Claudio Franceschi

Alma Mater Studiorum Università di Bologna, Italy
Lobachevsky State University
of Nizhny Novgorod, Russia

INFLAMMAGING: Invecchiamento e Longevita' Sana

FONDAZIONE ACQUA
per la cultura dell'acqua da bere

INVECCHIAMENTO
E UNA LONGEVITÀ SANA
FOCUS SULL'ACQUA DA BERE

Roma
10 ottobre 2022
Auditorium ENPAM
P.zza Vittorio Emanuele II, 78

BOLOGNA/UNIBO: the arcades of the oldest university in the Western world (founded in 1080)

New 2021
Impact Factor: 11.788

- **UN World Population Prospects July 2022: Summary of Results**

- The **population of older persons is increasing** both in numbers and as a share of the total.
- **The population above age 65 years is growing more rapidly than the population below that age,** and is projected to rise from 10 % in 2022 to 16% in 2050 and will be more than twice the number of children under age 5.
- Countries with ageing populations should take steps to **adapt public programmes to the growing numbers of older persons,** including long-term care systems, social security and pension systems.

- **UN World Population Prospects July 2022: Summary of Results**

- More and more countries have begun to experience **population decline**.
- **Fertility has fallen markedly in recent decades for many countries**. Today, two-thirds of the global population lives in a country or area where lifetime fertility is below 2.1 births per woman, roughly the level required for zero growth in the long run for a population with low mortality.

ISTAT PREDICTION IN ITALY

Date of publication: September 22, 2022

- 59,2 mln at 1° genn. 2021;
- 57,9 at 2030;
- 54,2 at 2050;
- 47,7 at 2070

- IN 2050 THE 65+ WILL BE 39.4% OF THE POPULATION (23.5% IN 2021)
- IN 2041, 10.2 MILLIONS PEOPLE WILL LIVE ALONE (8.5 MILLIONS IN 2021) AND 6,1 mln will be 65+

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...but this population of 65+ is highly heterogeneous

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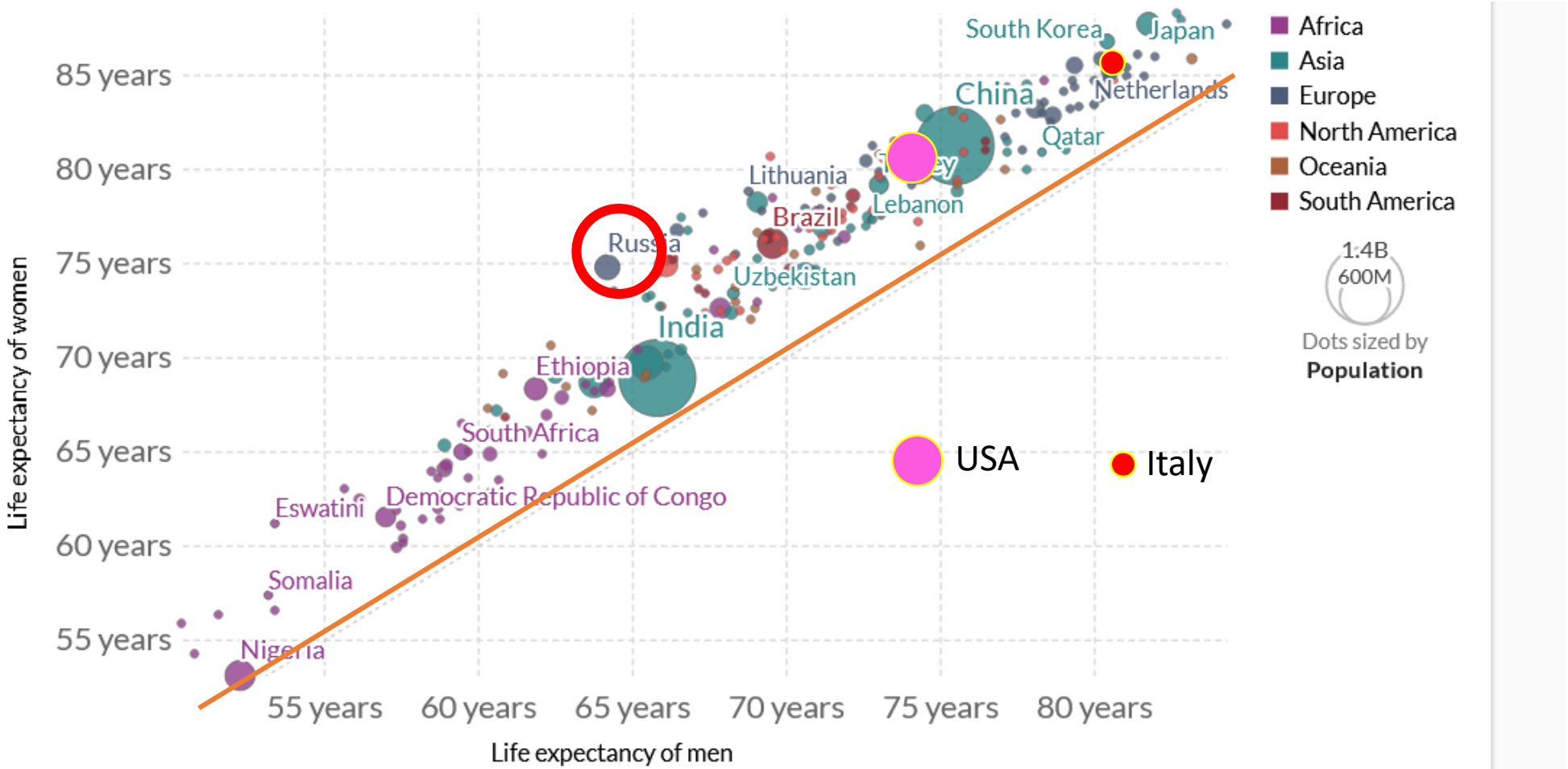
Life expectancy of women is universally higher than that of men, 2021

