years in 2021 and is expected to be 79.8 years in 2050[1]

## Life expectancy of women per country – 2020[2]




| Female life expectancy in years[1] | | |
|---|---|---|
| | 2021 | 2050 |
| Sub-Saharan Africa | 61.6 | 69.1 |
| Northern Africa and Western Asia | 74.8 | 80.8 |
| Central and Southern Asia | 69.9 | 79.4 |
| Eastern and South-Eastern Asia | 79.6 | 84.1 |
| Latin America and the Caribbean | 75.8 | 83.1 |
| Europe and Northern America | 80.4 | 86.1 |
| **World** | **73.8** | **79.8** |

1. UN World Population Prospects 2022 - Summary of Results Available at: https://reliefweb.int/report/world/world-population-prospects-2022-summary-results; Accessed on August 04th, 2022.
2. Our World in Data - Why do women live longer than men? Available at: https://ourworldindata.org/why-do-women-live-longer-than-men; Accessed on July 06th, 2022.

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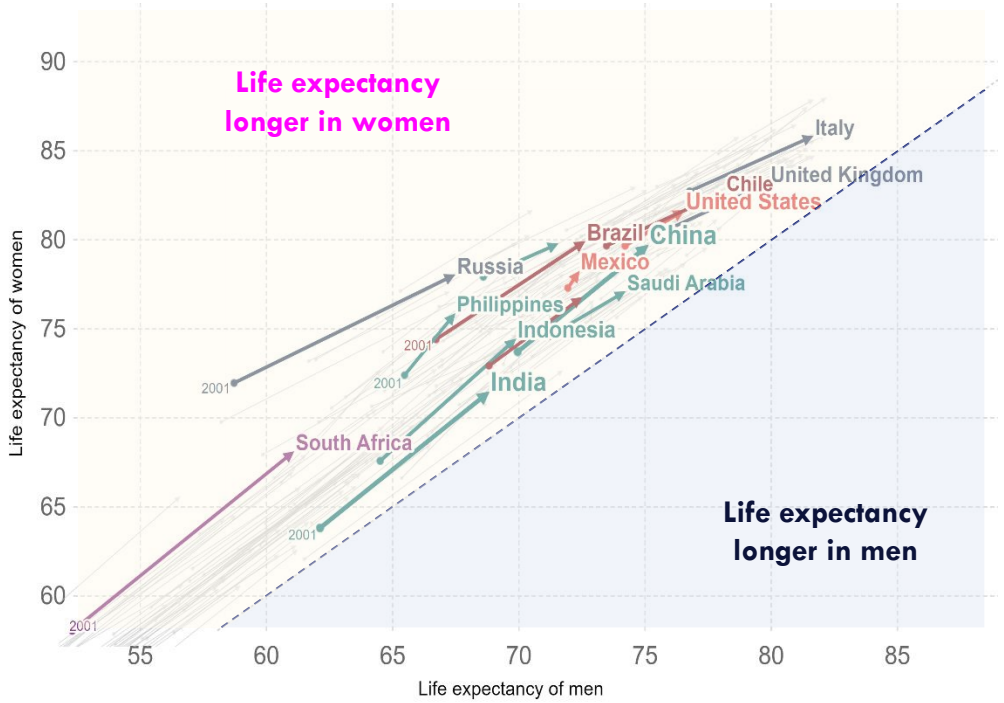
# Women have longer life expectancy than men

## The difference has not been reduced in the last 2 decades




| | Women | | Men | |
|---|---|---|---|---|
| | 2001 | 2020 | 2001 | 2020 |
| Worldwide | 68.9 | 75.2 | 64.3 | 70.4 |

Difference in 2001: 4,6 years

Difference in 2020: 4,8 years

Our World in Data - Why do women live longer than men? Available at: https://ourworldindata.org/why-do-women-live-longer-than-men; Accessed on July 06th, 2022.

# Women have longer life expectancy: differences across the globe in the last 2 decades

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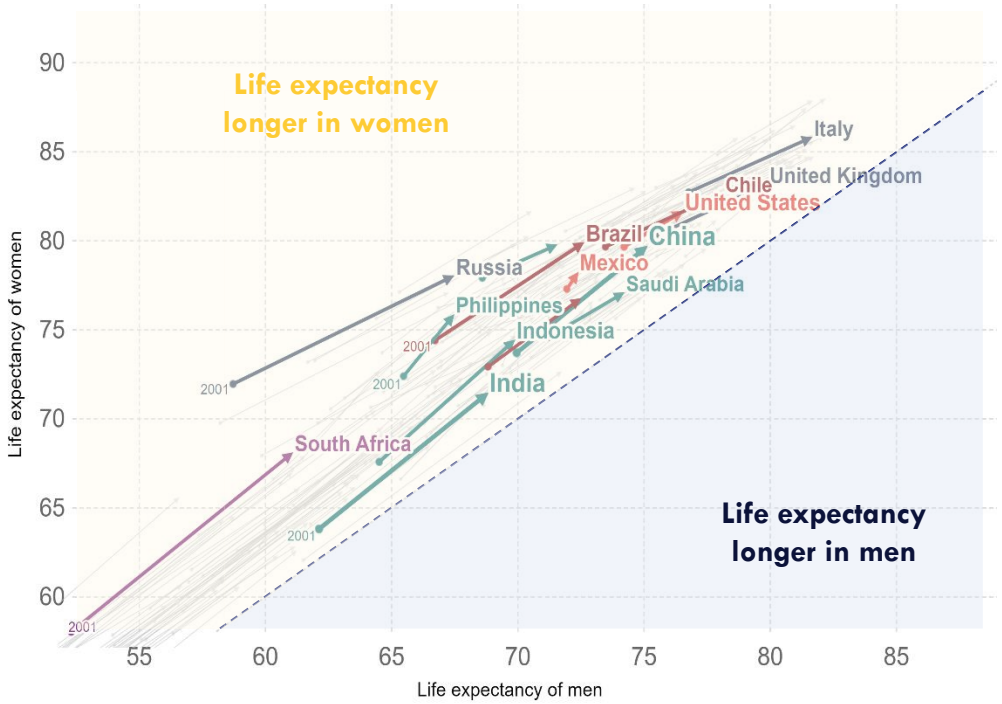


| | Women | | Men | |
|---|---|---|---|---|
| | 2001 | 2020 | 2001 | 2020 |
| Australia | 82.5 | 85.5 | 77.3 | 81.7 |
| Brazil | 74.4 | 79.7 | 66.8 | 72.5 |
| China | 73.7 | 79.4 | 70.0 | 75.0 |
| Colombia | 76.5 | 80.2 | 69.9 | 74.7 |
| India | 63.7 | 71.2 | 62.1 | 68.7 |
| Indonesia | 67.5 | 74.2 | 64.6 | 69.8 |
| Italy | 82.7 | 85.7 | 76.8 | 81.5 |
| Mexico | 77.3 | 77.9 | 72.0 | 72.3 |
| Philippines | 72.4 | 75.6 | 65.5 | 67.4 |
| Russia | 71.9 | 77.9 | 58.7 | 67.3 |
| Saudi Arabia | 74.6 | 76.9 | 71.3 | 74.1 |
| South Africa | 58.0 | 67.9 | 52.3 | 61.0 |
| United Kingdom | 80.3 | 83.1 | 75.6 | 79.8 |
| **WORLD** | **68.9** | **75.2** | **64.3** | **70.4** |

Our World in Data - Why do women live longer than men? Available at: https://ourworldindata.org/why-do-women-live-longer-than-men; Accessed on July 06th, 2022.

# The evolving pyramid in EU

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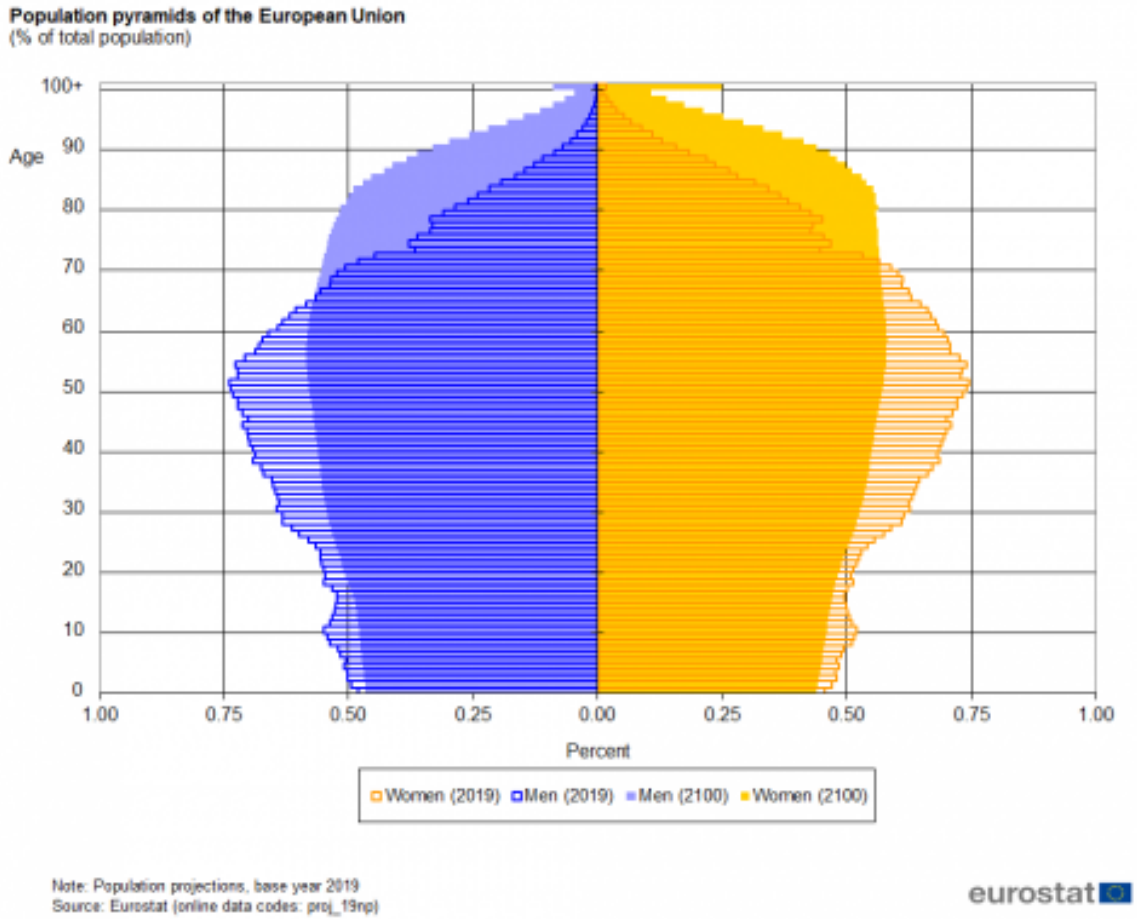
- **In 2021, more than one fifth (20.8%) of the EU population was aged 65 and over.**
- **The share of people aged 80 years or above in the EU's population is projected to have a two and a half fold increase between 2021 and 2100, from 6.0% to 14.6%.**




2022

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# Years of good life is a well-being indicator designed to serve research on sustainability

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YoGL and life expectancy at age 50 for 14 European countries, 2013.

*Lutz et al, 2021*

# Disability-free life expectancy in EU

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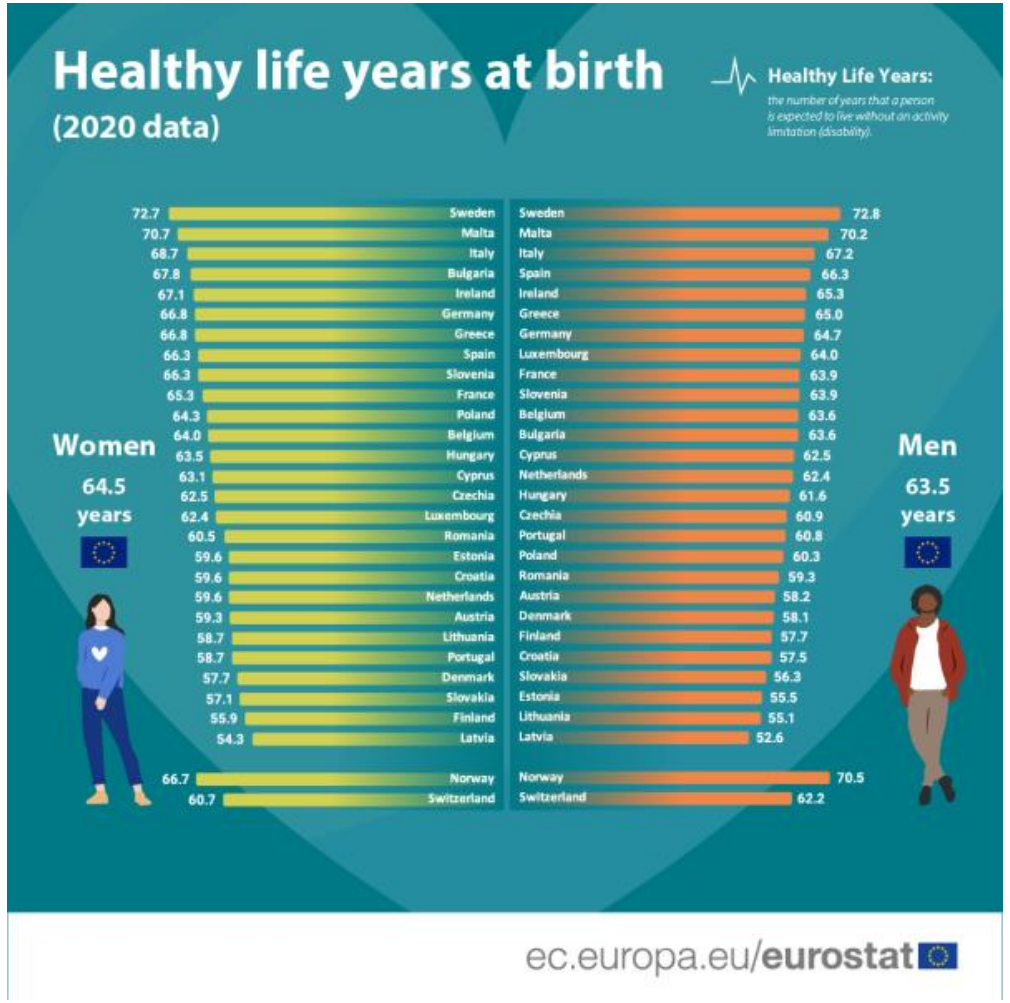
- **In the EU, this represented approximately 77.6% and 81.9% of the total life expectancy for women and men, respectively.**

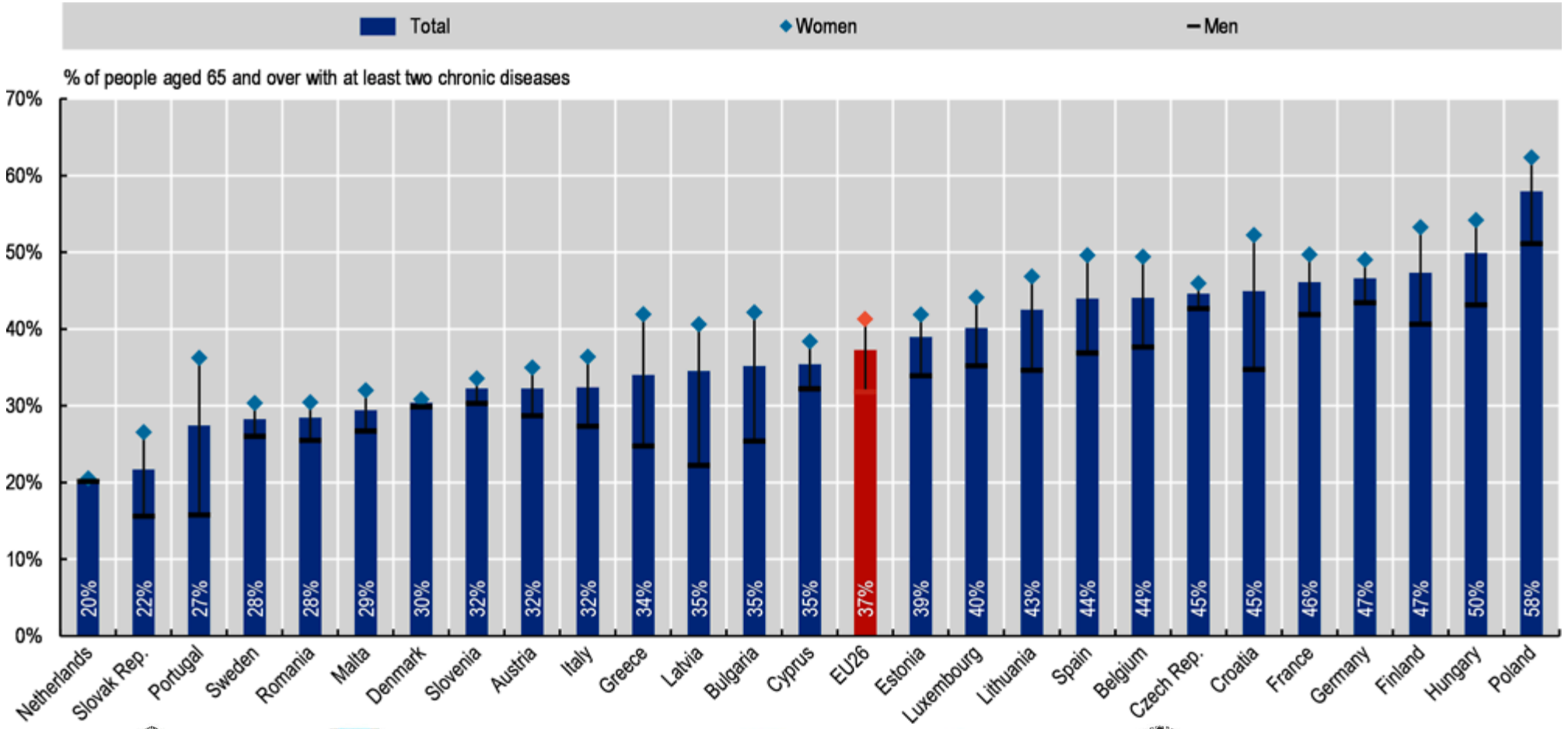



*EUROSTAT, 2022*

# Multiple chronic conditions among people 65+ by gender in EU

Co-funded by the Erasmus+ Programme of the European Union

Note: The EU average is unweighted. Chronic diseases include Alzheimer's disease, cancer, chronic kidney diseases, chronic lung diseases, diabetes, heart attack, hip fracture, Parkinson's disease, stroke, rheumatoid arthritis and osteoarthritis. **(Wave 7, 2017)**




*Survey on Health, Ageing and Retirement in Europe (SHARE)*

# Diseases & Aging

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**92 diseases out of 293 were identified as age-related, accounting for 51.3% (95% UI 48.5–53.9) of all global burden among adults in 2017.**

**AGE RELATED DISEASE**

**CARDIOVASCULAR DISEASES**
Atrial fibrillation and flutter; endocarditis; hypertensive heart disease; intracerebral haemorrhage; ischaemic heart disease; ischaemic stroke; myocarditis; non-rheumatic valve disease; other cardiomyopathy; other cardiovascular and circulatory diseases; peripheral artery disease.

**NEOPLASMS**
Leukaemia, lymphoma, multiple myeloma, myelodysplastic syndroms and other hematopoietic neoplasms; brain and nervous system cancer; breast cancer; prostate cancer; larynx cancer; lip and oral cavity cancer; oesophageal cancer; stomach cancer; colon and rectum cancer; liver cancer; gallbladder and biliary tract cancer; pancreatic cancer; kidney cancer; bladder cancer; melanoma and non-melanoma skin cancer; ovarian cancer; uterine cancer; thyroid cancer; tracheal, bronchus, and lung cancer; mesothelioma; other malignant neoplasms; other benign and in-situ neoplasms.

**GASTROINTESTINAL, ENDOCRINE AND KIDNEY DISEASES**
Chronic kidney disease; type 2 diabetes mellitus; cirrhosis due to non-alcoholic steatohepatitis.; pancreatitis; paralytic ileus and intestinal obstruction; peptic ulcer disease; vascular intestinal disorders; diarrhoeal diseases.

**SKIN AND SUBCUTANEOUS DISEASES**
Cellulitis; decubitus ulcer; fungal skin diseases; pyoderma; other skin and subcutaneous diseases.

**CHRONIC RESPIRATORY DISEASES**
Asbestosis; chronic obstructive pulmonary disease; coal worker pneumoconiosis; interstitial lung disease and pulmonary sarcoidosis; other pneumoconiosis; silicosis; lower respiratory infections.

**NEUROLOGICAL DISORDERS**
Alzheimer's disease and other dementias; motor neuron disease; Parkinson's disease; encephalitis; pneumococcal meningitis.

**SENSE ORGAN DISEASES**
Hearing loss; vision loss (ex: age-related macular degeneration; cataract; glaucoma); other sense organ diseases; refraction disorders; trachoma.

**INJURIES**
Drowning; environmental heat and cold exposure; falls; foreign body in other body part; other transport injuries; other unintentional injuries.

**OTHER DISEASES**
Congenital musculoskeletal and limb anomalies; digestive congenital anomalies; endocrine, metabolic, blood, and immune disorders; other haemoglobinopathies and haemolytic anaemias.

*Adapted from Chang et al, 2019 by Colloca et al, 2020*

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# Human Aging: Usual and Successful

- Research in aging has emphasized average age-related losses and neglected the substantial heterogeneity of older persons.
- The effects of the aging process itself have been exaggerated, and the modifying effects of diet, exercise, personal habits, and psychosocial factors underestimated.
- Within the category of normal aging, a distinction can be made between:
  usual aging ➡ **extrinsic factors heighten the effects of aging alone**
  successful aging ➡ **extrinsic factors play a neutral or positive role**.
- Research on the risks associated with usual aging and strategies to modify them should help elucidate how a transition from usual to successful aging can be facilitated.