Above the red line life expectancy is higher



Source: United Nations - Population Division (2022)
Note: Shown is the period life expectancy at birth measured in years.

OurWorldInData.org/life-expectancy • CC BY

The female post-reproductive survival advantage is a relatively recent phenomenon observed only in the cohorts born towards the end of the 19th century, both in Italy and elsewhere, and coincides with the fertility decline.

But when this women advantage did start?

ORIGINAL ARTICLE Open Access

Fertility decline and the emergence of excess female survival in post-reproductive ages in Italy

Gianbattista Salinari[1*], Gustavo De Santis[2], Virginia Zarulli[3], Cristina Giuliani[4], Claudio Franceschi[5] and Marco Breschi[1]

Salinari *et al*., GENUS, 78, 19, 2022

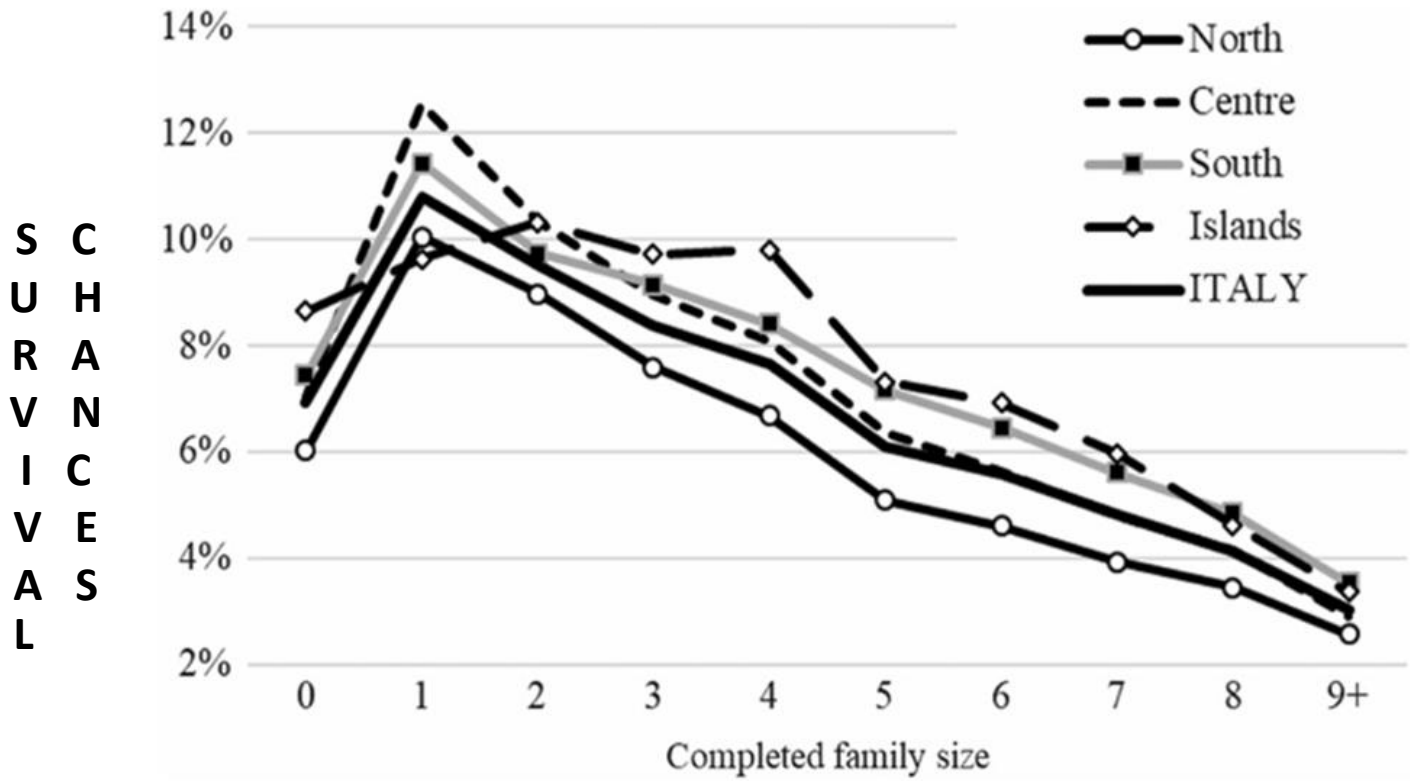


Fig. 1 Survival chances between 1931 and 1961 of the cohorts born before 1887 by completed family size (CFS), in Italy (ever-married women, aged 45 years and over at the start of the period and 75 years and over at its end). Ever-married women observed in 1931 at 45 years and over, and in 1961 at 75 years and over. *Source*: Istat (1936, 1974) and authors' calculations

Centenarians (100+) in Italy (59.2 mln) an increasing population

Women outnumber men:
at January 1st 2021, 100+ were 17.177
and 83% were women

Semi-supercentenarians (105+)
were 1.111

Supercentenarians (110+)
were 17 & all women
(the oldest was 112 years old)

Gender, aging and longevity in humans: an update of an intriguing/neglected scenario paving the way to a gender-specific medicine

Rita Ostan*[1], Daniela Monti†[1], Paola Gueresi‡, Mauro Bussolotto§, Claudio Franceschi‖[2] and Giovannella Baggio§[2]

*Interdepartmental Centre "L. Galvani" (CIG) and Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Via San Giacomo 12, 40126 Bologna, Italy
†Department of Clinical and Experimental Biomedical Sciences, University of Florence, Viale Morgagni 50, 50134 Florence, Italy
‡Department of Statistical Sciences "Paolo Fortunati", University of Bologna, Via Belle Arti 41, 40126 Bologna
§Internal Medicine Unit, Department of Molecular Medicine, University of Padua, Italy
‖IRCCS, Institute of Neurological Sciences of Bologna, 40139 Bologna, Italy

Clinical Science (2016) **130**, 1711–1725

GENDER MEDICINE: Gender difference regards prevalence and incidence of the most important age-related diseases (CVD, neurodegenerative diseases, cancer, T2D, disability, autoimmunity and infections). We focus on three basic biological phenomena: i) **age-related X chromosome inactivation skewing**; ii) **gut microbiome;** iii) **maternally inherited mitochondrial DNA genetic variants**.