***Rowe & Kahn, 1987***

# Successful aging is too individualistic!

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- It fails to capture developmental processes of continuity and change in function over time.
- Aging starts long before: **growth and development**; **maturation, senescence (decline of functioning starts at 30+**, but many individuals have a **functional reserve to age "well"**, whereas the aging of some systems, for instance reproductive system in women, starts long before, already in the intrauterine life!)-
- **It is not always our fault!**

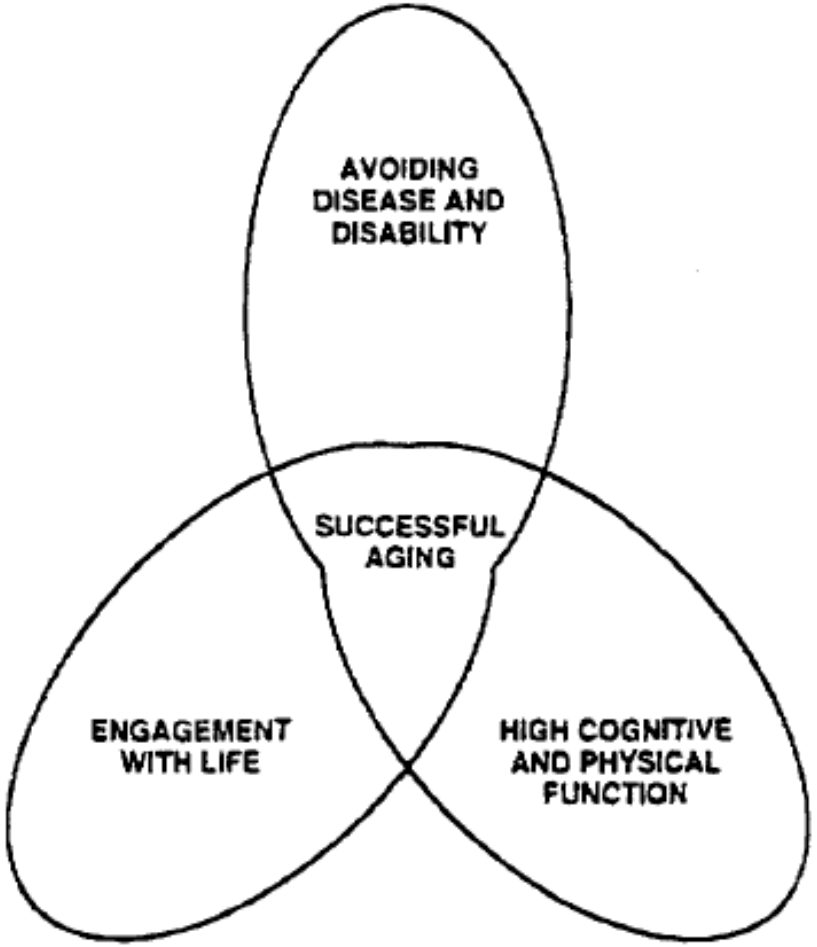


**Figure 1.** A model of successful aging.

*Rowe & Kahn, 2000*

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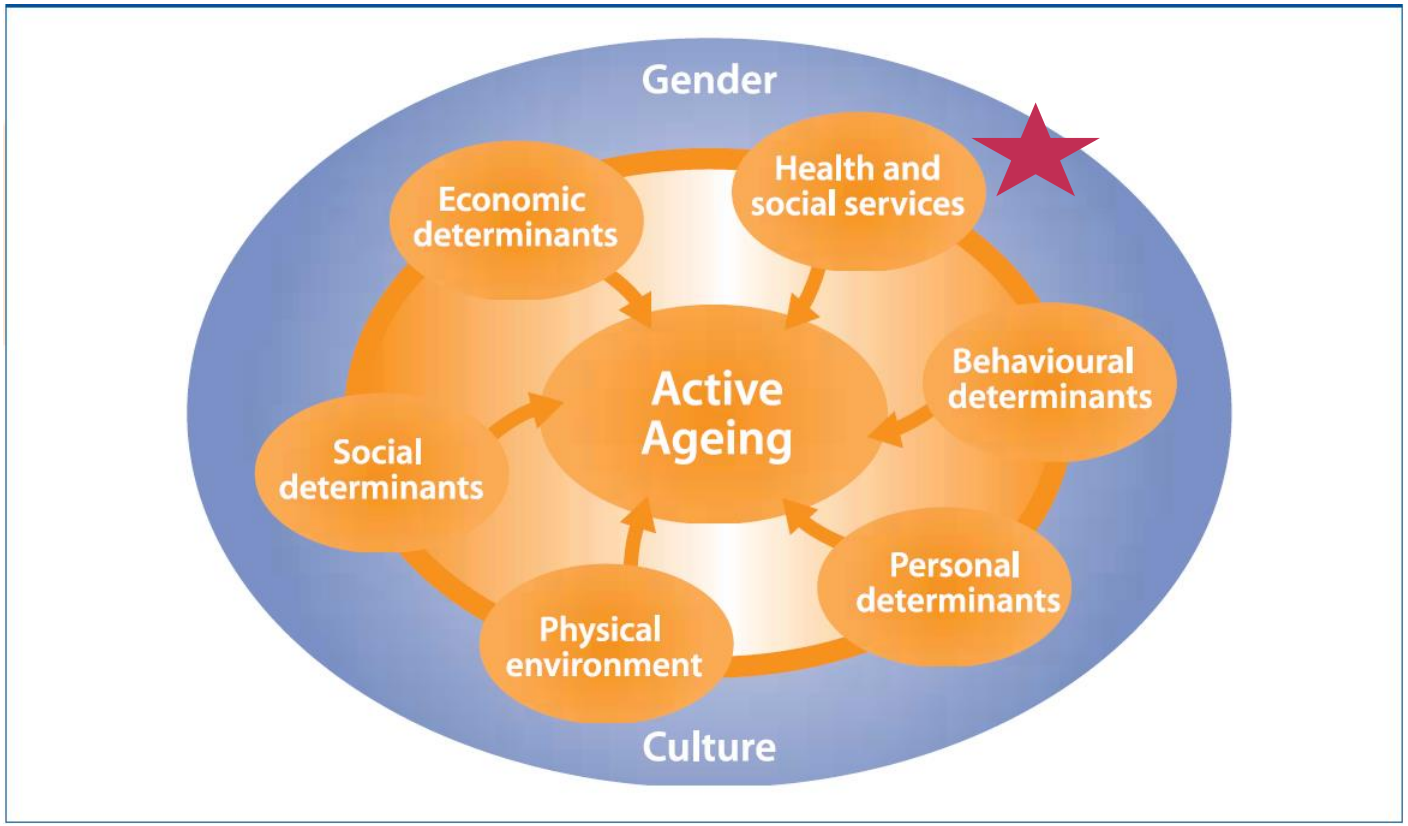
# Determinants of active aging

## Well-being is linked to Welfare




- **Aging is not a measure of the life span, but is the result of a set of factors that, influencing each other, are able to guide aging in good health and good quality of life towards a lived aging as a slow decline.**

*WHO, 2002*

# Subjective well-being as a criterion of a successful aging process

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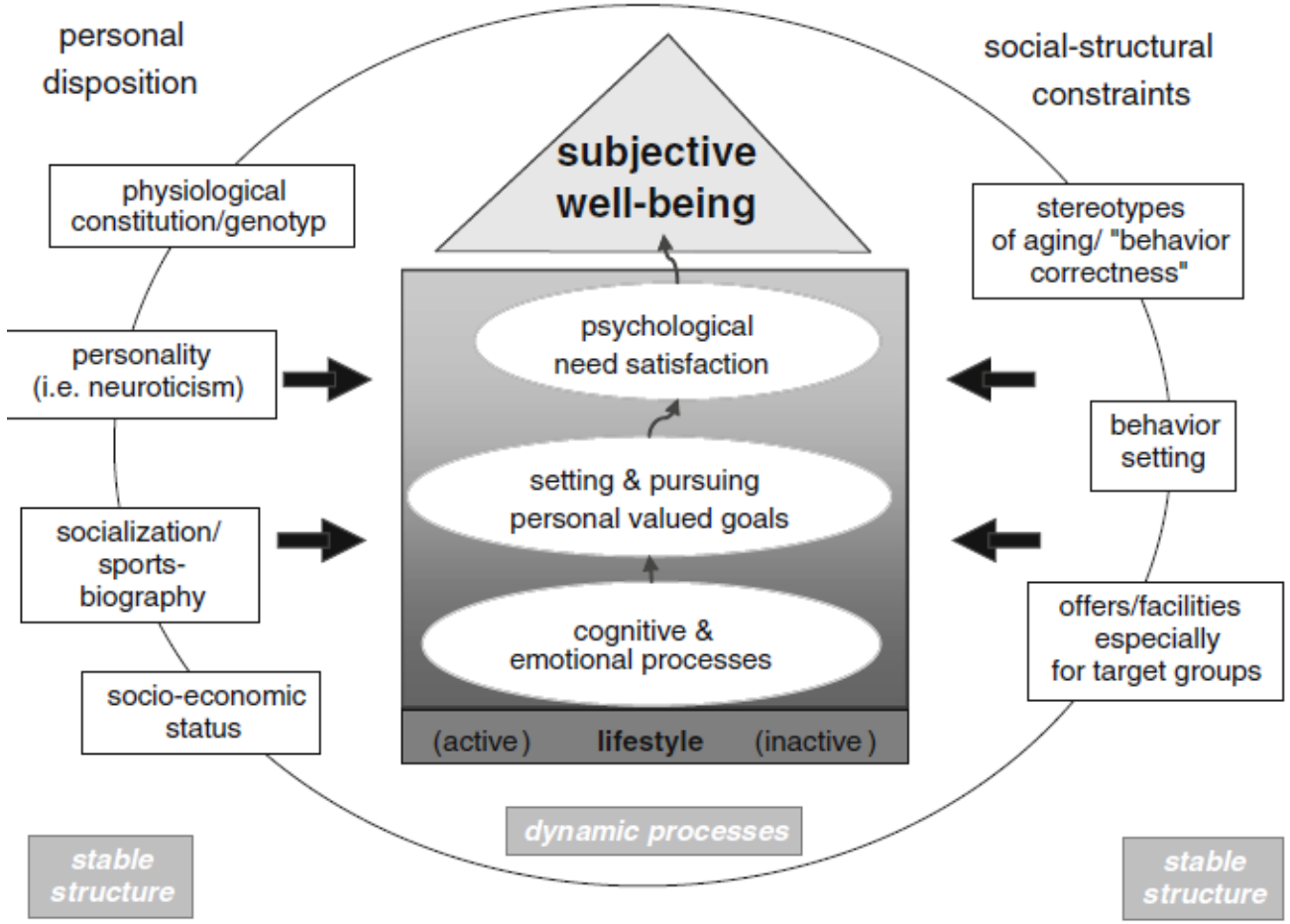


*Kanning & Schlicht, 2008*

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# Standard aging categories

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**Chronological Aging  is the number of years a person has lived so far, but it encompasses biological, psychological, and social age.**

a) **Young old: Year (65 to 74)**
b) **Middle Old: Year (75 to 84)**
c) **Old-Old: Years (85+)**
d) **Centenarians (100+)**

*«Old age is like everything else. To make a success of it, you've got to start young.»*
Theodore Roosevelt

# BUT…
# HOW MUCH YOUNG?

# Health span

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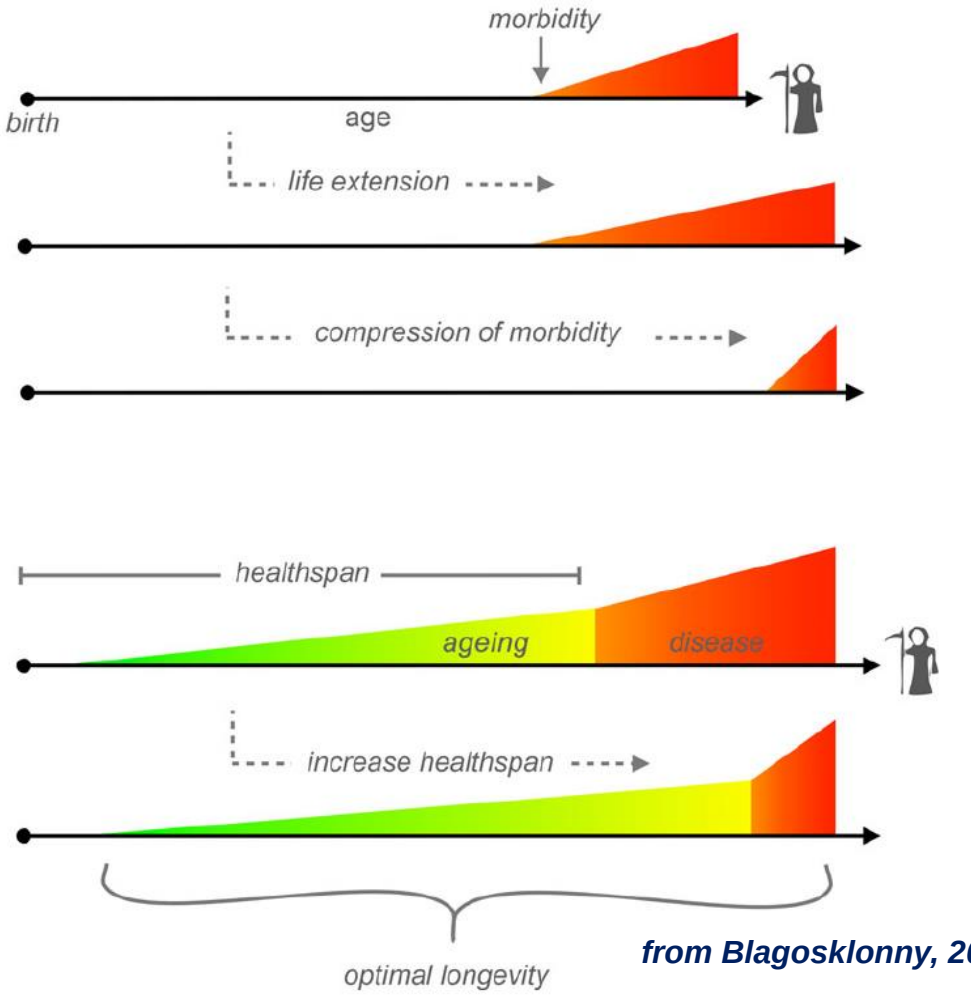
- Health span is a period of healthy ageing with a modestly increasing ('subclinical') chronic disease burden, followed by a period of age-related clinical disease.
- To achieve optimal longevity (living long, but primarily in wellness) in the future, health span must be significantly extended.




*from Blagosklonny, 2012*

*Seal et al, 2015*

# From longer life span to longer health span (and life span)

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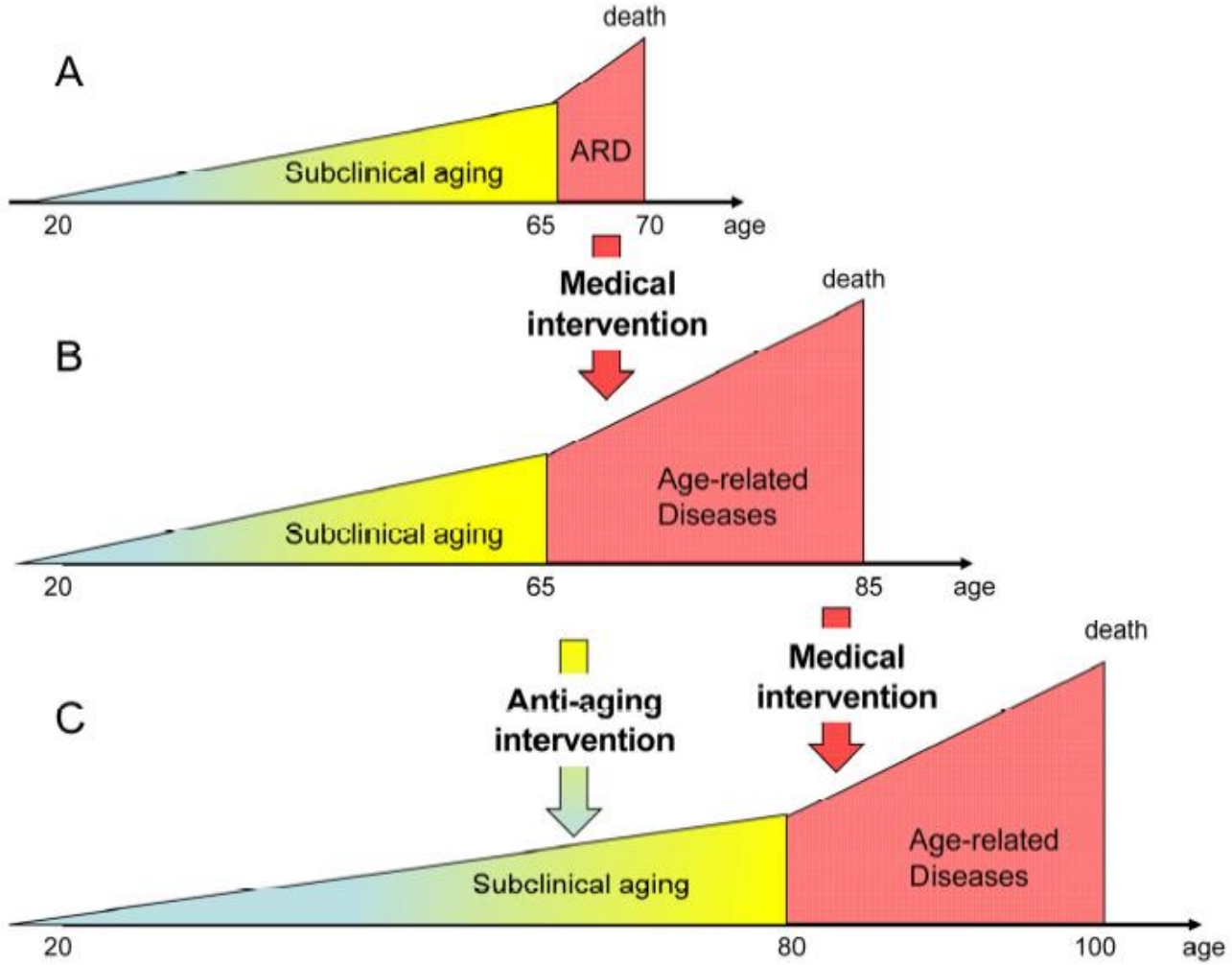
- Primary prevention of the aging process should start very early and does not include only medical intervention but every biopsychosocial strategy capable of enhancing individual health and well-being.
- The first step in changing frame of mind is to start thinking that aging has to do with living day by day and is shaped by our genetic and epigenetic inheritance, individual behavior and environmental condition.




*Blagosklonny, 2012*

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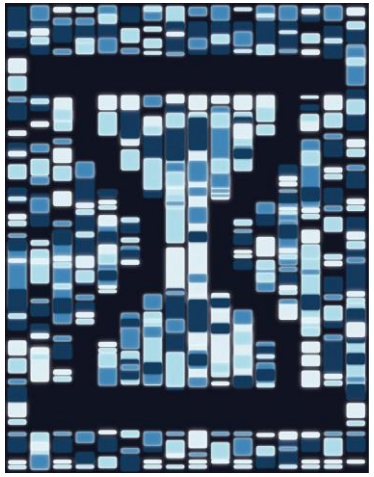
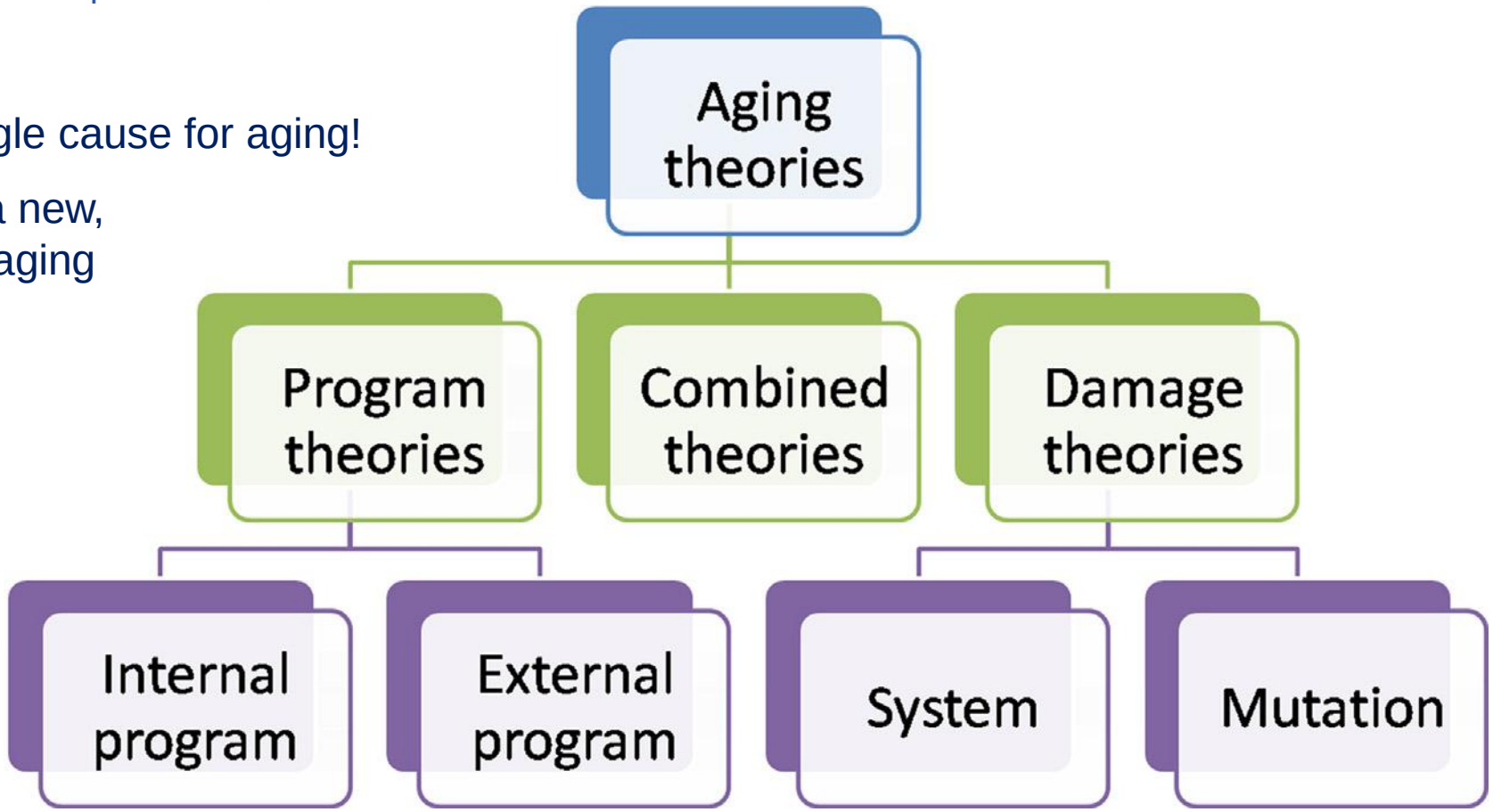
# Categorization of the main theories of aging

- There is no one single cause for aging!
- There is a need of a new, integrative view on aging research.