Heterogeneity and non linearity of the aging process

nature medicine

LETTERS

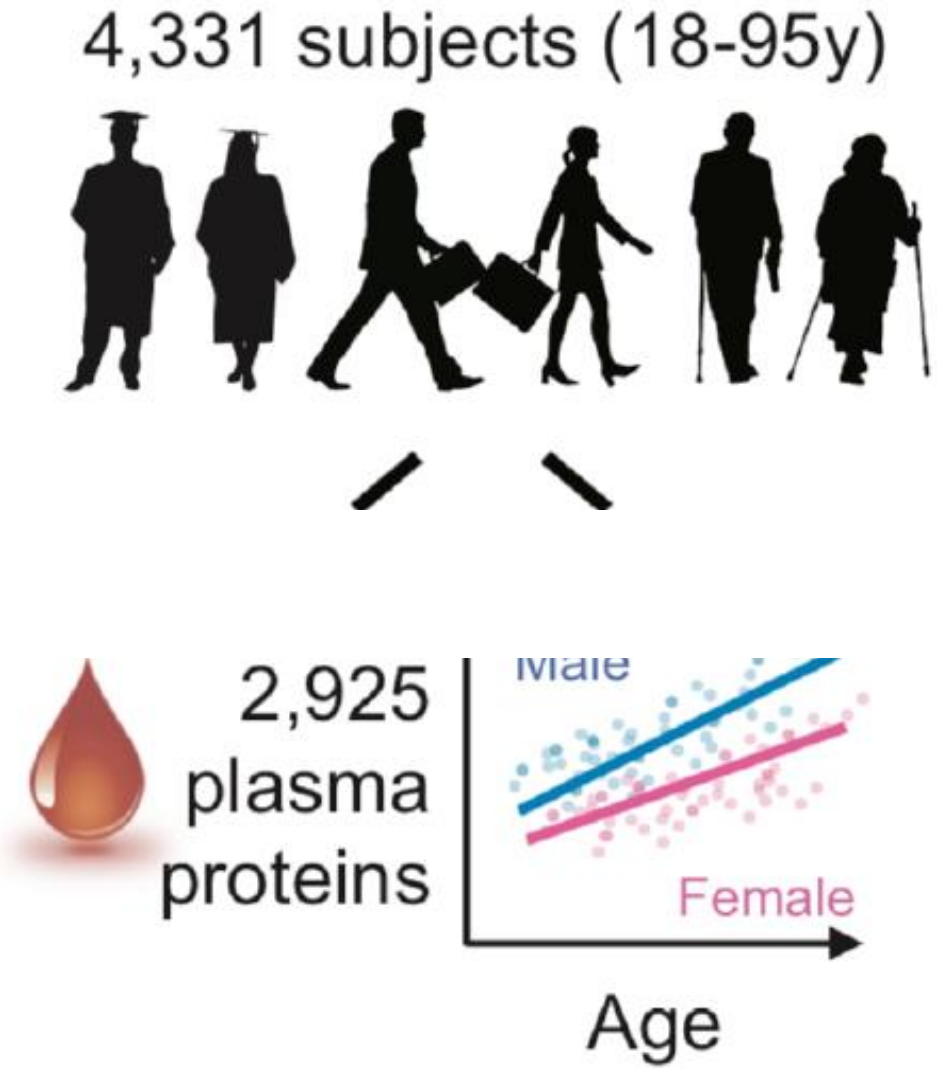
https://doi.org/10.1038/s41591-019-0673-2

Undulating changes in human plasma proteome profiles across the lifespan

Benoit Lehallier[1,2,3*], David Gate[1,2,3,4], Nicholas Schaum[5], Tibor Nanasi[1,2,3,6], Song Eun Lee[1,2,3,4], Hanadie Yousef[1,2,3,4], Patricia Moran Losada[1,2,3], Daniela Berdnik[1,2,3,4], Andreas Keller[7], Joe Verghese[8,9], Sanish Sathyan[8,9], Claudio Franceschi[10,11], Sofiya Milman[8,12], Nir Barzilai[8,12] and Tony Wyss-Coray[1,2,3,4*]

NATURE MEDICINE | VOL 25 | DECEMBER 2019 | 1843–1850 |

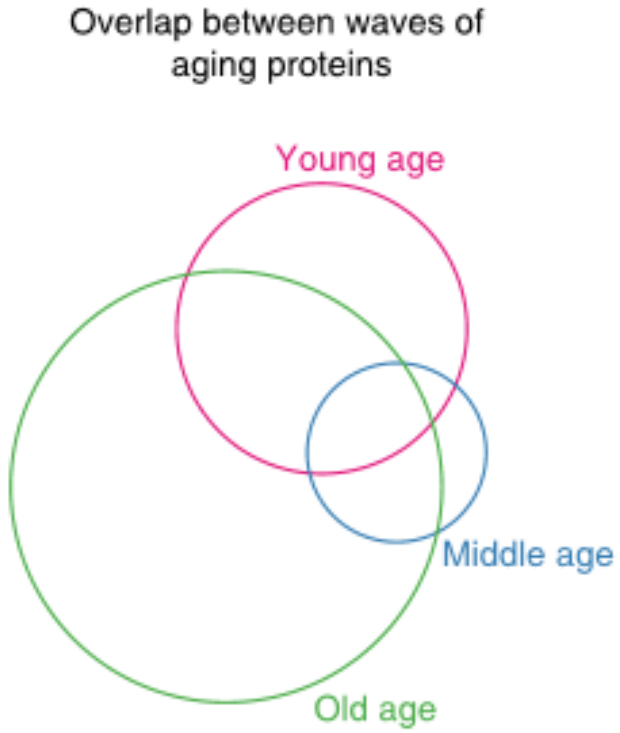
285 citations (23/09/2022)

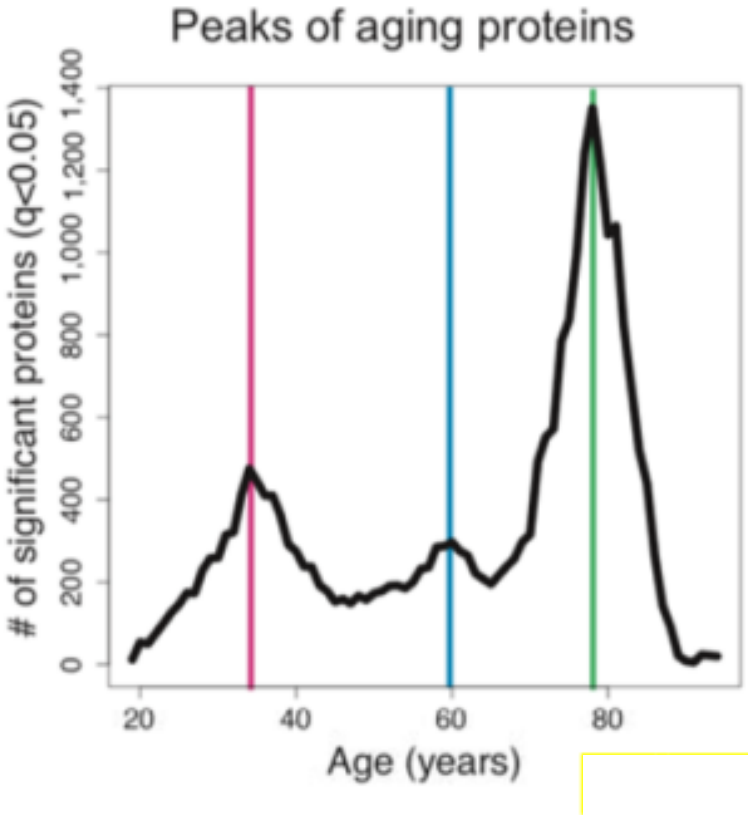


Nature Medicine 2019 December ; 25(12): 1843–1850.

Non-linear waves of changes in the proteome in the fourth, seventh, and eighth decades of life

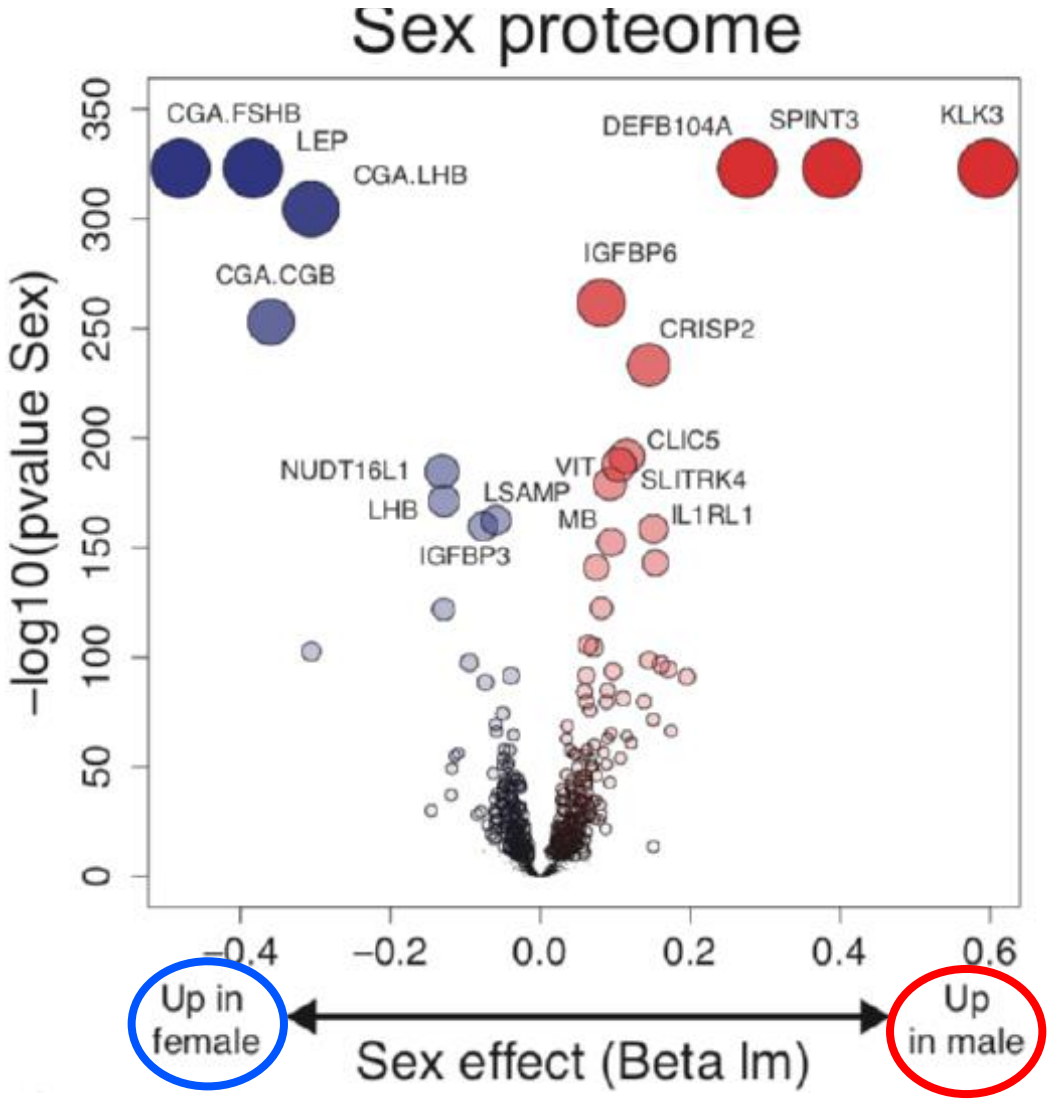
reflect distinct biological pathways and phenotypic traits