**(based on the worked developed by Semsei, 2000 and de Magalhães, 2013)**

*Da Costa et al, 2016*

# Human aging is complex

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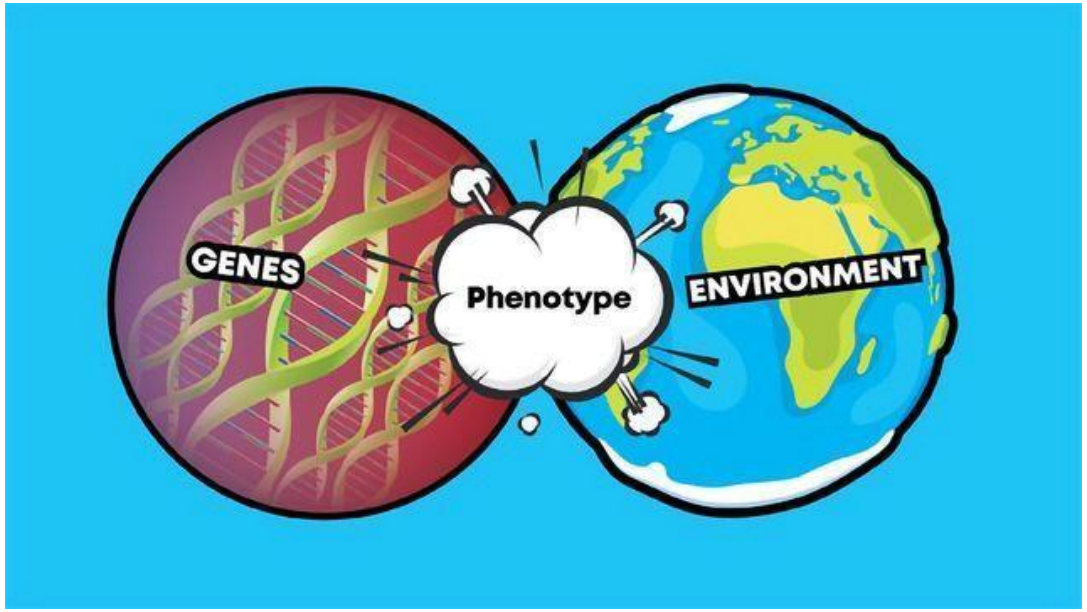
$$[\text{phenotype}] = [\text{genotype}] + [(\text{diet, lifestyleandenvironment})]$$




Less than 30% of the overall variation in adult life-span may be attributed to genetic variation.

*Da Costa et al, 2016*

# Major influences and mechanisms of human aging

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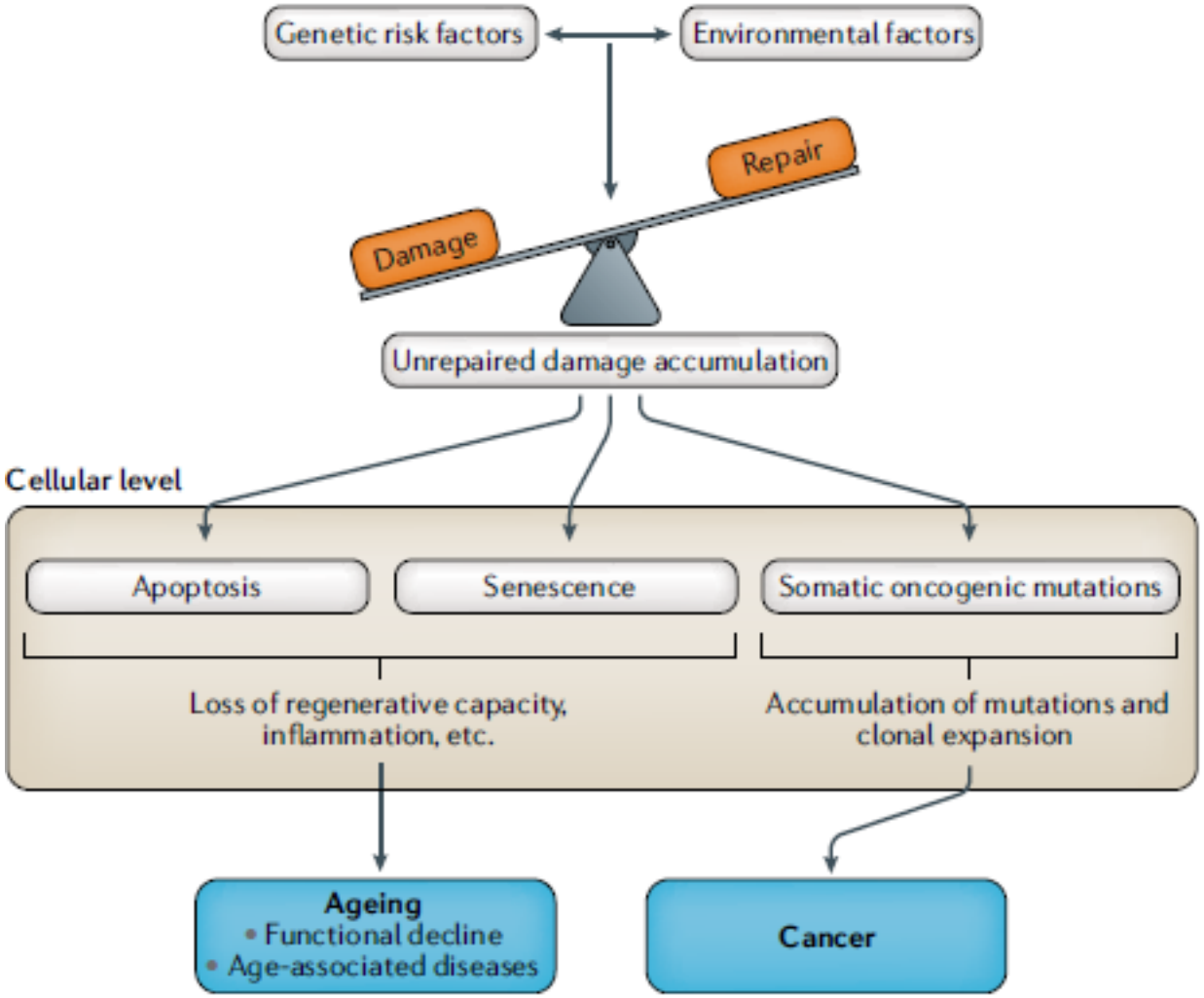
- Genetic studies supports the hypothesis that ageing is driven by **the balance of damage and repair processes**. There is genetic evidence for the importance of several damage pathways in humans. Damage can be intrinsic, for example, through somatic mutations arising during cell division.
- Also important are **health behavioral risk factors** such as smoking and obesity, which are also influenced by gene-environment interactions.
- The net impact of damage depends on the activity of **repair and response mechanisms**. At the cellular level, complete repair can yield undamaged cells. By contrast, unrepaired damage can lead to cell death (apoptosis), preventing cancers but leading to the **depletion of stem cells and loss of regenerative capacity**.
- Cells with somatic oncogene mutations can survive and replicate, sometimes leading to **tumour development**. Alternatively, damaged cells can enter senescent states and produce a secretory senescence phenotype (SASP), resulting in **inflammation** and reduced repair that contributes to degenerative diseases.
- These mechanisms can result in reduced repair and increasing incidence of chronic diseases of ageing but with decreased cancer risks, or vice versa. This **ageing versus cancer trade-off** is evident for several of the loci described, notably in the 9p21 cell cycle and senescence-related locus, telomere variation and in the *SH2B3* locus.




***Melzer et al, 2020***

# The intersection of basic aging biology, chronic disease, and health

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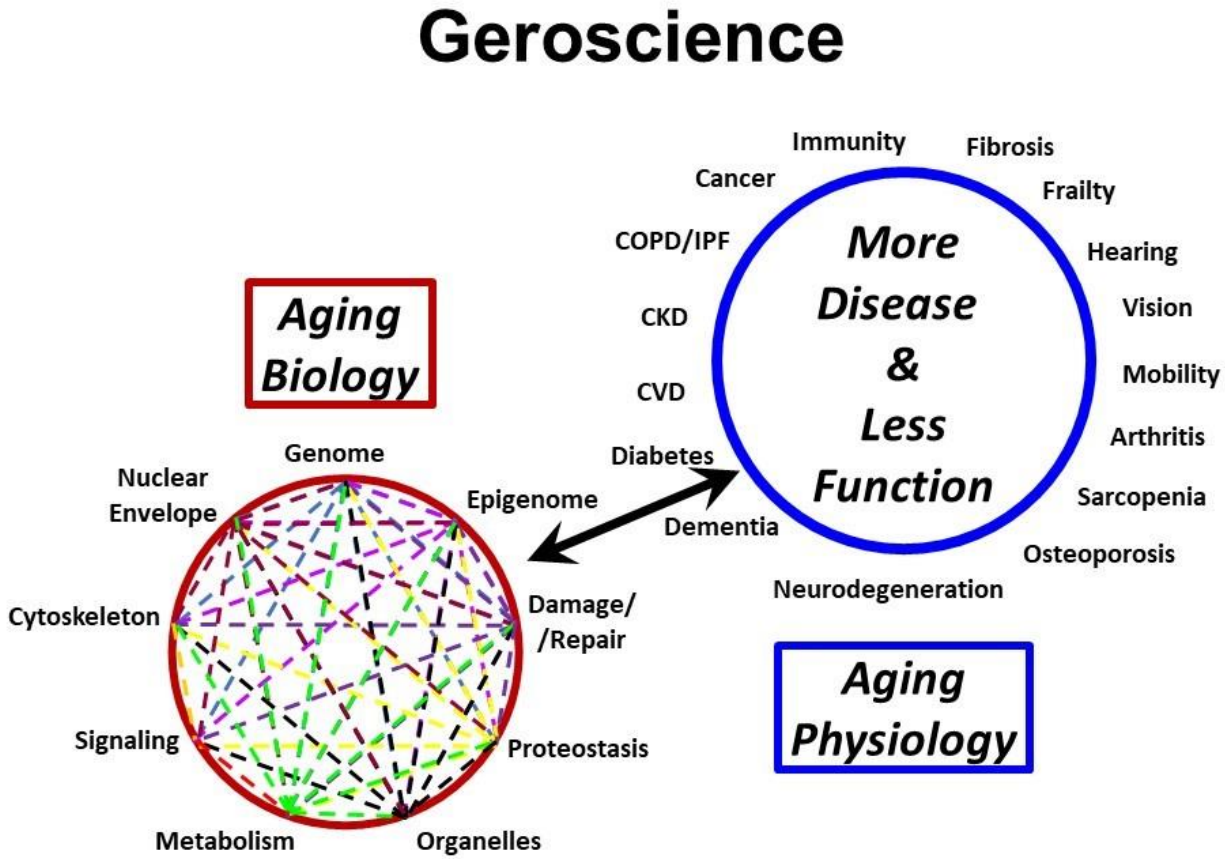
- Aging itself is not a disease (senescence is the progressive deterioration of bodily functions over time), but **the aging process represents a major risk factor for several chronic diseases and conditions, including frailty and lack of resilience**.
- The aging process is the **breakdown of self-organizing systems and reduced ability to adapt to the environment**.




*Burch et al, 2014*

# Systemic consequences of aging

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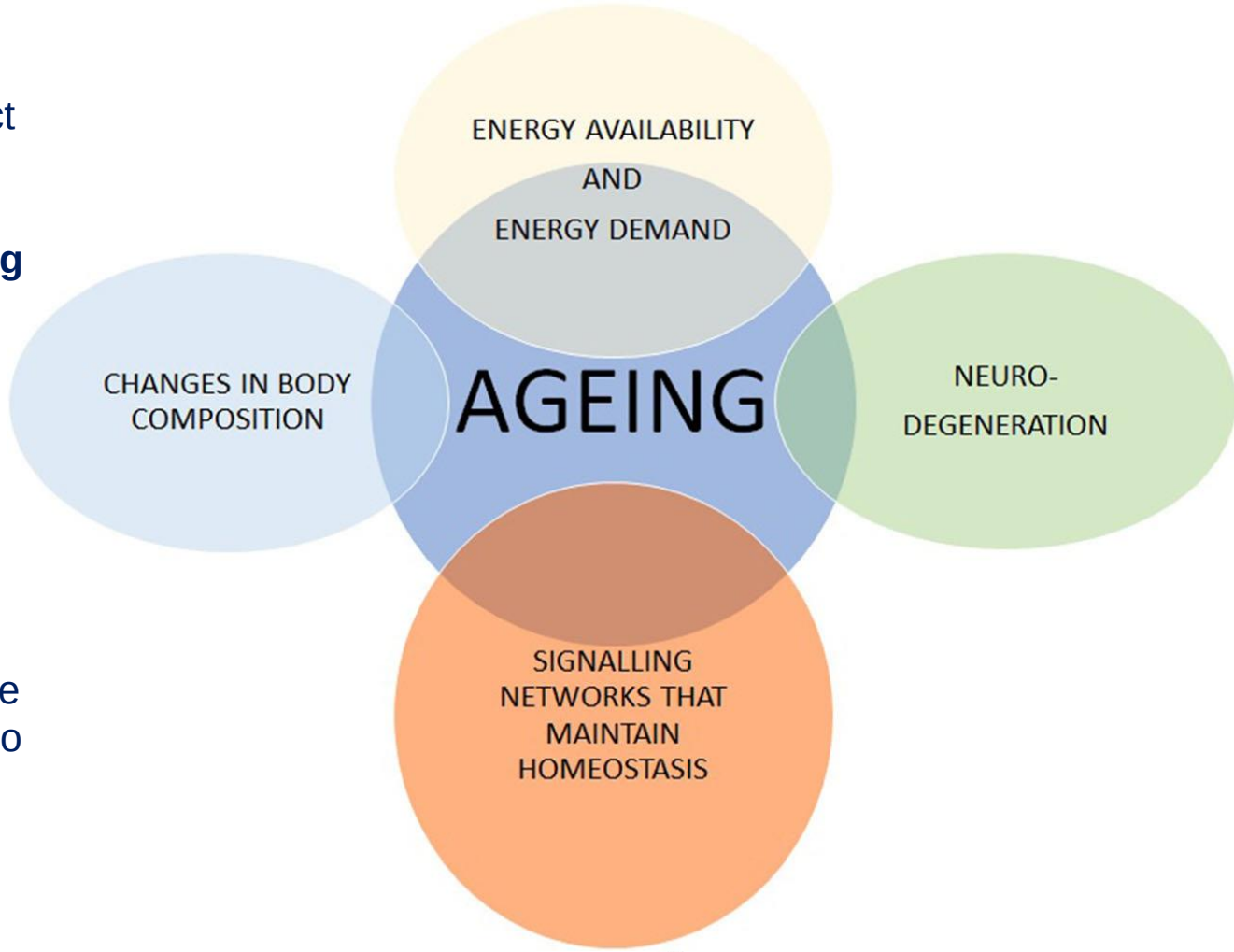
- These changes develop in parallel and affect each other through many feed-forward and feedback loop.
- **The phenotype that results from the aging process is characterized by increased susceptibility to disease, high risk of multiple coexisting diseases, impaired response to stress, the emergence of "geriatric syndromes," altered response to treatment, high risk of disability, and loss of personal autonomy with all its psychological and social consequences.**
- On the other hand, all these factors influence aging itself, in a dynamic and parallel way, so that they can be considered as not only a consequence of aging but also an integral part of the aging process.




*Colloca et al, 2020*

# The unifying theory of geroscience

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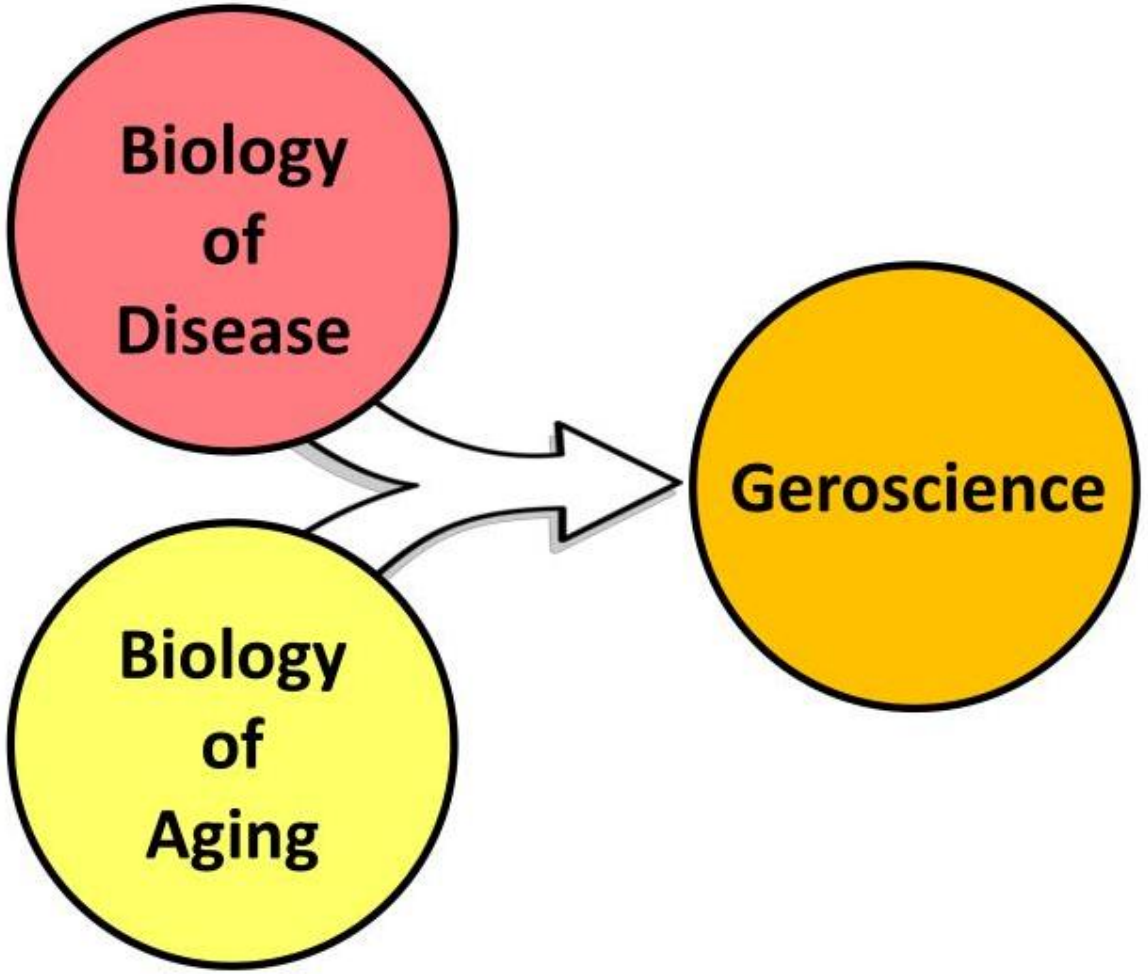
- **Geroscience is an emerging interdisciplinary scientific field that aims to understand the relationship between aging and age-related diseases/dysfunctions, and how these intersect with frailty and resilience.**
- **Researchers in the field hypothesize that slowing the rate of aging will have a beneficial impact on the health of older adults by delaying the onset or reducing the severity of most chronic diseases and frailty; i.e., improving health span.**




*Kelley et al, 2017*

# Different pathway of accelerating aging

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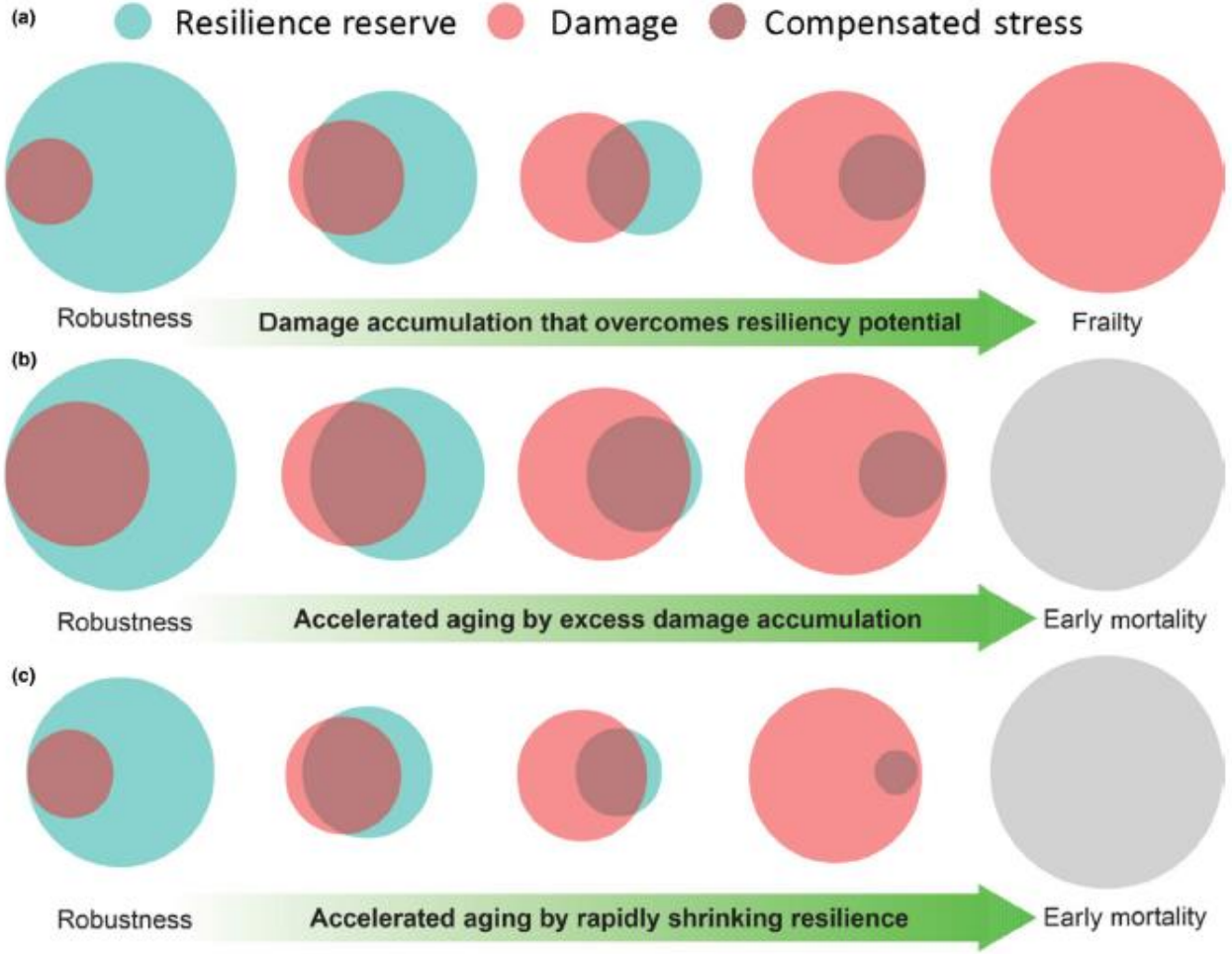
**Normal aging (a)** and different pathways to **accelerated aging (b and c)**. A. Robust resilience at a young age fully compensates damage. Over time, damage accumulates that is not fully compensated by resilience. Toward the end of life, resiliency is overwhelmed, and new stresses cause fast, unopposed damage accumulation that leads to frailty and eventually to death. Accelerated aging may occur either because of **faster rates of damage** accumulation (b) or because of **rapid shrinking and eventual collapse of resilience** (c). Note that even in the state of robustness, damage can be already abnormally high (b) and resilience already abnormally low (c).