3 crests
at ages 34, 60 and 78

Nature Medicine 2019 December ; 25(12): 1843–1850.



The proteins most strongly associated with age also changed significantly with **sex**.

895 proteins out of the 1,379 proteins altered with age were significantly different between males and females.

Nat Med 2019 Dec; 25(12): 1843–1850.

L’invecchiamento è differente negli uomini e nelle donne

I nostri risultati sono allineati con un crescente numero di studi che dimostrano come l’invecchiamento sia **sesso/genere-specifico**

21. Ostan, R. et al. Gender, aging and longevity in humans: an update of an intriguing/neglected scenario paving the way to a gender-specific medicine. *Clin. Sci.* **130**, 1711–1725 (2016).

THE EPIGENETIC CLOCK

Steve Horvath (UCLA) in 82 databases on **DNA methylation data** obtained by Illumina 450 BeadChip platforms (**485,577 CpG/Genome**) identified in the whole genome

353 CpGs

whose methylation level is a

MULTI-TISSUES PREDICTOR OF AGE

which allows to estimate

DNA METHYLATION AGE *vs* CHRONOLOGICAL AGE

Steve Horvath
DNA methylation age
of human tissues and cell types
***Genome Biology* 2013, 14:R115**

Correlation 0.97 between DNAm age and chronol age
error = 2.9 years

105+ and their offspring are younger than their chronological age

www.impactaging.com AGING, December 2015, Vol 7 N 12

Research Paper

Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring

Steve Horvath[1,2*], Chiara Pirazzini[3,4*], Maria Giulia Bacalini[3,4,5], Davide Gentilini[6], Anna Maria Di Blasio[6], Massimo Delledonne[5,7], Daniela Mari[8,9], Beatrice Arosio[8,9], Daniela Monti[10], Giuseppe Passarino[11], Francesco De Rango[11], Patrizia D'Aquila[11], Cristina Giuliani[12], Elena Marasco[3,4], Sebastiano Collino[13], Patrick Descombes[14], Paolo Garagnani[3,4,15,§], and Claudio Franceschi[3,4,16,17,§]

DNAmeth age *versus* Chronological age in 105+ and their offspring (OFF)

According to the Horvath's DNAmet clock:

- **semi-supercentenarians are** on average **8.7 years younger** than expected based on chronological age;
- **105+ OFF are 5.2 years younger than age-matched controls (p=0.00051)**
- **In OFF' controls** DNAmethyl age and chronological age overlap

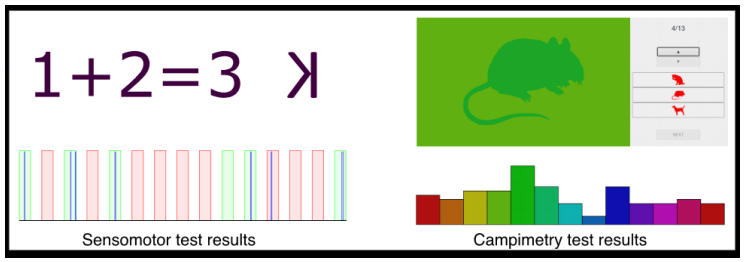
Horvath et al., AGING 2015

M. I. Krivonosov, E. V. Kondakova, N. A. Bulanov, S. A. Polevaya, C. Franceschi, M. V. Ivanchenko & M. V. Vedunova

A new cognitive clock matching phenotypic and epigenetic ages.