*Ferrucci et al, 2020*

# Resilience (ability to recover) vs. robustness (ability to resist deviation and avoid damage)

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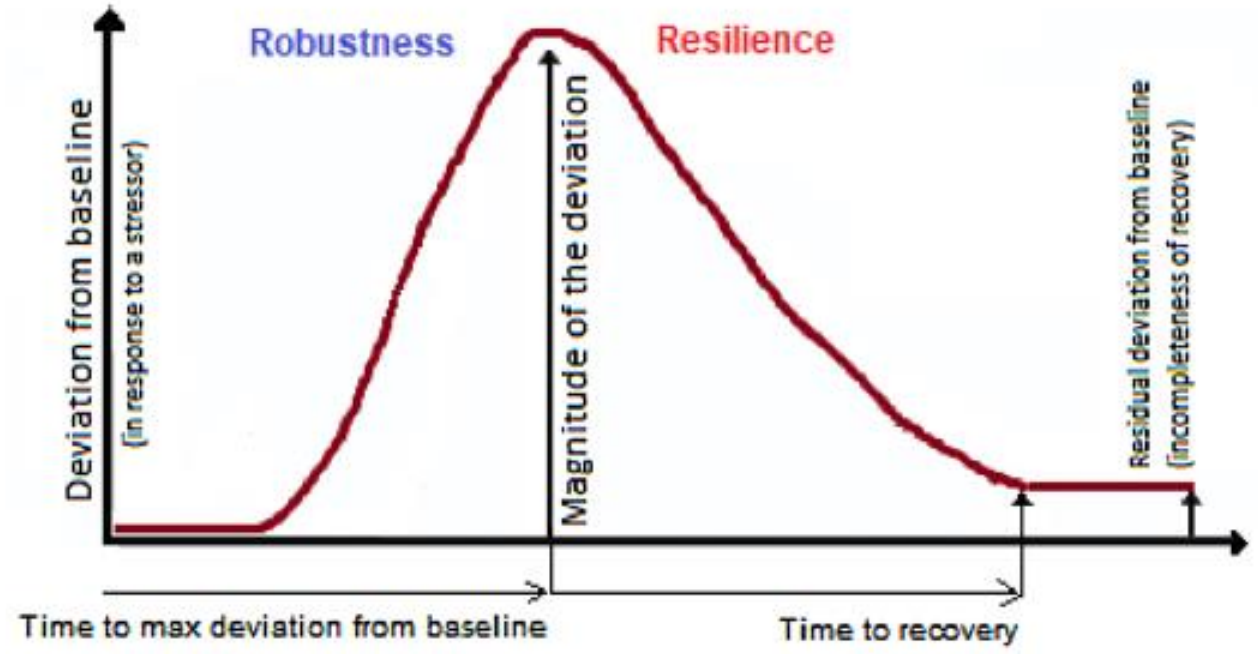



*Ukraintseva et al, 2021*

# Epigenetic model of continuous transcriptional tuning leading to the aging phenotype

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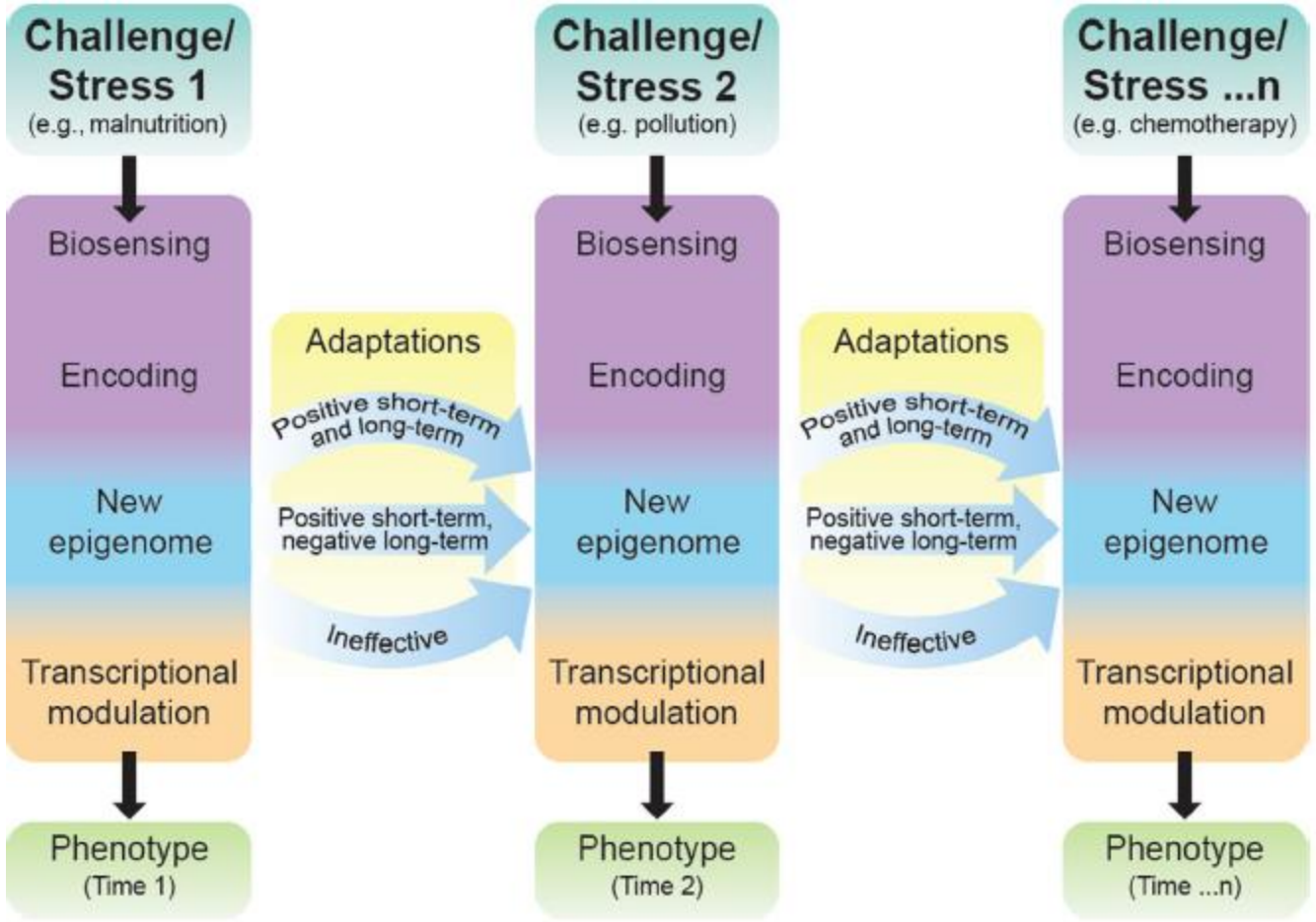
- Long-term adaptation within the lifespan requires epigenetic modulation of the transcriptional machinery. Environmental clues are read by specific biosensors and encoded into epigenetic changes that modulate transcriptional subroutines. The new epigenetic landscape is meant to be adaptive but may fail its purpose and become maladaptive in either the short or long term. **Ineffective adaptation/compensation negatively impacts the rate of biological aging and, in turn, phenotypic and functional aging.**
- In the scheme, we show only three cycles of epigenetic adaptation, at any point in time; the epigenetic landscape results from the sum of hundreds or even thousands of adaptive cycles that occur throughout life; and some more relevant than others. Importantly, very little is known about how environmental stresses are sensed and encoded into epigenetic changes.




*Ferrucci et al, 2020*

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# The Geroscience's manifesto

**Table 1. Critical Areas of Aging Research and Important Goals**

| Areas of Aging Research | Important Goals |
|---|---|
| Adaptation to stress | Bridge continuum from psychological to molecular stresses<br>Differentiate hormesis from toxic stress<br>Better align human and animal studies |
| Epigenetics | Biomarker development: chronologic vs. biologic aging<br>Link age-related environmental inputs to epigenetic signatures<br>Test small molecules that regulate enzymes controlling epigenetic events |
| Inflammation | Differentiate adaptive and maladaptive inflammatory responses<br>Define age-related inflammatory sources and their systemic effects<br>Determine how obesity and metabolic dysfunction alter inflammation with age |
| Macromolecular damage | Generate systems-level understanding of the types of macromolecular damage and their roles in chronic disease states<br>Understand how stochastic damage influences the variability of aging |
| Metabolism | Define role of signal transduction pathways linked to metabolism in the aging process<br>Understand contribution of circadian clocks to aging and metabolism<br>Connect metabolic dysfunction with tissue-specific decline in aging |
| Proteostasis | Identify proteostatic pathways that are overwhelmed in specific chronic disease states<br>Examine crosstalk between proteostasis machineries<br>Understand non-cell-autonomous signaling and activation of proteostasis pathways |
| Stem cells and regeneration | Determine whether declining adult stem cell function drives aging and chronic disease<br>Examine how aging and associated disease impair adult stem cell function<br>Determine how macromolecular damage accumulates in aging adult stem cell pools |

*Kennedy et al, 2014*

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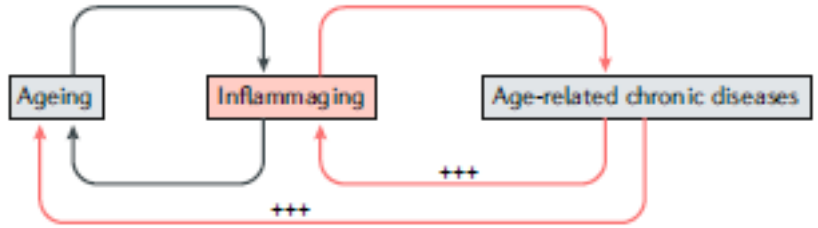
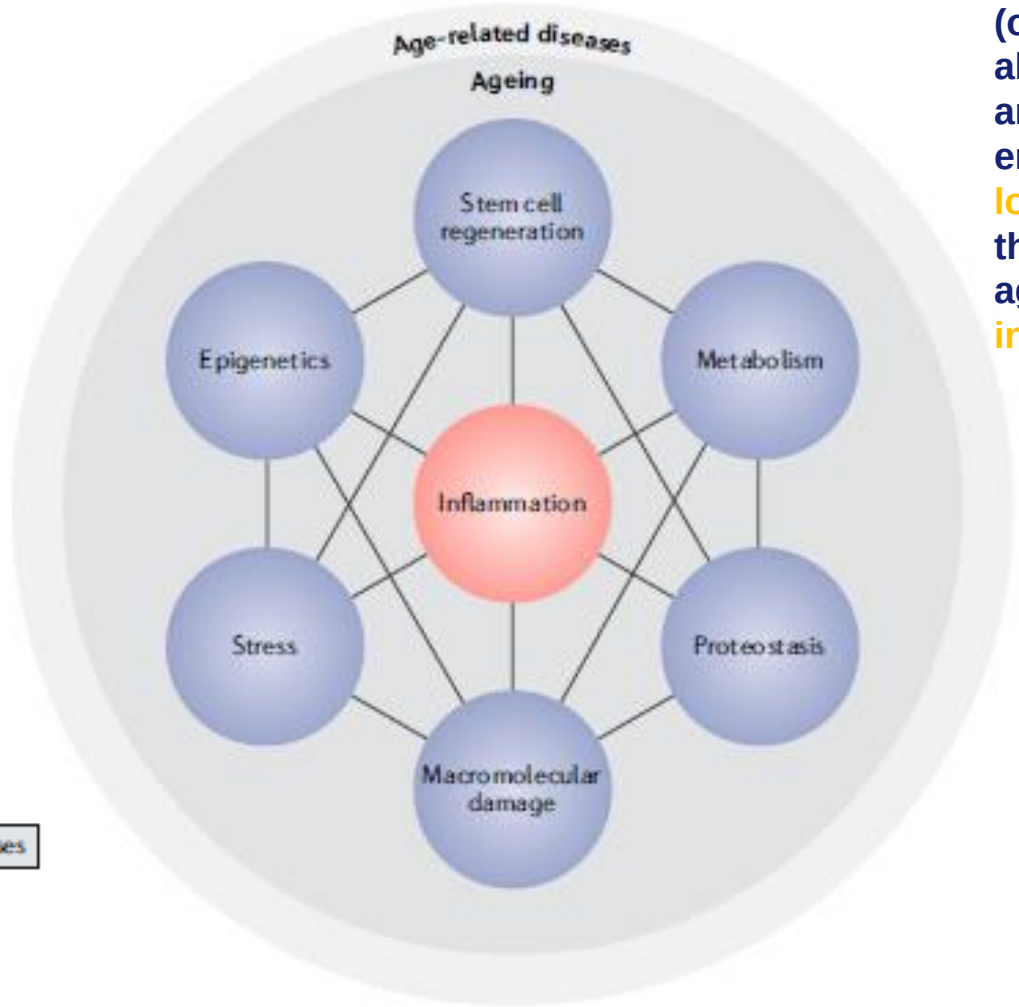
# The seven pillars of ageing

- The new geroscience approach proposes to counteract all major age-related diseases together, and not individually, by focusing on the basic ageing mechanisms underlying these diseases.
- Inflammaging is the basis of ageing and many age- related chronic diseases, which in turn increase the rate of ageing.
- Age-related diseases can be conceptualized as the
- manifestations of accelerated inflammaging or ageing.




*Franceschi et al, 2018*




- The chronic, sterile (occurring in the absence of infection and primarily driven by endogenous signals), low-grade inflammation that occurs during ageing is called inflammaging.

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# Low-grade inflammatory state causes the development of the principal chronic-degenerative pathologies related with aging

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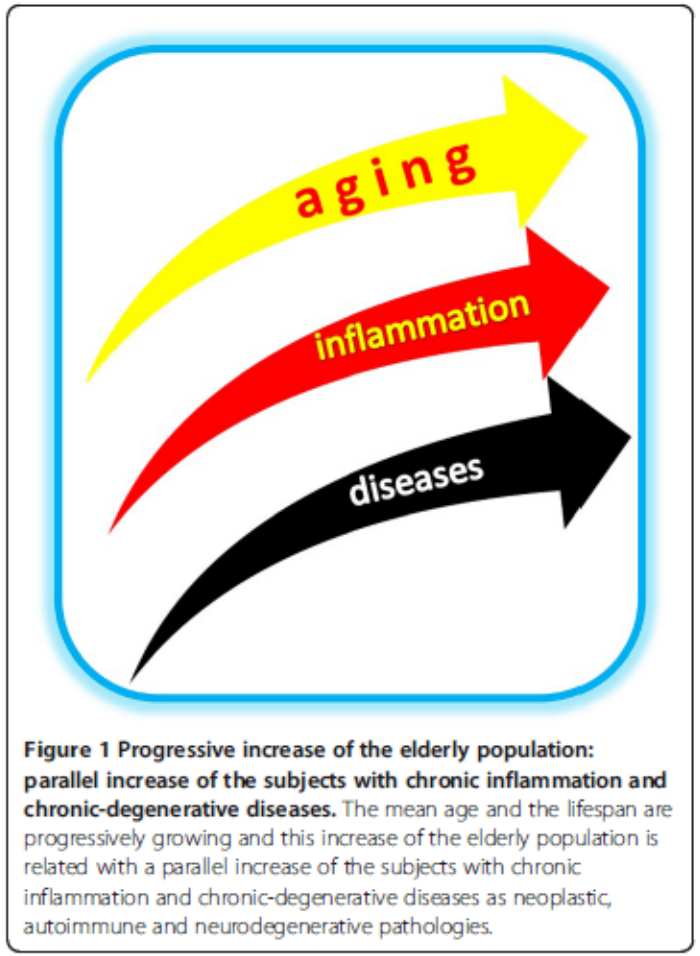


**Figure 1 Progressive increase of the elderly population: parallel increase of the subjects with chronic inflammation and chronic-degenerative diseases.** The mean age and the lifespan are progressively growing and this increase of the elderly population is related with a parallel increase of the subjects with chronic inflammation and chronic-degenerative diseases as neoplastic, autoimmune and neurodegenerative pathologies.

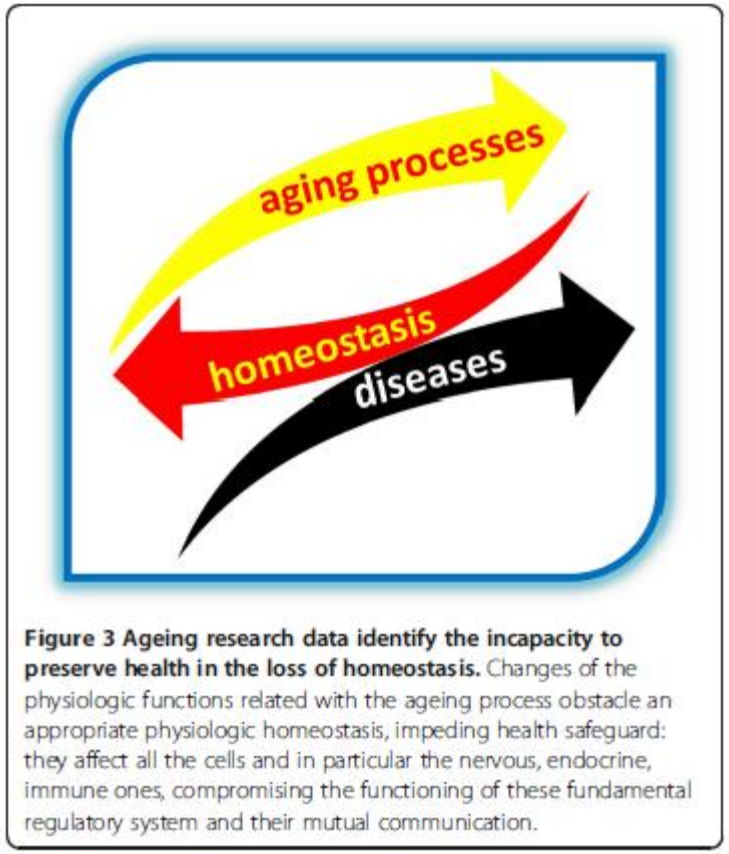


**Figure 3 Ageing research data identify the incapacity to preserve health in the loss of homeostasis.** Changes of the physiologic functions related with the ageing process obstacle an appropriate physiologic homeostasis, impeding health safeguard: they affect all the cells and in particular the nervous, endocrine, immune ones, compromising the functioning of these fundamental regulatory system and their mutual communication.

- **Apart genetic, a large class of factors, as smoke, infections, obesity, and the decrease of the sexual hormones could contribute to the systemic low-grade pro-inflammatory state.**

*Berghella et al, 2014*

# Inflammaging & chronic diseases

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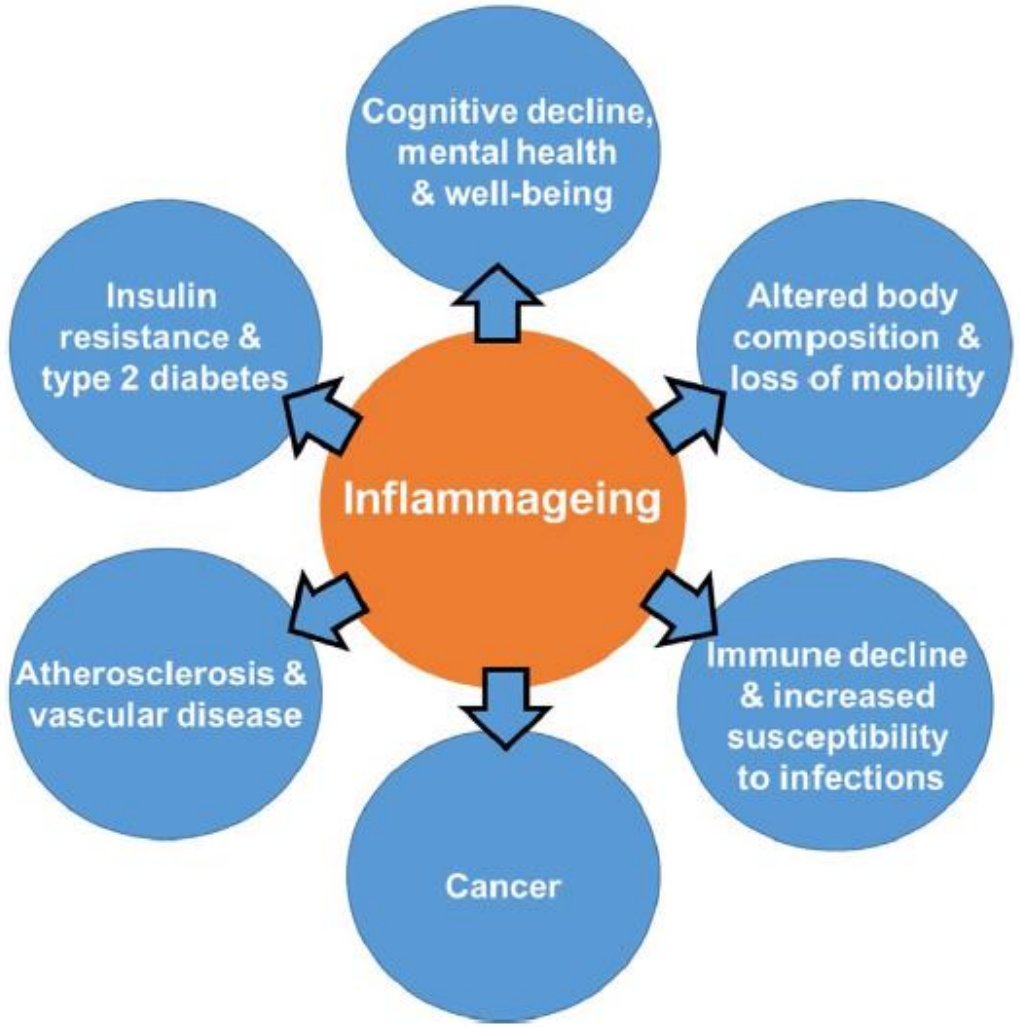
- **The modulation of inflammageing is a promising strategy to slow the decline of health that occurs with ageing.**




*Calder et al, 2017*

# Mechanisms connecting different clusters of aging biomarkers

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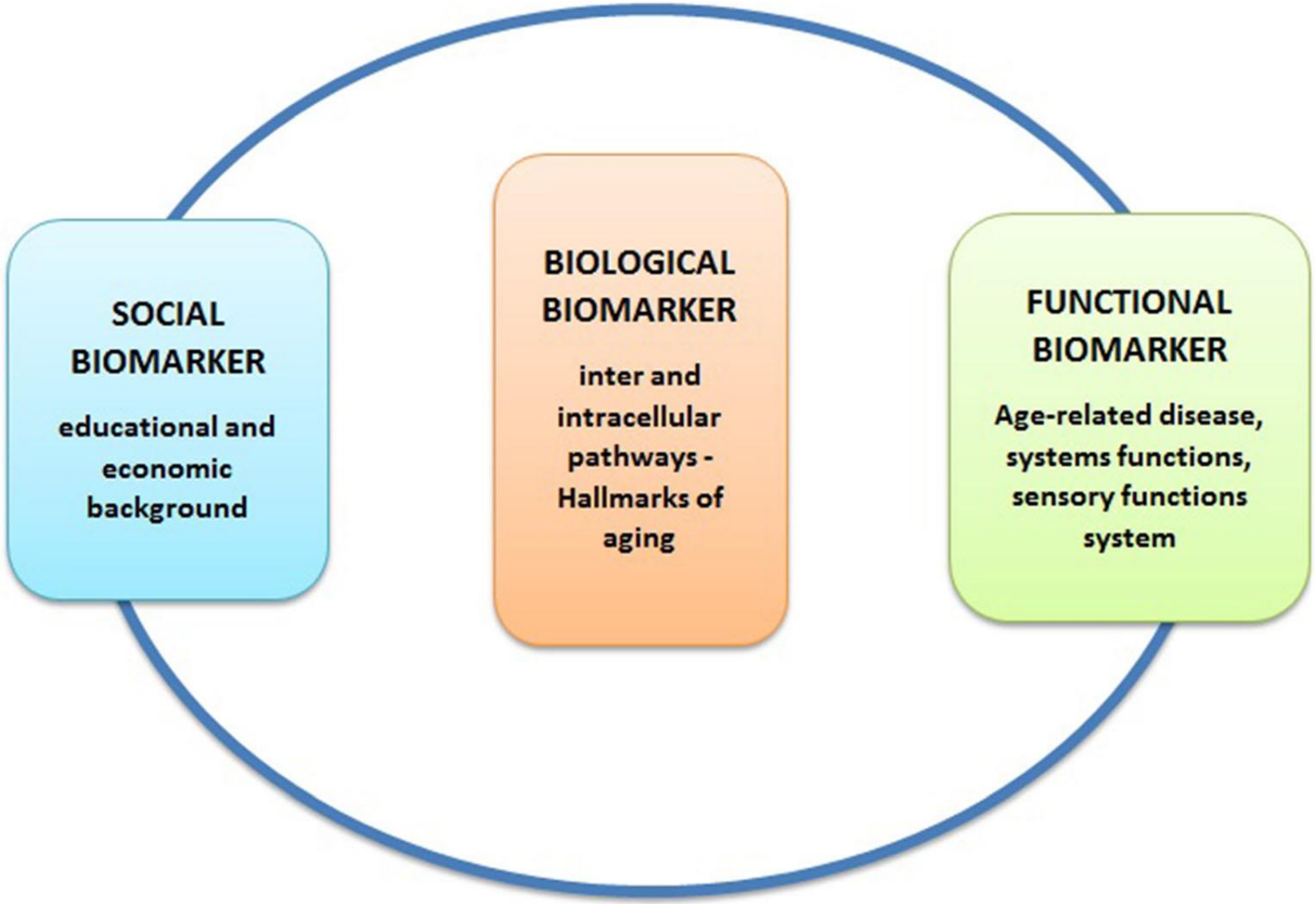
- Aging must no longer be described as a simple demographic event but as a complex mosaic in which several tesserae relate to each other, some in a very evident way others often in a more subdued but all fundamental way.




*Colloca et al, 2020*

# The hallmarks of aging are specific biological mechanisms that drive the rate of biological aging

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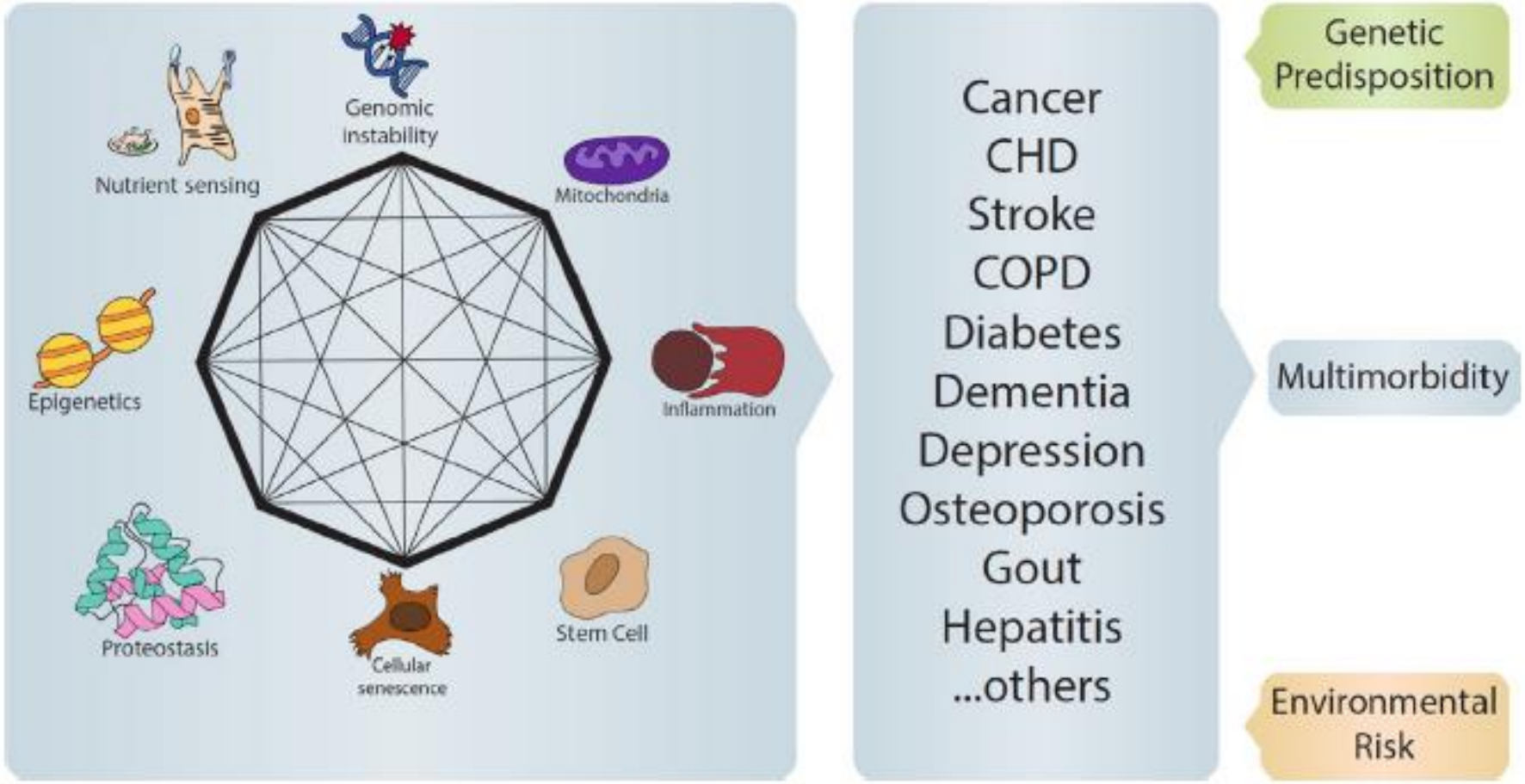


*Ferrucci et al, 2019*

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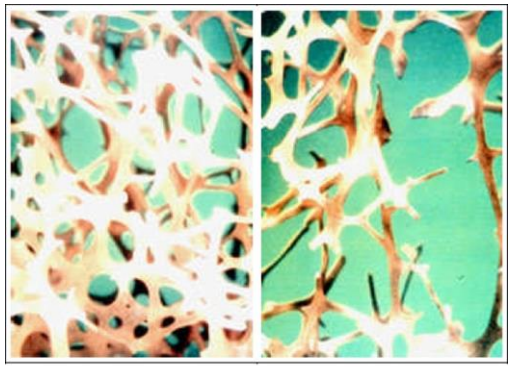
# Let's make an example: osteoporosis

**Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture.**



Normal Osteoporotic

**Bone strength**

**Bone density** → *grams of mineral per area or volume determined by peak bone mass and amount of bone loss*

**Bone quality** → *architecture, turnover, damage accumulation (eg, microfractures), mineralization*

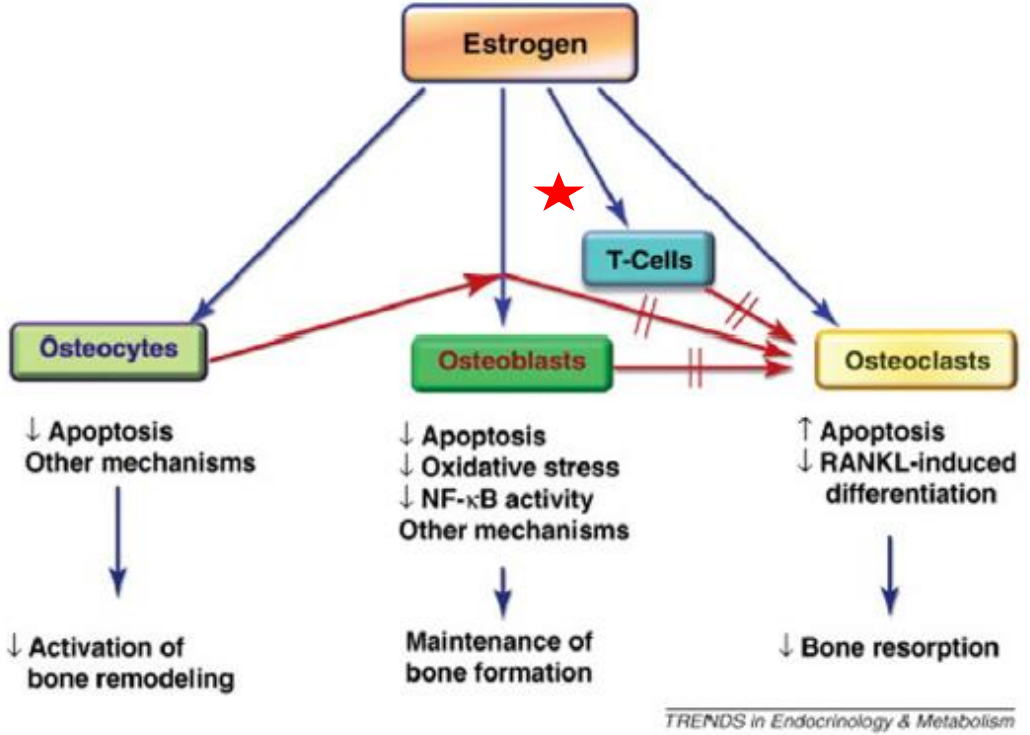
*Courtesy of Flavia Magri-UNIPV, 2011*

# Working model for estrogen regulation of bone turnover

Co-funded by the Erasmus+ Programme of the European Union

- Menopause and the accompanying loss of ovarian estrogens are associated with declines in bone mineral density (BMD): 10-year cumulative loss was 9.1% at the femoral neck and 10.6%, lumbar spine. Estradiol concentrations also predict fractures. Total estradiol levels, <5 pg/ml were associated with a 2.5-fold increase in hip and vertebral fractures in older women, an association that was independent of age and body weight.
- The adaptive **immune system** plays a fundamental role in the development of postmenopausal osteoporosis (Wu et al, 2021)

*Cauley, 2015*




Reprinted from Trends Endocrinol Metab , 23(11), Sundeep Khosla, et al., Estrogen and the skeleton, 576-581, 2012, with permission from Elsevier.

# The cellular and molecular mechanisms by which estrogen deficiency leads to bone loss

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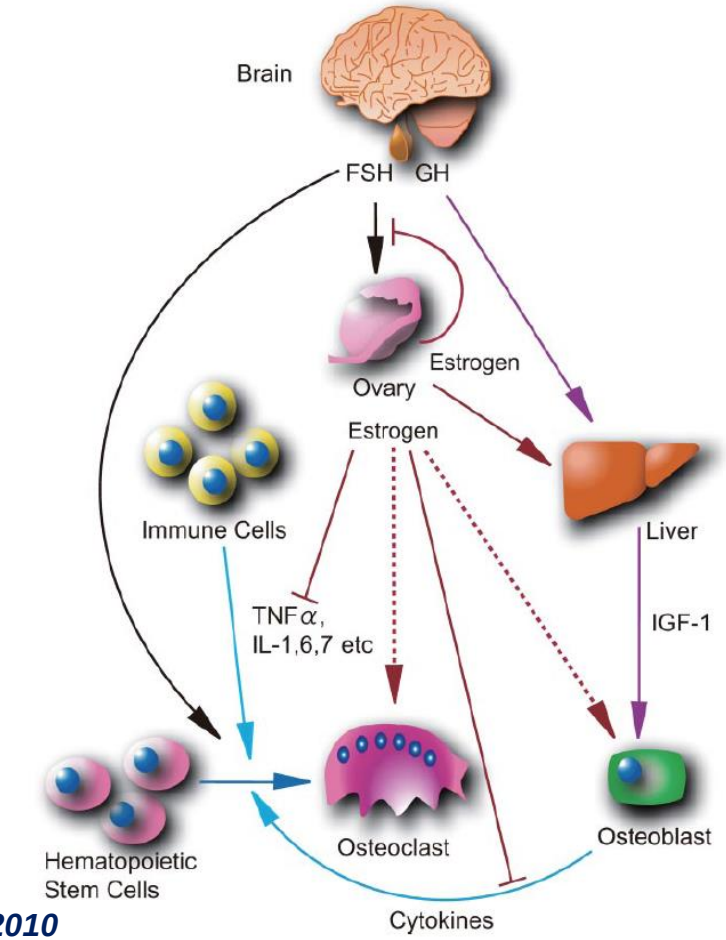


*Imai et al, 2010*

| Physiological changes caused by estrogen deficiency | Potential mechanism(s) causing bone loss |
|---|---|
| Increased receptor activator of nuclear factor kappa b (RANK) ligand expression by osteoblasts and T- and B-lymphocytes | Increased osteoclast recruitment and activation, decreased osteoclast apoptosis |
| Decreased osteoprotegerin production by osteoblasts | Increased osteoclast recruitment and activation, decreased osteoclast apoptosis |
| Decreased osteoclast precursor apoptosis and increased osteoclast differentiation | Increased osteoclast recruitment and activation |
| Decreased inhibition of osteoclast activity mediated by estrogen receptors | Increased osteoclast activity |
| Increased interleukin-1 (IL-1) by bone marrow stromal cells and osteoblasts | Increased osteoclast recruitment and activation, decreased osteoclast apoptosis |
| Increased interleukin-6 (IL-6) by bone marrow stromal cells and osteoblasts | Increased osteoclast recruitment and activation, decreased osteoclast apoptosis |
| Increased tumor necrosis factor-alpha (TNF-α) by bone marrow stromal cells and osteoblasts | Increased osteoclast recruitment and activation, decreased osteoclast apoptosis |
| Increased macrophage-colony-stimulating factor (M-CSF) by bone marrow stromal cells and osteoblasts | Increased osteoclast recruitment and activation, decreased osteoclast apoptosis |
| Increased prostaglandins by bone marrow stromal cells and osteoblasts | Increased osteoclast recruitment and activation, decreased osteoclast apoptosis |
| Decreased transforming growth factor-β (TGF-β) by osteoblast precursors | Decreased osteoclast apoptosis |
| Decreased intestinal calcium absorption | Decreased calcium for bone formation |
| Decreased renal tubular calcium reabsorption | Decreased calcium for bone formation |

*Clarke & Khosla, 2010*

# Non only estrogens, but inflammaging in bone turnover!

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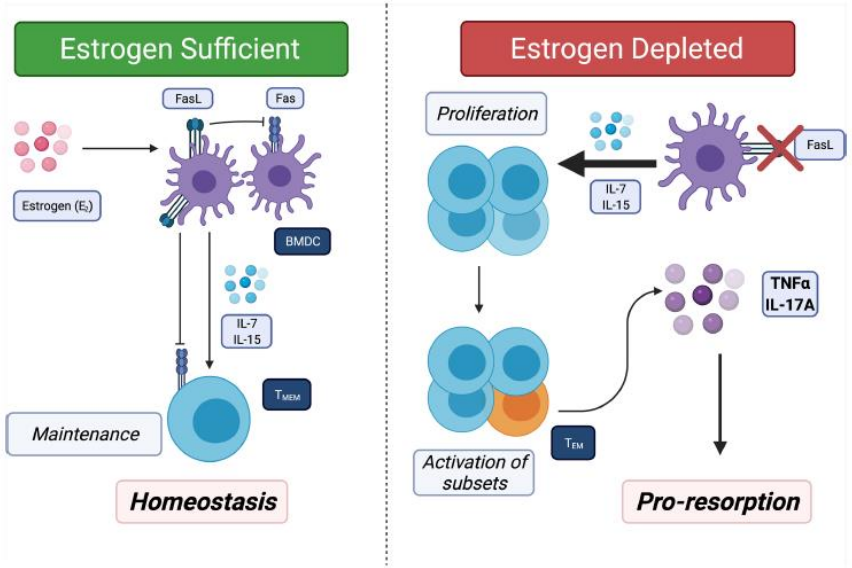
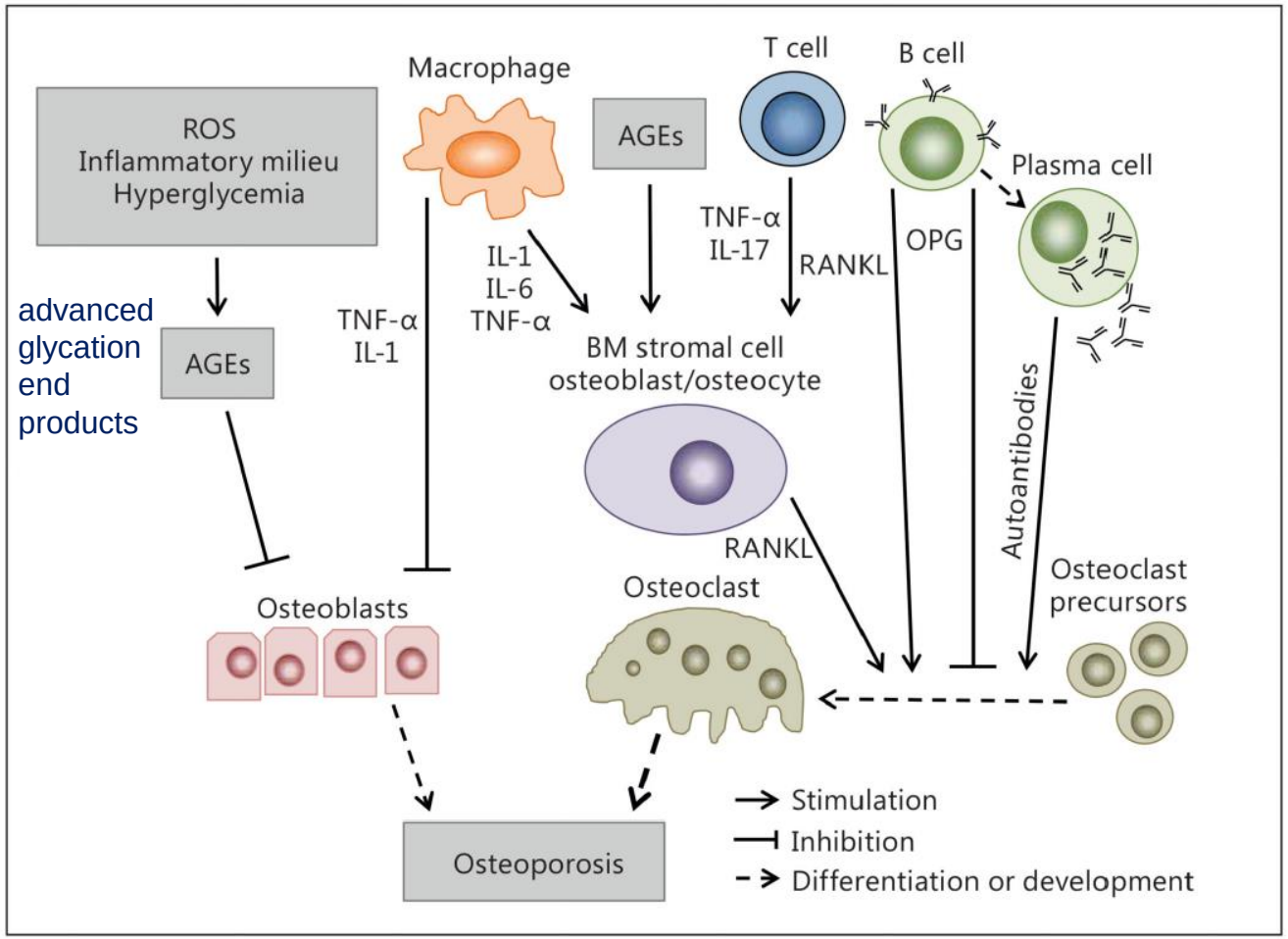
Apart the crucial role of estrogen deficiency on several pathways, oxidative stress and the generation of advanced glycation end products have emerged as links between inflammation and bone destruction.