Translational Psychiatry ***12****, 364 (2022).*

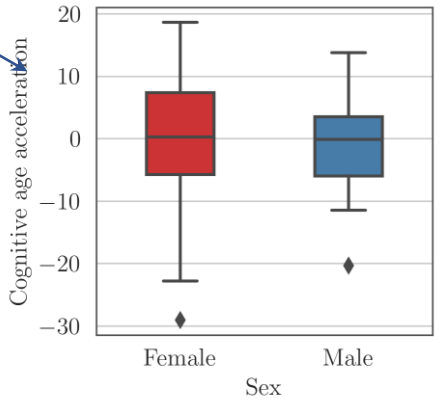
Cognitive clock



Sensomotor and Campimetry tests

Cognitive age based on 3 tests: reversed letters, arithmetic expression and color discrimination

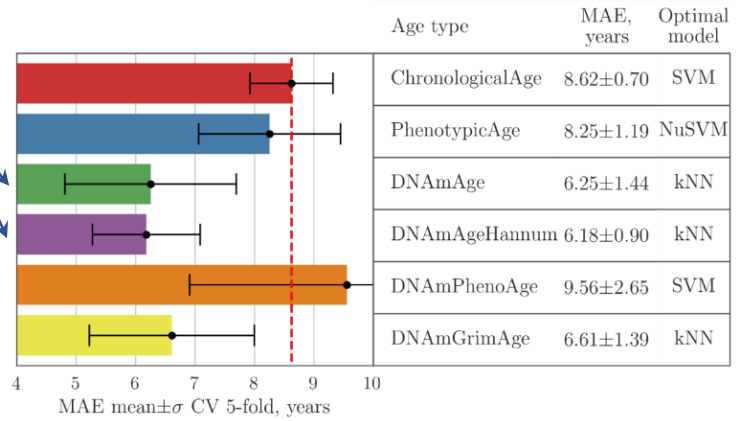
Females have a higher variance in cognitive age accelerations than males

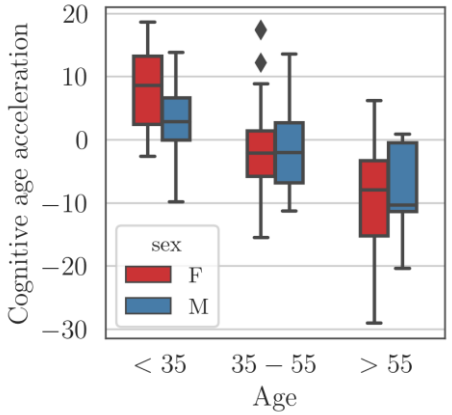


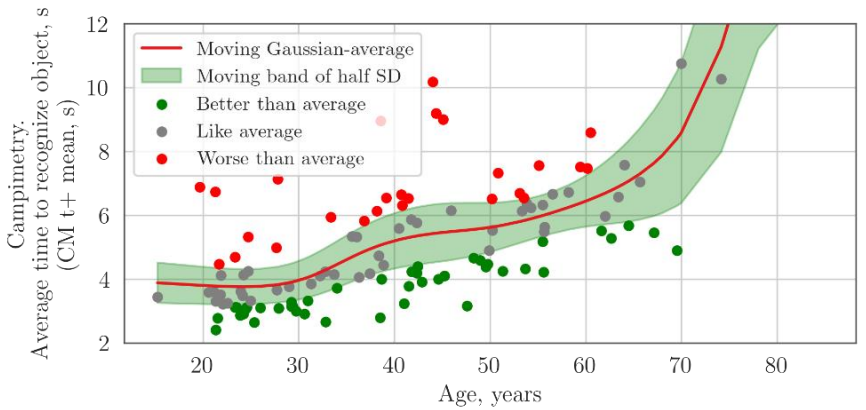
Cognitive age acceleration associated with non-linear performance