*Wu et al, 2021*

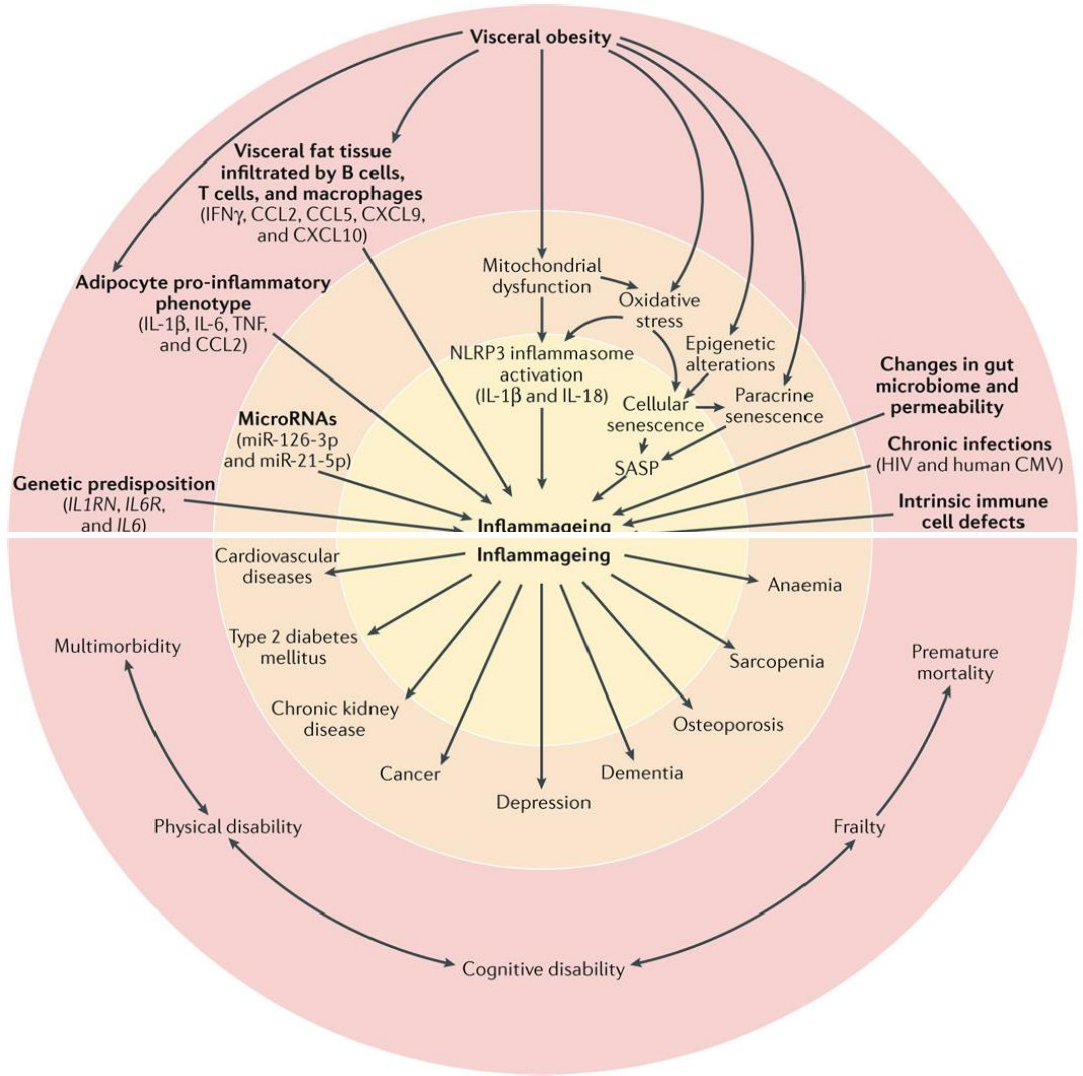



*Pietschmann et al, 2016*

# Inflammaging – a multidimensional view

Co-funded by the Erasmus+ Programme of the European Union

- **INFLAMMAGEING is a multi-causal phenomenon consisting in an age-related increase in the levels of pro-inflammatory markers in blood and tissues.**
- **It is a strong risk factor for multiple diseases that are highly prevalent and frequent causes of disability in elderly individuals but are patho-physiologically uncorrelated.**
- **Mild chronic inflammation is generally considered to be a biomarker of accelerated biological ageing or one of the mechanisms by which the ageing process is associated with increased global susceptibility to all diseases.**




*Ferrucci & Fabbri, 2018*

# Biomarkers of “damage” and “compensation” for the different hallmarks of aging (1)

Co-funded by the Erasmus+ Programme of the European Union

| Hallmark | Damage | Resilience (compensation) response | Measures |
|---|---|---|---|
| Genomic instability | • Somatic mutations (including in stem cells)<br>• Inappropriate clonal expansion<br>• DNA modifications (8-oxoG, gamma H2AX, etc.) | • DNA repair mechanisms<br>• Cellular checkpoint responses (e.g., cell cycle arrest, senescence, apoptosis)<br>• Integrity of replication fidelity mechanisms<br>• Antioxidant mechanisms | • Single-cell/clonal NGS<br>• Tests of DNA repair mechanisms<br>• Measures of DNA modifications |
| Telomere shortening | • Telomere dysfunction in mitotic cells, stem cells, and germline cells | • Telomerase<br>• Cellular checkpoint responses | • Telomere length<br>• Markers of DNA damage response<br>• Telomerase activity |
| Cellular senescence | • Arrested cell proliferation<br>• SASP, chronic inflammation | • Immune clearance of senescent cells<br>• SASP suppression by mTOR signaling<br>• Prevention of irreversible senescence | • Senescent markers in blood and tissue<br>• SASP proteins in blood and tissue |
| Epigenetic changes | • Inappropriate increase or decrease in DNA methylation at specific sites<br>• Inappropriate increase or decrease in specific histone modifications<br>• Maladaptive epigenetic changes | • Epigenetic maintenance system<br>• Mechanism of epigenomic reprogramming<br>• Adaptive changes in epigenetic markers<br>• Suppression of negative and enhancement of positive transcriptional programs | • Methylation<br>• Histone acetylation |

*Ferrucci et al, 2019*

# Biomarkers of “damage” and “compensation” for the different hallmarks of aging (2)

Co-funded by the Erasmus+ Programme of the European Union

| | | | |
|---|---|---|---|
| Mitochondrial dysfunction | • Impaired respiration/ox/phosph<br>• Ineffective mitochondrial biogenesis<br>• Ineffective mitochondrial recycling<br>• Mitochondrial disorganization<br>• ROS-mediated oxidative damage | • Mitochondrial biogenesis<br>• Mitochondrial remodeling (fission/fusion cycles), mitophagy<br>• Maintained mtDNA replication fidelity<br>• Antioxidant defenses | • Mitochondrial volume/number/shape<br>• Mito respiration<br>• $P^{31}$ MRI spectroscopy<br>• Markers of biogenesis<br>• mtDNA copy number and haplotypes |
| Decreased autophagy, proteostasis | • Increased damaged/misfolded proteins<br>• Decreased protein function<br>• Permanence of unrecycled proteins/organelles<br>• Cell death due to increased autophagy | • Activity of macro-, micro-, and chaperone-mediated autophagy-related proteins<br>• Enhanced signaling pathways (e.g., mTOR signaling) that regulate levels of autophagy | • Autophagy markers and flux (+ TEM)<br>• Chaperon proteins |
| Stem cell exhaustion | • Reduced stem cell number<br>• Decreased proliferative capacity<br>• Decreased differentiation capacity | • Reprogramming?<br>• Quiescence maintenance | • Proliferative capacity in vitro<br>• Resistance to stress |

*Ferrucci et al, 2019*

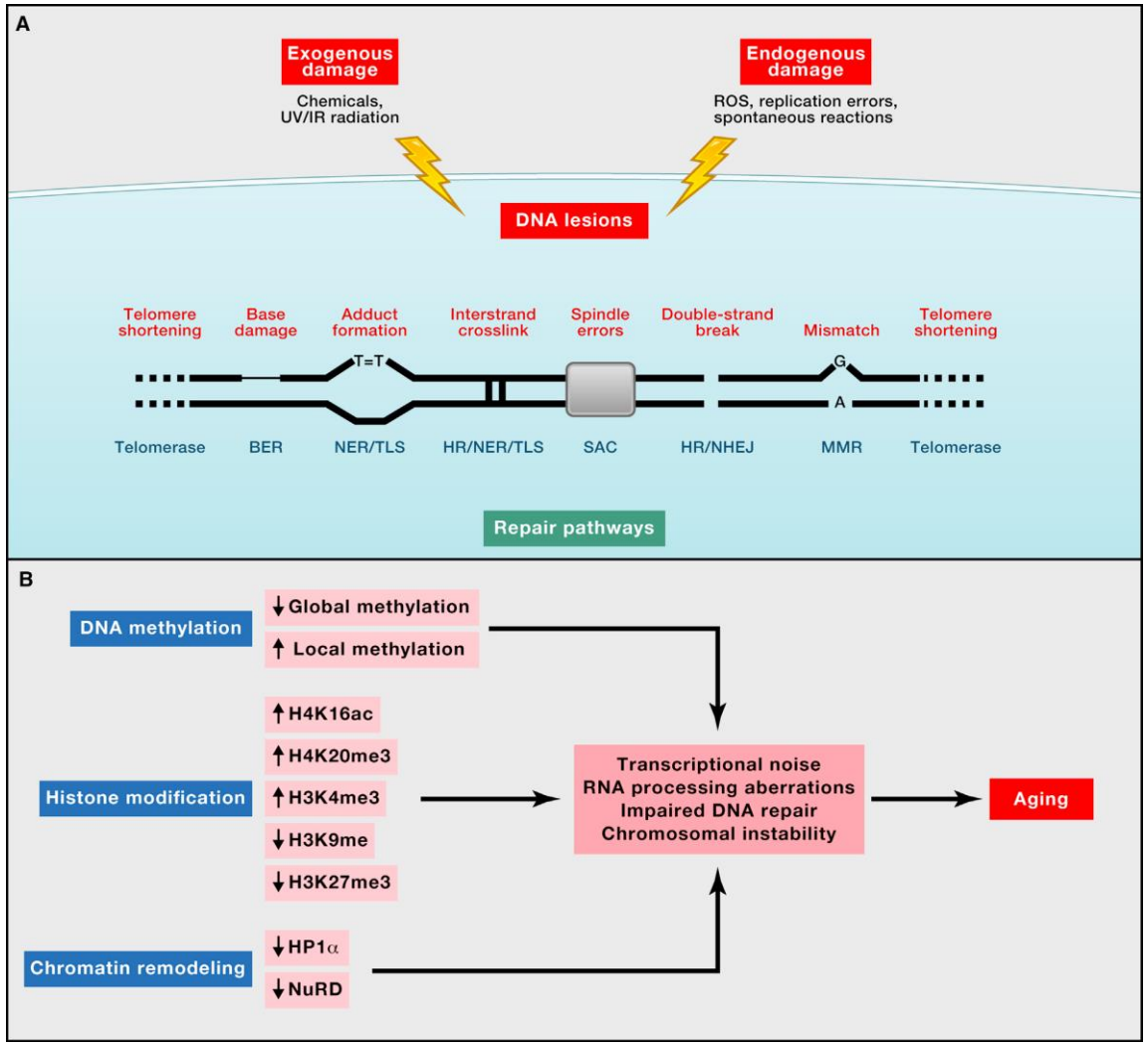
# Genomic and Epigenomic Alterations in Aging Process

Co-funded by the Erasmus+ Programme of the European Union

**(A) Genomic instability and telomere attrition**. Endogenous or exogenous agents can stimulate a variety of DNA lesions that are schematically represented on one single chromosome. Such lesions can be repaired by a variety of mechanisms. Excessive DNA damage or insufficient DNA repair favors the aging process. Note that both nuclear DNA and mitochondrial DNA (not represented here) are subjected to age-associated genomic alterations.

BER, base excision repair; HR, homologous recombination; NER, nucleotide excision repair; NHEJ, nonhomologous end-joining; MMR, mismatch repair; ROS, reactive oxygen species; TLS, translesion synthesis; SAC, spindle assembly checkpoint.

**(B) Epigenetic alterations.** Alterations in the methylation of DNA or acetylation and methylation of histones, as well as of other chromatin-associated proteins, can induce epigenetic changes that contribute to the aging process.




*Lopez-Ortin et al, 2013*

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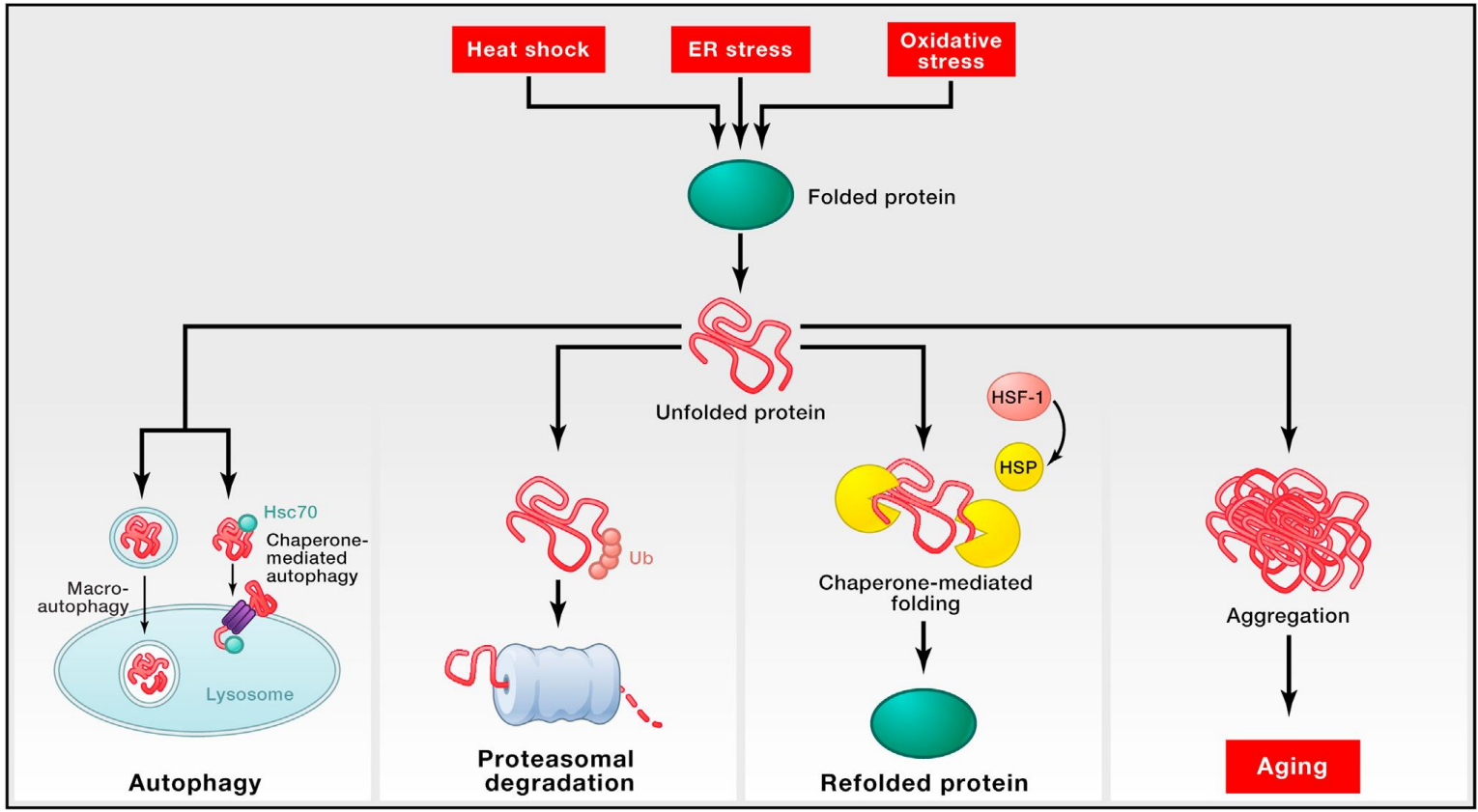
# Loss of Proteostasis in Aging Process

Endogenous and exogenous stress causes the unfolding of proteins (or impairs proper folding during protein synthesis). Unfolded proteins are usually refolded by heat-shock proteins (HSP) or are targeted to destruction by the ubiquitin-proteasome or lysosomal (autophagic) pathways. The autophagic pathways include
recognition of unfolded proteins by the chaperone Hsc70 and their subsequent import into lysosomes (chaperone-mediated autophagy) or sequestration of damaged proteins and organelles in autophagosomes that later fuse with lysosomes (macroautophagy). **Failure to refold or degrade unfolded proteins can lead to their accumulation and aggregation, resulting in proteotoxic effects.**




*Lopez-Ortin et al, 2013*

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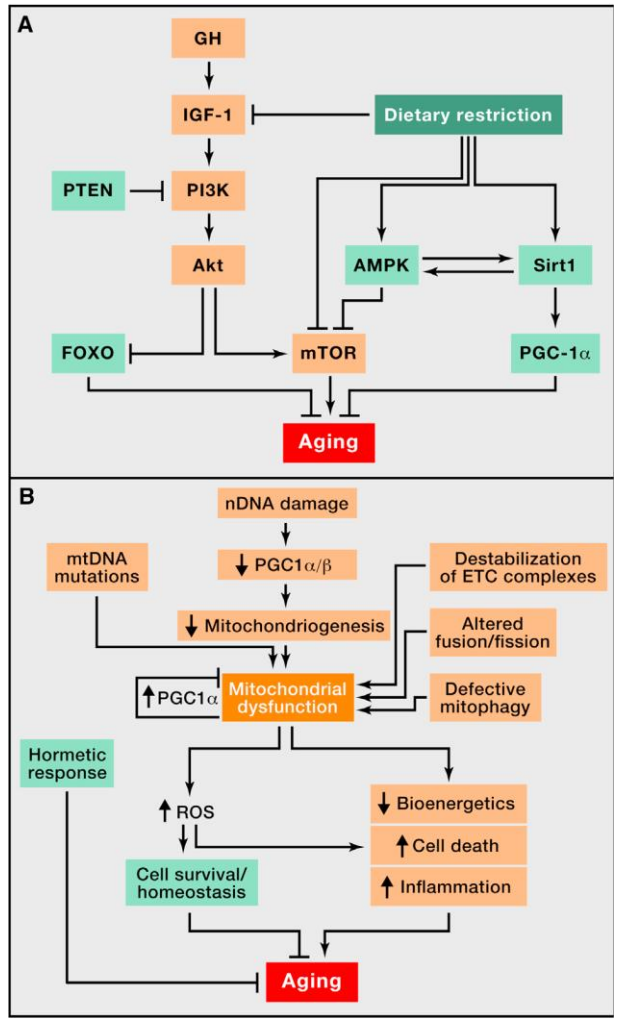
# Metabolic alterations in Aging Process



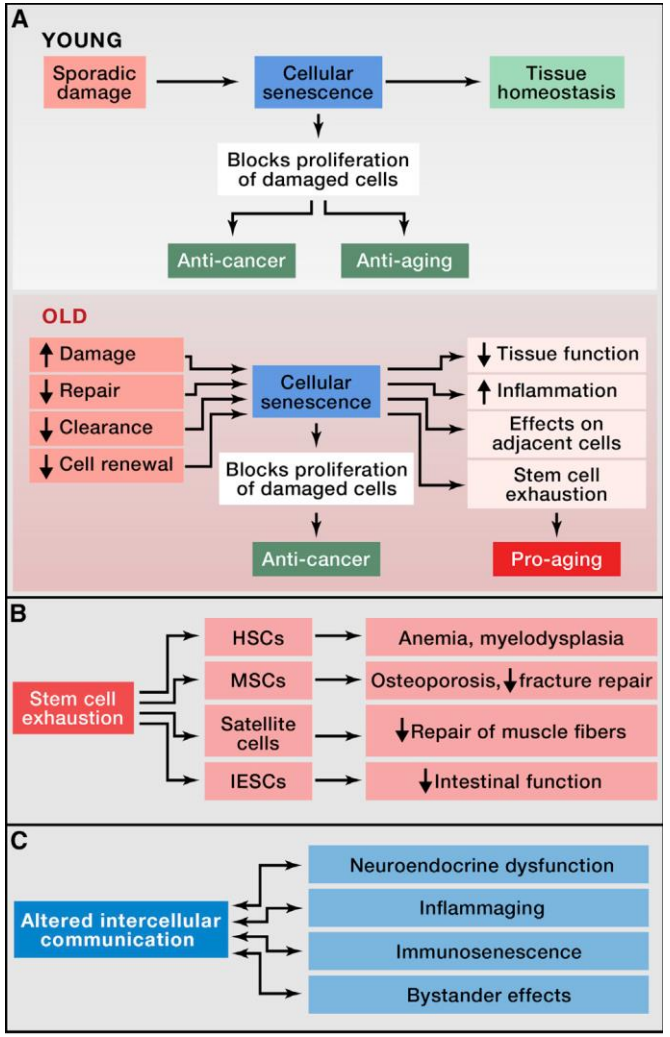

**(A) Deregulated nutrient sensing.** Overview of the somatroph axis involving growth hormone (GH) and the insulin/insulin growth factor 1 (IGF-1) signaling pathway and its relationship to dietary restriction and aging. Molecules that favor aging are shown in orange, and molecules with anti-aging properties are shown in light green.

**(B) Mitochondrial dysfunction.** Mitochondrial function becomes perturbed by aging-associated mtDNA mutations, reduced mitochondriogenesis, destabilization of the electron transport chain (ETC) complexes, altered mitochondrial dynamics, or defective quality control by mitophagy. Stress signals and defective mitochondrial function generate ROS that, below a certain threshold, induce survival signals to restore cellular homeostasis but, at higher or continued levels, can contribute to aging. Similarly, mild mitochondrial damage can induce a hormetic response (mitohormesis) that triggers adaptive compensatory processes.

*Lopez-Ortin et al, 2013*

# Cellular Senescence, Stem Cell Exhaustion, and Altered Intercellular Communication in Aging Process

Co-funded by the Erasmus+ Programme of the European Union




**(A) Cellular senescence.** In young organisms, cellular senescence prevents the proliferation of damaged cells, thus protecting from cancer and contributing to tissue homeostasis. In old organisms, the pervasive damage and the deficient clearance of senescent cells result in their accumulation, and this has a number of deleterious effects on tissue homeostasis that contribute to aging.

**(B) Stem cell exhaustion.** Consequences of the exhaustion of hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), satellite cells, and intestinal epithelial stem cells (IESCs) are exemplified.

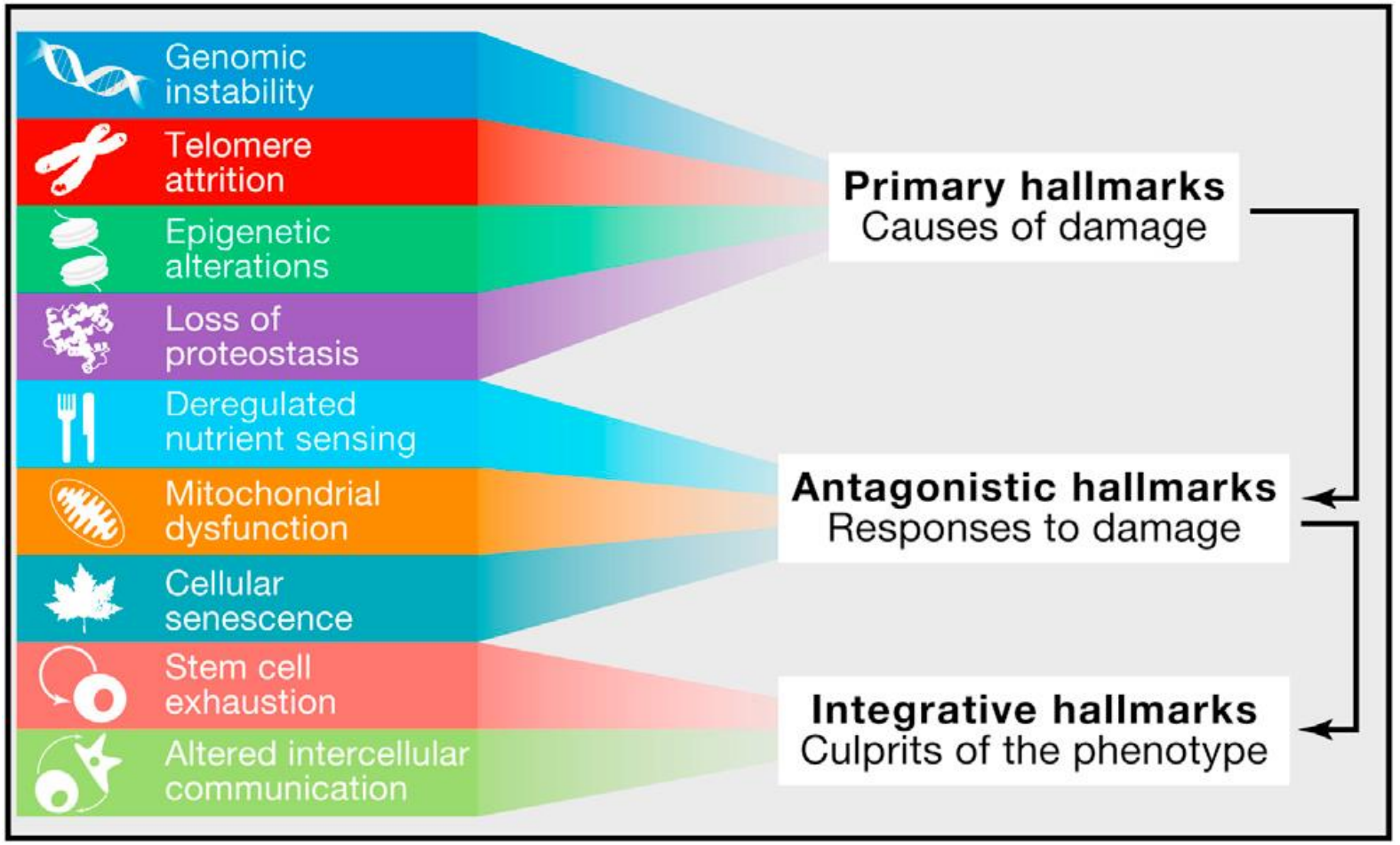
**(C) Altered intercellular communication.** Examples of altered intercellular communication associated with aging.

*Lopez-Ortin et al, 2013*

# Functional Interconnections between the Hallmarks of Aging

Co-funded by the Erasmus+ Programme of the European Union

The proposed nine hallmarks of aging are grouped into three categories.
**(Top)** Those hallmarks considered to be the **primary causes of cellular damage**.
**(Middle)** Those considered to be **part of compensatory or antagonistic responses to the damage**. These responses initially mitigate the damage, but eventually, if chronic or exacerbated, they become deleterious themselves.
**(Bottom)** Integrative hallmarks that are the end result of the previous two groups of hallmarks and are **ultimately responsible for the functional decline associated with aging**.




*Lopez-Ortin et al, 2013*

# Possible biomarkers of aging

Co-funded by the Erasmus+ Programme of the European Union

- The key to study the complexity of aging is **not only to consider something measurable** through blood analysis but also a **functional assessment** of the patient we have in front, with his/her context and social network.

| | |
|---|---|
| Parameters of organ functionality | Blood pressure |
| | Forced expiratory volume in 1 s (FEV 1); |
| | Bone density |
| | Memory executive function |
| | Body composition and muscle mass (sarcopenia) |
| Parameters of physical function | Walking speed, timed get up and go, chair rising, grip strength, balance tests, pegboard test |
| Blood parameters from clinical routine | Homocysteine, cholesterol profile, glycosylated hemoglobin, fasting glucose, growth hormone, insulin-like growth factor 1, DHEAS, DHEAS/ cortisol ratio, adiponectin, leptin, ghrelin, melatonin, estrogen, somatostatin, testosterone, thyroid hormones, Cystatin C, NT-proBNP |
| Biomarkers of immune function | IL-6, TNF-alpha, TNF-RII, C-reactive protein |
| Specific molecular biomarkers | Leukocyte telomere length, γ-H2A.X immunohistochemistry, DNA methylation, heterogeneity of CD38 in CD4+ and CD27+ T cells, heterogeneity of CD197 in CD4+ and CD27+ T cells, dosage of circulating microRNAs (miR-34a, miR-21, miR-126-3p, miR-151a-3p, miR-181a-5p, miR-1248), MIR31HG, AK156230, Meg3, target of rapamycin (TOR) proteins, pS6RP, NAD+, SIRT1, SIRT2, SIRT3, SIRT6, protein carbamylation, advanced glycation end products, N-glycans, growth differentiating factor 15 |

*Colloca et al, 2020*

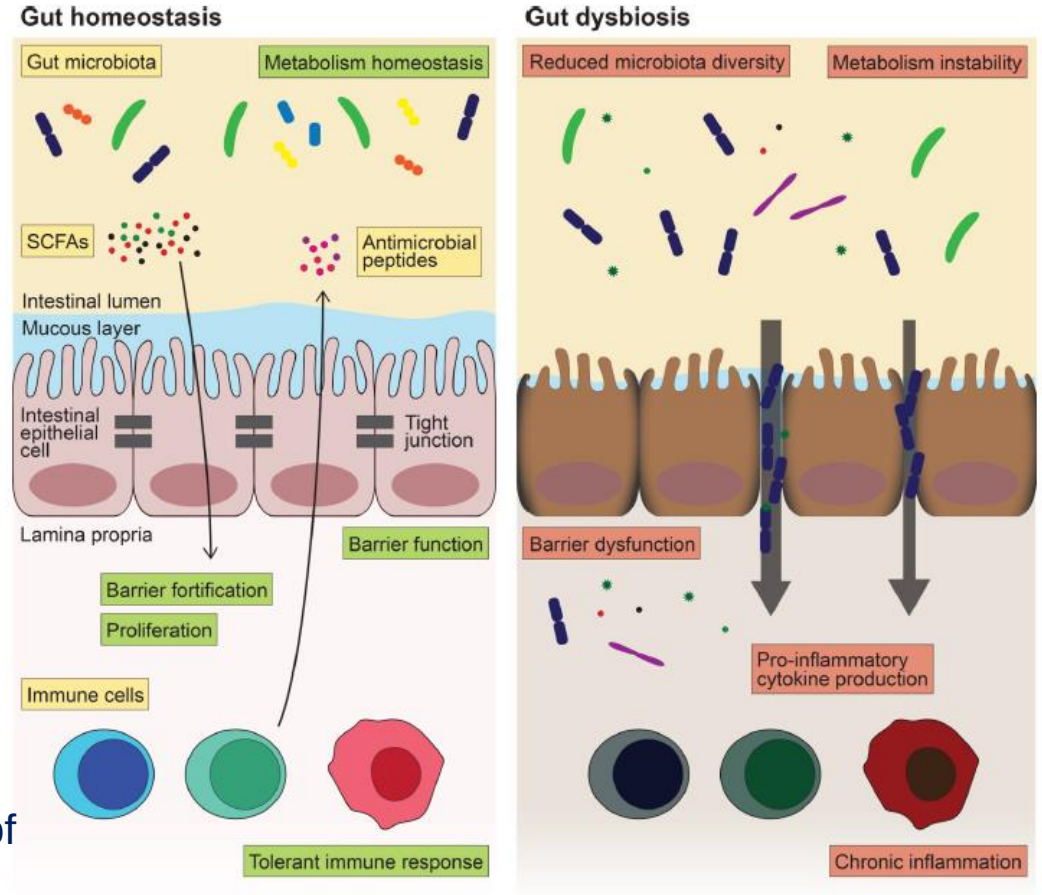
# The microbiome: an emerging key player in aging and longevity

Co-funded by the Erasmus+ Programme of the European Union

**The bidirectional relationship between the gut microbiome and aging**

**(Left panel)** In a healthy gut, balanced microbial composition and intestinal barrier integrity maintains gut homeostasis and contains the microbiota in the intestinal lumen. Microbiota-derived metabolites, including SCFAs, participate in a feedback mechanism with the host immune system to fortify the barrier function, produce mucus and promote intestinal stem cell proliferation. An efficient immune system tolerates the host immune responses to avoid excessive activation. **(Right panel)** In gut dysbiosis (such as with aging), declined intestinal barrier integrity results in translocation of microbes and microbial particles through the intestinal epithelial cell lining. Reduced microbiota diversity leads to overgrowth of distinct microbes and metabolism instability. Aberrant levels of microbiota-derived metabolites instigate abnormal immune responses resulting in chronic inflammation.

SCFA: Short-chain fatty acid.

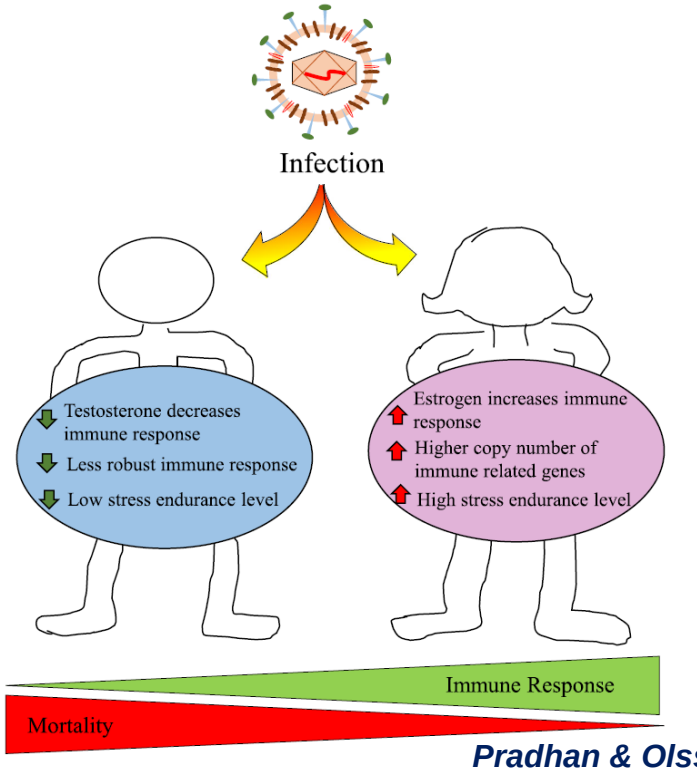



Kim & Benayoun, 2020

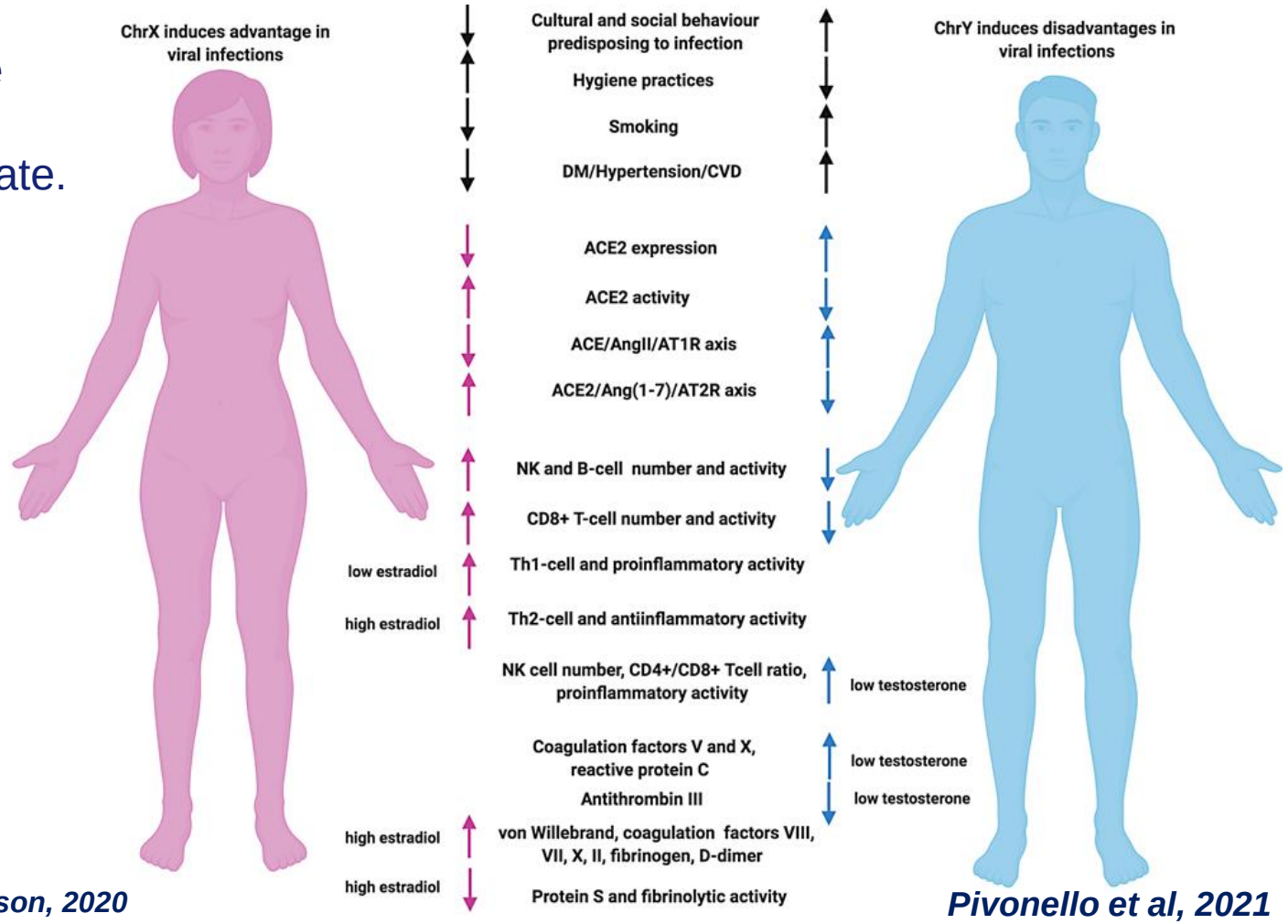
# Sex differences in susceptibility to SARS-CoV-2 infection

Co-funded by the Erasmus+ Programme of the European Union

- Sex hormone influence on innate and adaptive immune response, inflammation, and coagulatory state.




*Pradhan & Olsson, 2020*




*Pivonello et al, 2021*

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# Age-related changes in innate and adaptive immunity and their contribution to inflammaging

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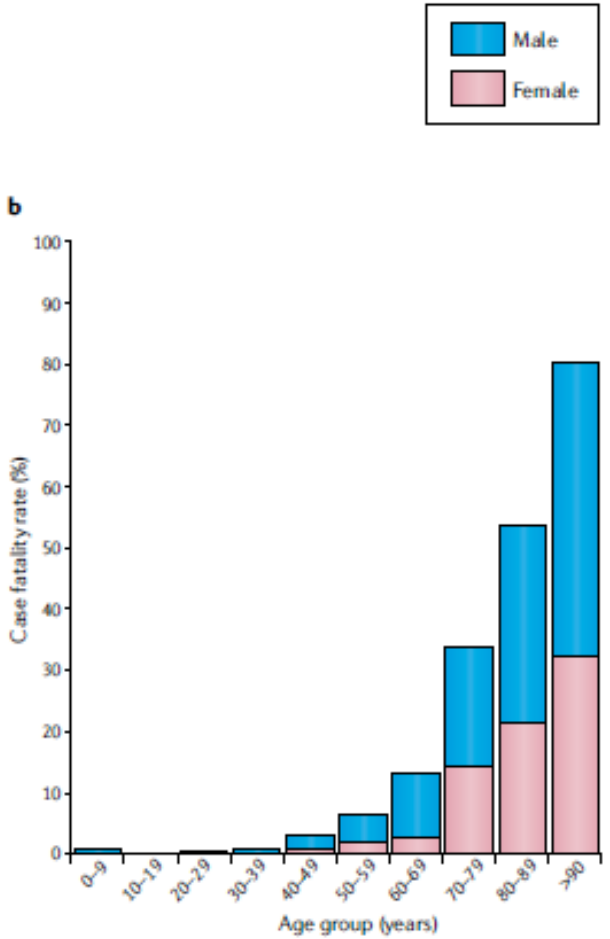
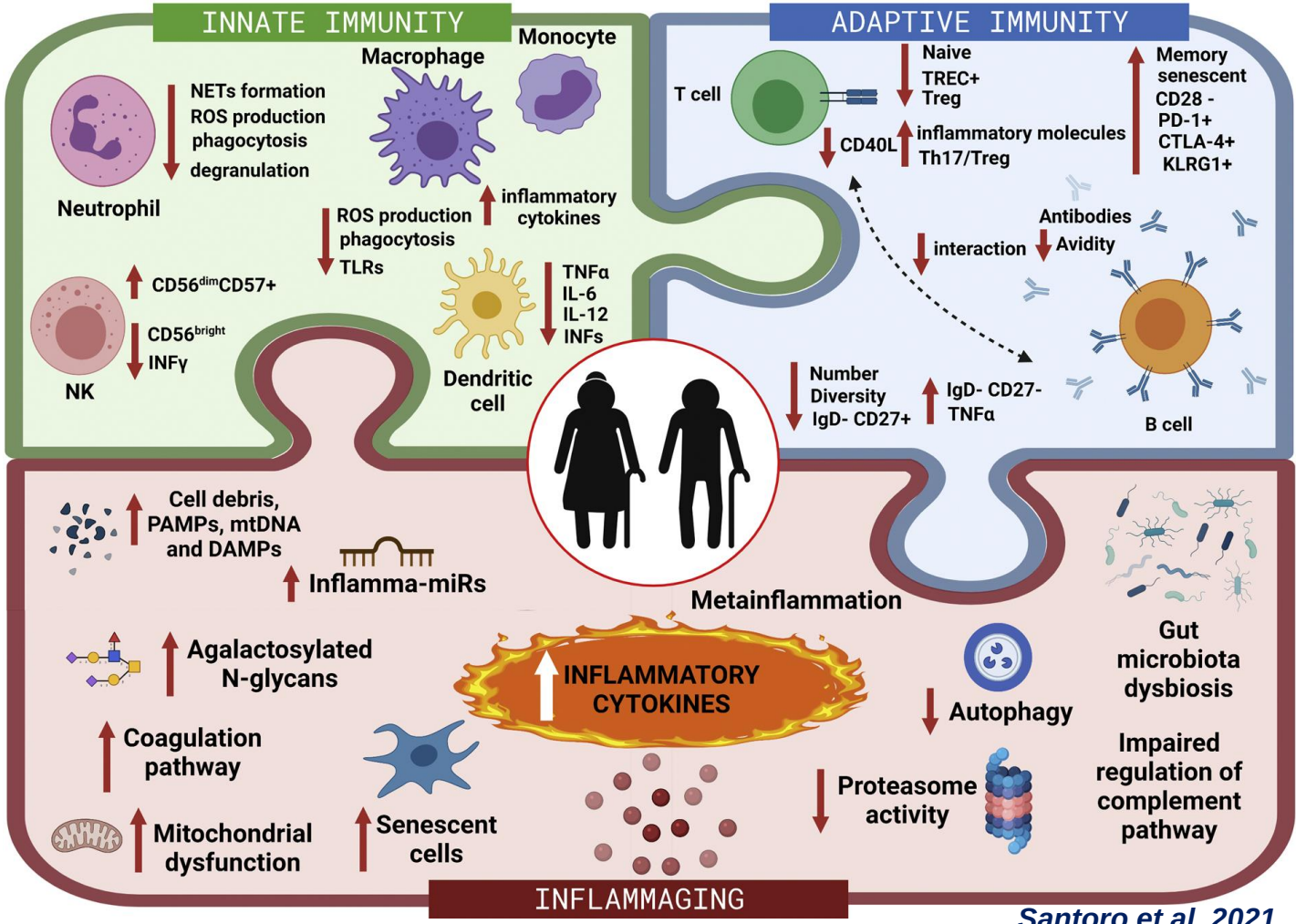



Scully et al, 2020




Santoro et al, 2021

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# Sex differences in innate and adaptive immunity throughout the life course

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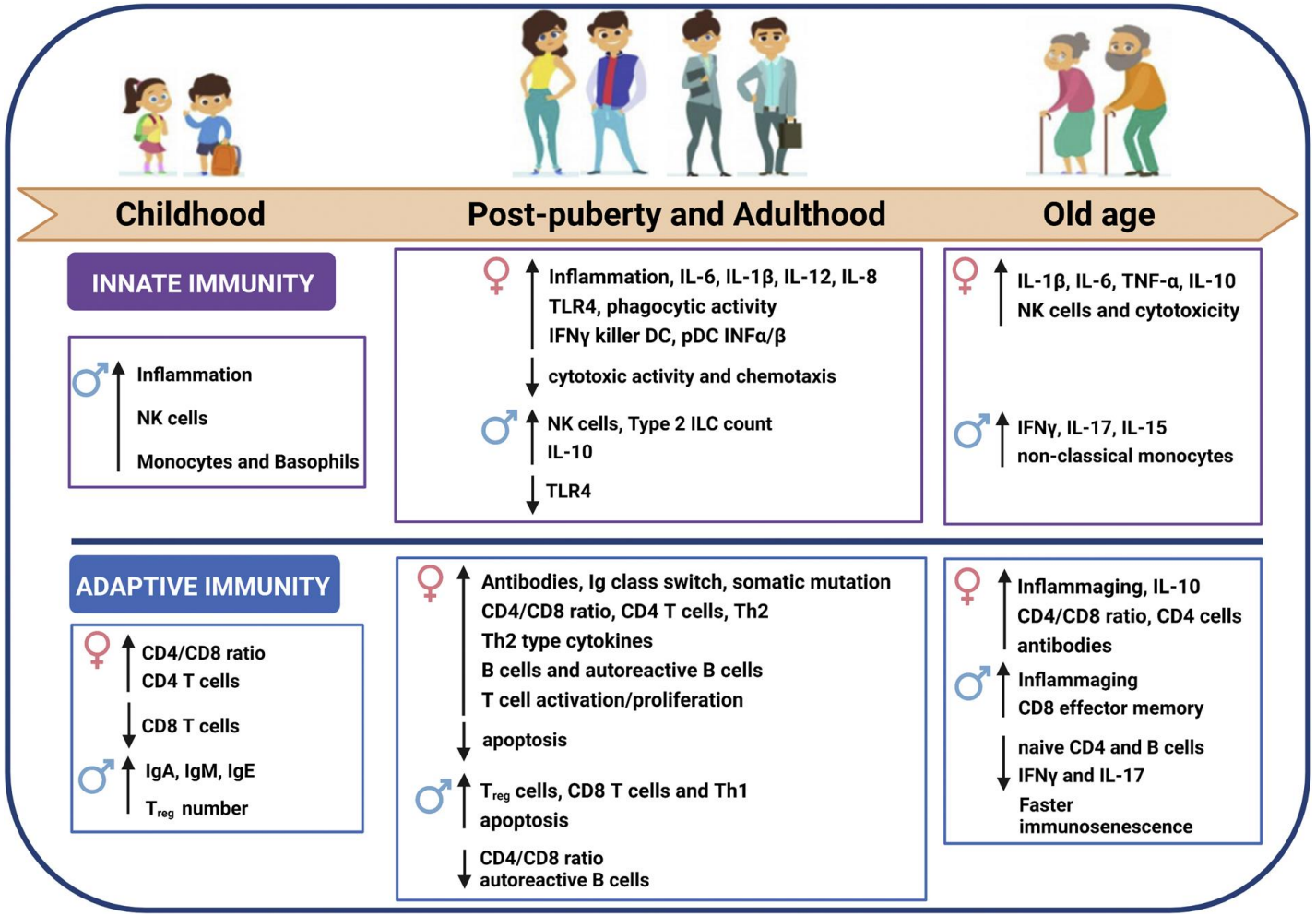
- A series of immunological components differ between human females and males across the course of life. Besides genes and hormones, environmental factors can modulate the functioning of the immune system differentially between males and females. Men experience a faster progression to immunosenescence than women, highlighted by changes in immune cells and inflammatory mediators.

**Abbreviations:** TLR, Toll-like receptor; TNF, tumour necrosis factor; Treg, regulatory T cells, IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; DC, dendritic cells; pDC, plasmacytoid dendritic cells; NK, Natural Killer cells; ILC, innate lymphoid cells; Th, T helper lymphocytes.




*Santoro et al, 2021*

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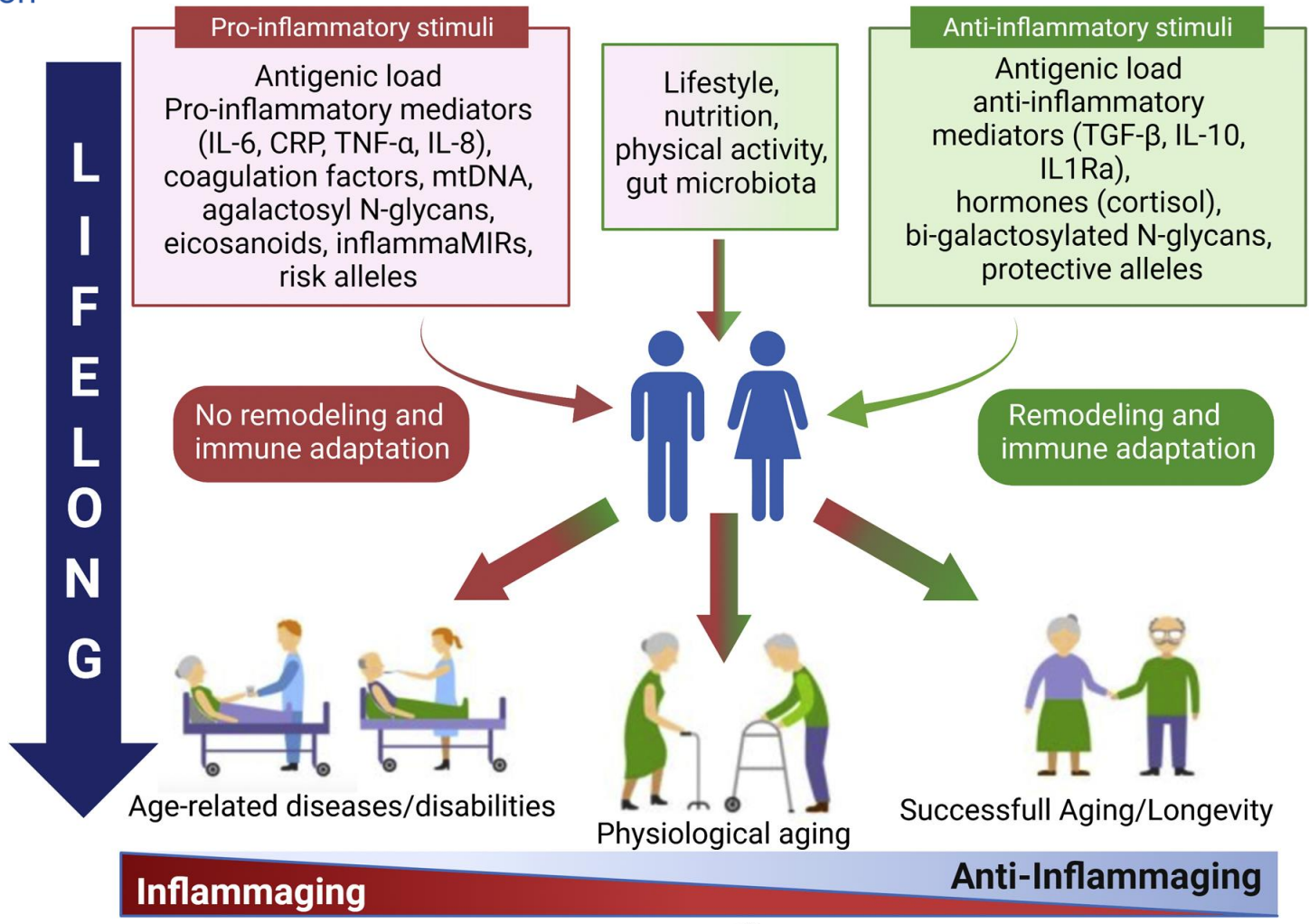
# Adaptation or maladaptation to lifelong pro- and anti-inflammatory stimuli leads to longevity or diseases

Co-funded by the Erasmus+ Programme of the European Union

- The pro- and anti-inflammatory stimuli that our organism is exposed to lifelong combined with a healthy or unhealthy lifestyle (nutrition and physical activity) and gut microbiota affect the IS remodeling triggering an adaptive or a maladaptive response.
- Excessive stimulation of pro-inflammatory pathways and an ineffective anti-inflammatory response constitutes a driving force for developing age-related diseases and disabilities.
- Instead, achieving successful aging and longevity is determined by a lower predisposition to mount inflammatory response combined with an efficient anti-inflammatory network.

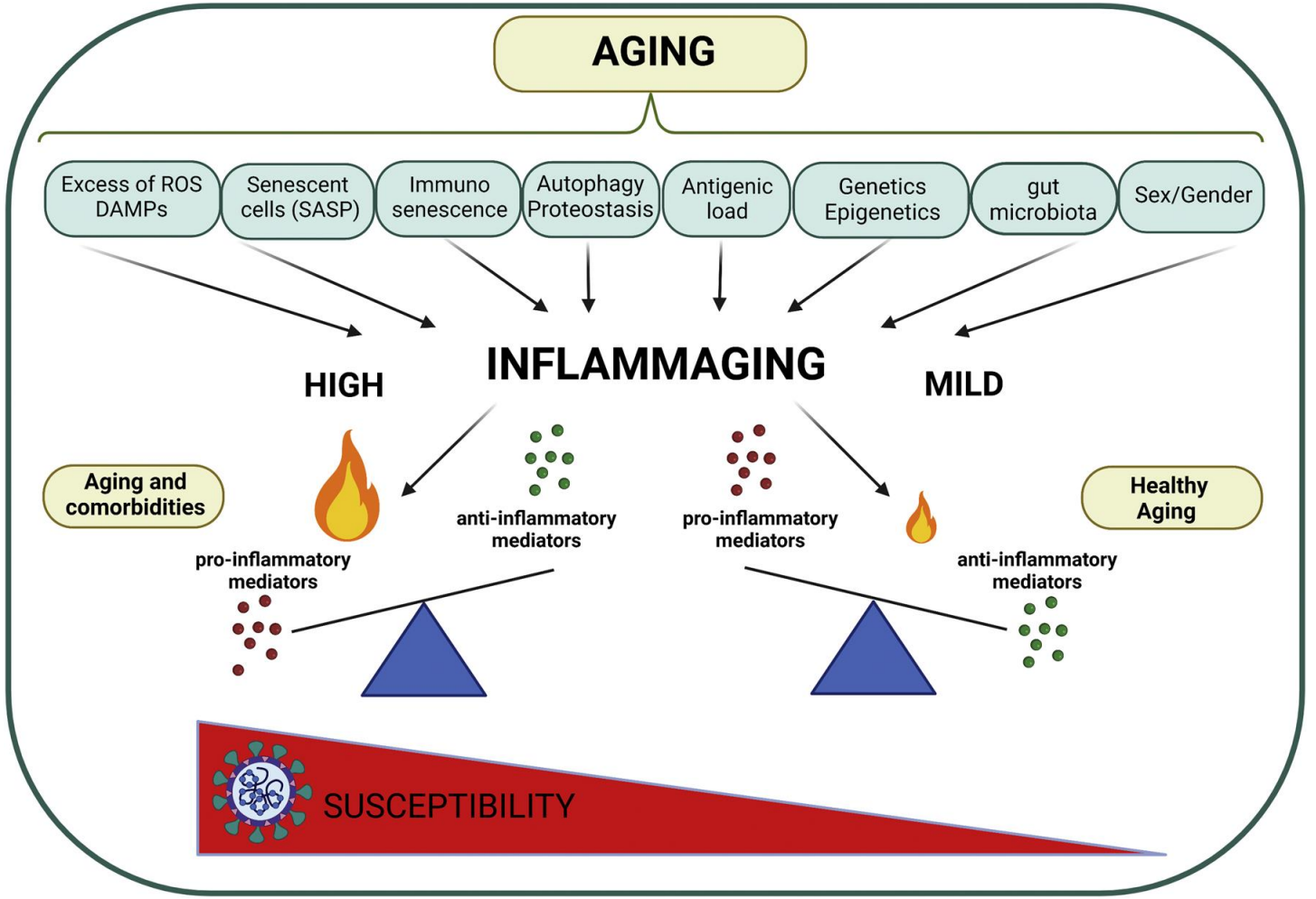



*Santoro et al, 2021*

# Inflammaging and susceptibility to COVID 19

Co-funded by the Erasmus+ Programme of the European Union

- Aging is characterized by extreme heterogeneity due to the numerous and different exposures to lifelong factors determining each individual's different immune responses.
- The different remodeling and adaptive reaction of the immune system triggered by inflammaging could explain the different susceptibility to COVID-19 among aged people.
- The adaptive anti-inflammatory response triggered by a mild inflammaging could reduce the susceptibility to COVID-19 or the disease severity.
- A poor remodeling and the consequent maladaptation of the immune system, triggered by a high inflammaging, could increase the risk of SARS-CoV-2 infection and the severity of the disease.




*Santoro et al, 2021*

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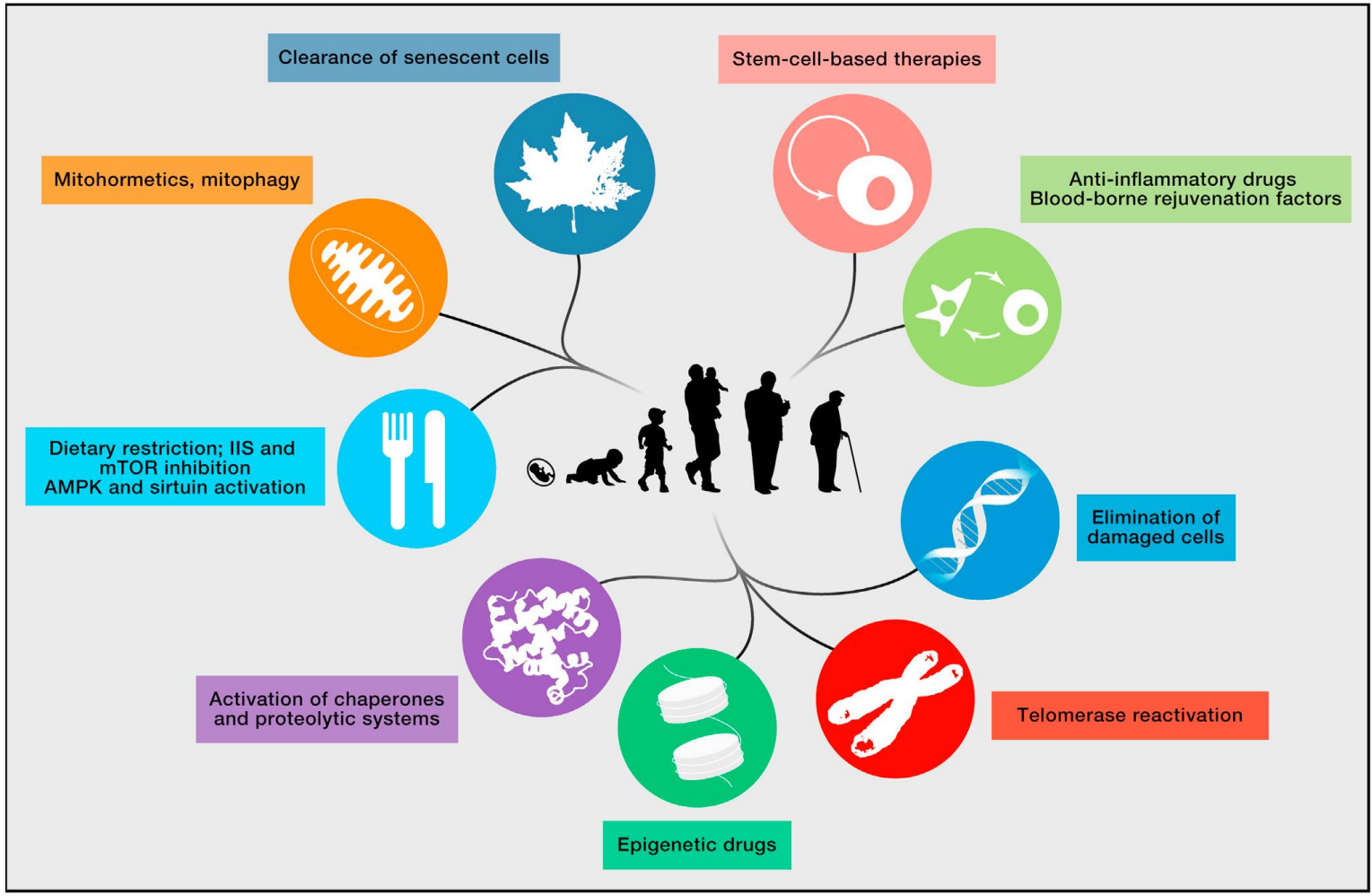
# Interventions that Might Extend Human Healthspan

- The nine hallmarks of aging are shown together with **those therapeutic strategies** for which there is proof of principle in mice.




*Lopez-Ortin et al, 2013*

# Less aging – more health span

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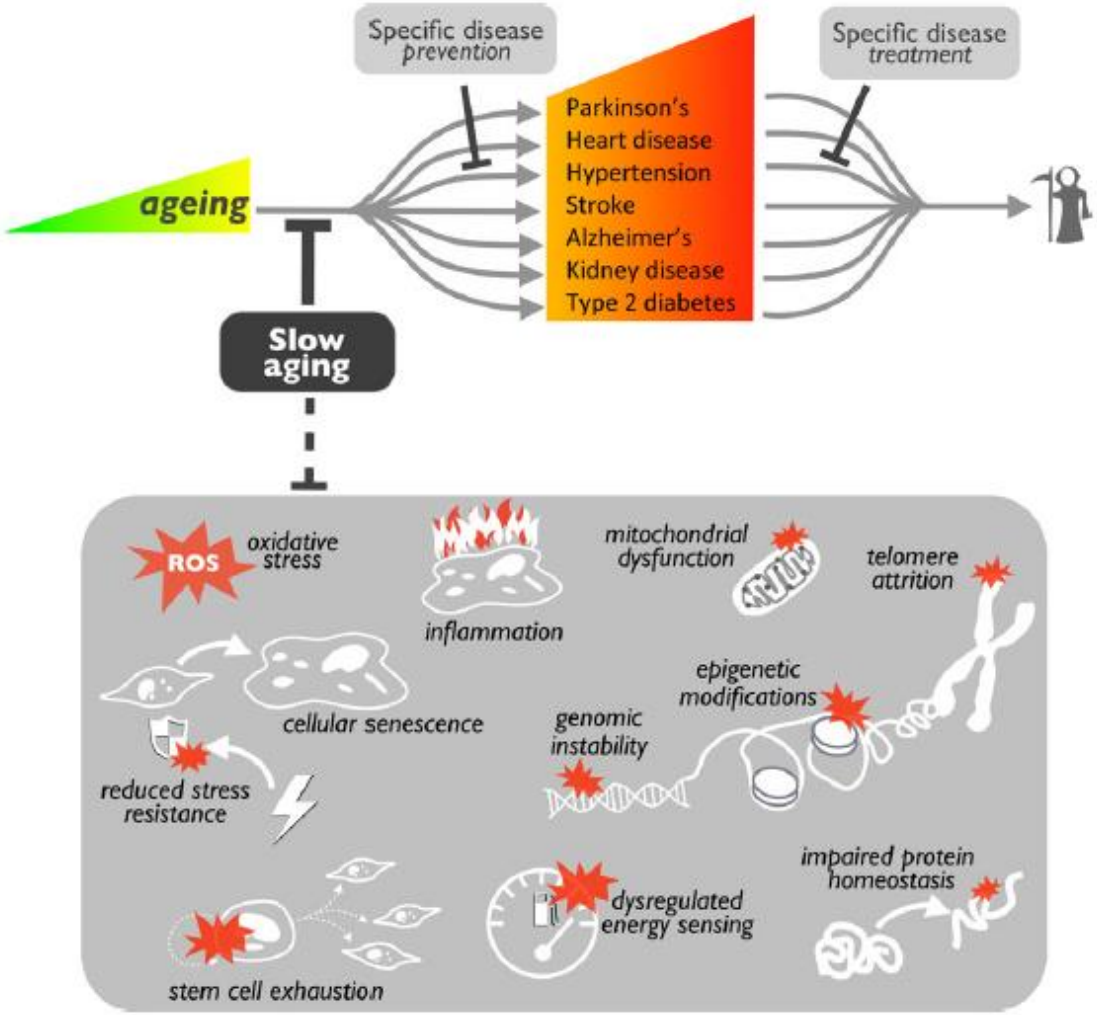
- Delaying age-related disorders as a group may be a more effective way to increase health span than preventing or treating individual chronic diseases.
- The former would involve inhibiting the basic mechanisms of ageing.




*Seals et al, 2016*

# Preventive strategies for health span

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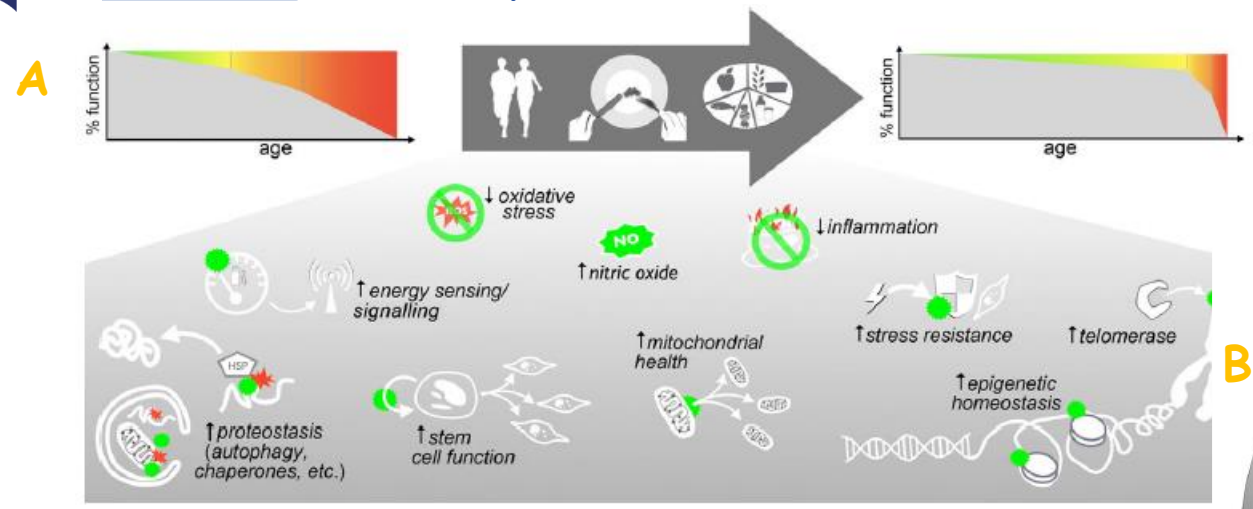


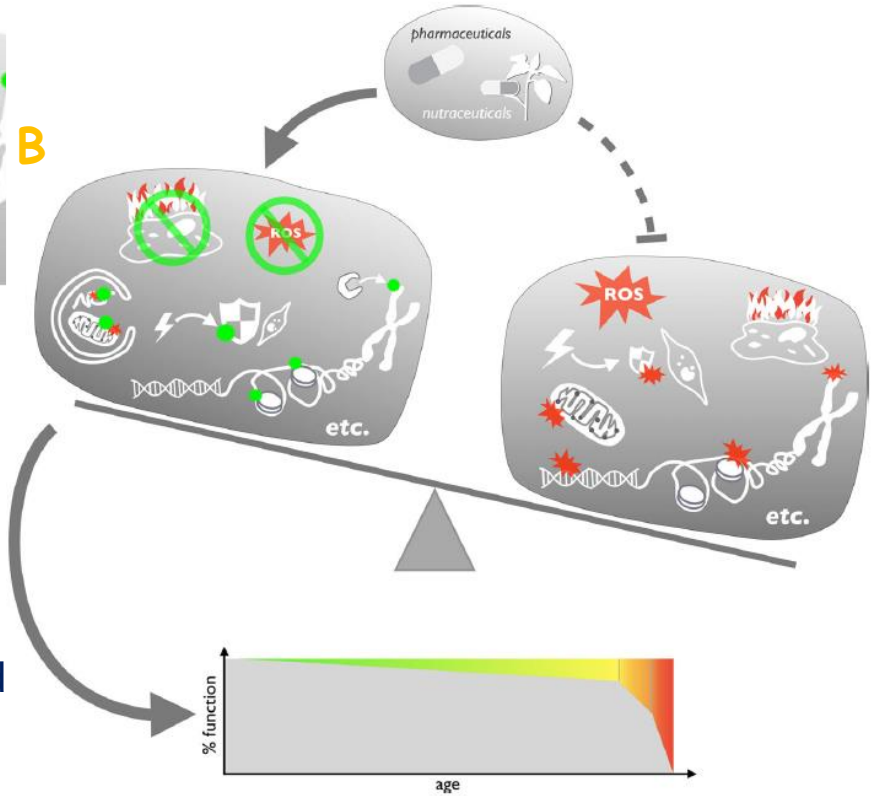


A. Regular physical activity, restricted energy intake and healthy diet composition enhance physiological function and healthspan, promoting optimal longevity. The molecular/biological mechanisms underlying these benefits may involve inhibiting or reversing several fundamental processes of ageing.

B. Certain prescription drugs and nutraceuticals may have some potential to enhance physiological function with ageing by targeting the same signalling networks that exercise and healthy diet modulate, and/or by suppressing key processes of ageing.

*Seals et al, 2016*

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# Thank You!

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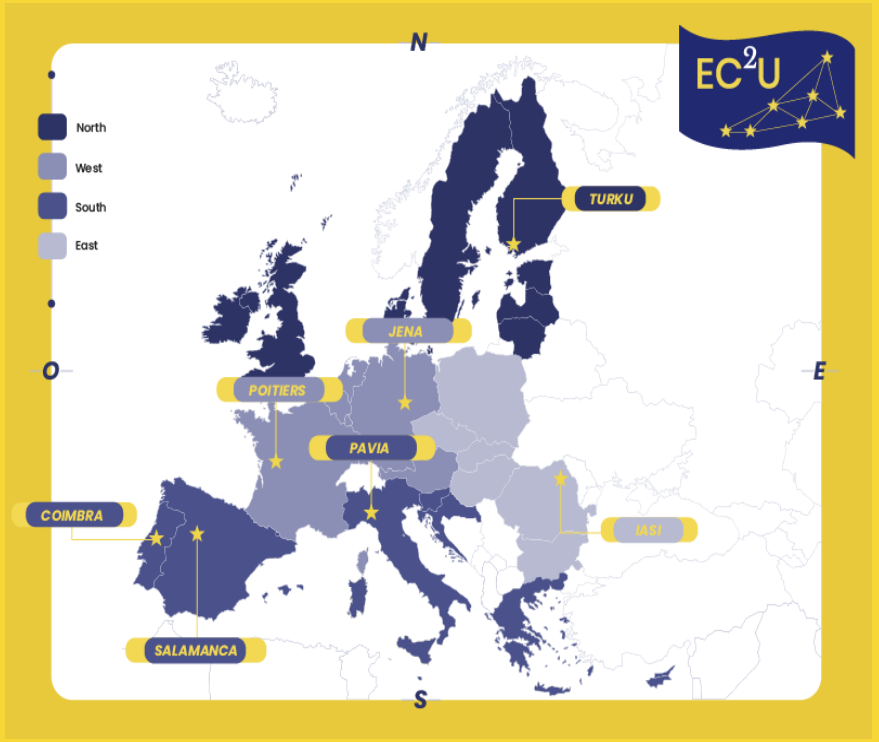


# Thank you !

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