Young females shows higher cognitive age acceleration than males

DNAmAge is better associated with
Cognitive abilities than chronological age







Inflamm-aging

An Evolutionary Perspective on Immunosenescence

CLAUDIO FRANCESCHI,[a,b,e] MASSIMILIANO BONAFÈ,[a] SILVANA VALENSIN,[a] FABIOLA OLIVIERI,[b] MARIA DE LUCA,[d] ENZO OTTAVIANI,[c] AND GIOVANNA DE BENEDICTIS[d]

[a]*Department of Experimental Pathology, University of Bologna, Bologna, Italy*

[b]*Department of Gerontological Research, Italian National Research Center on Aging (INRCA), Ancona, Italy*

[c]*Department of Animal Biology, University of Modena and Reggio Emilia, Modena, Italy*

[d]*Department of Cell Biology, University of Calabria, Calabria, Italy*

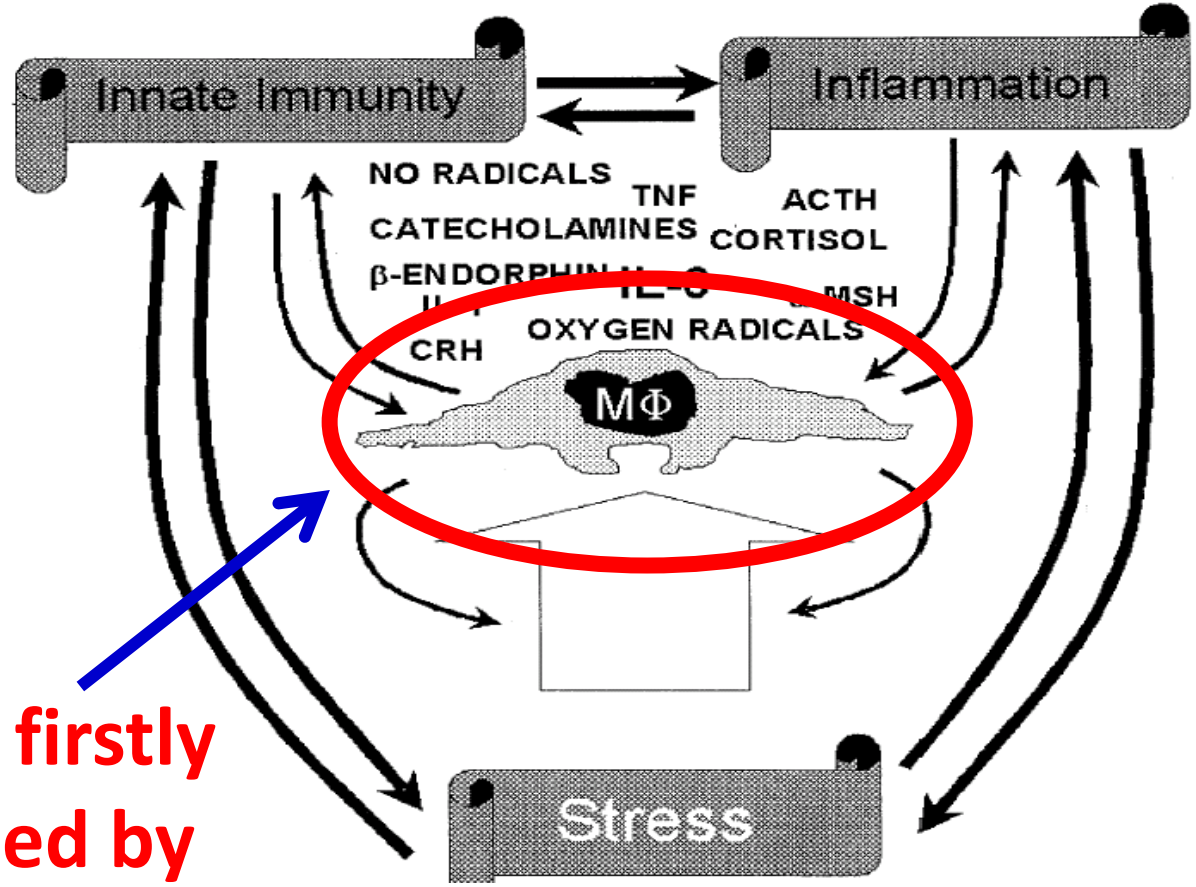
"chronic", "low grade", "sterile"

Inflammaging is based on studies on the **evolution** of immune response and **stress** from invertebrates to mammals

Ann. N.Y. Acad. Sci., 908, 244-254, 2000

4311 citations (24/09/2022)

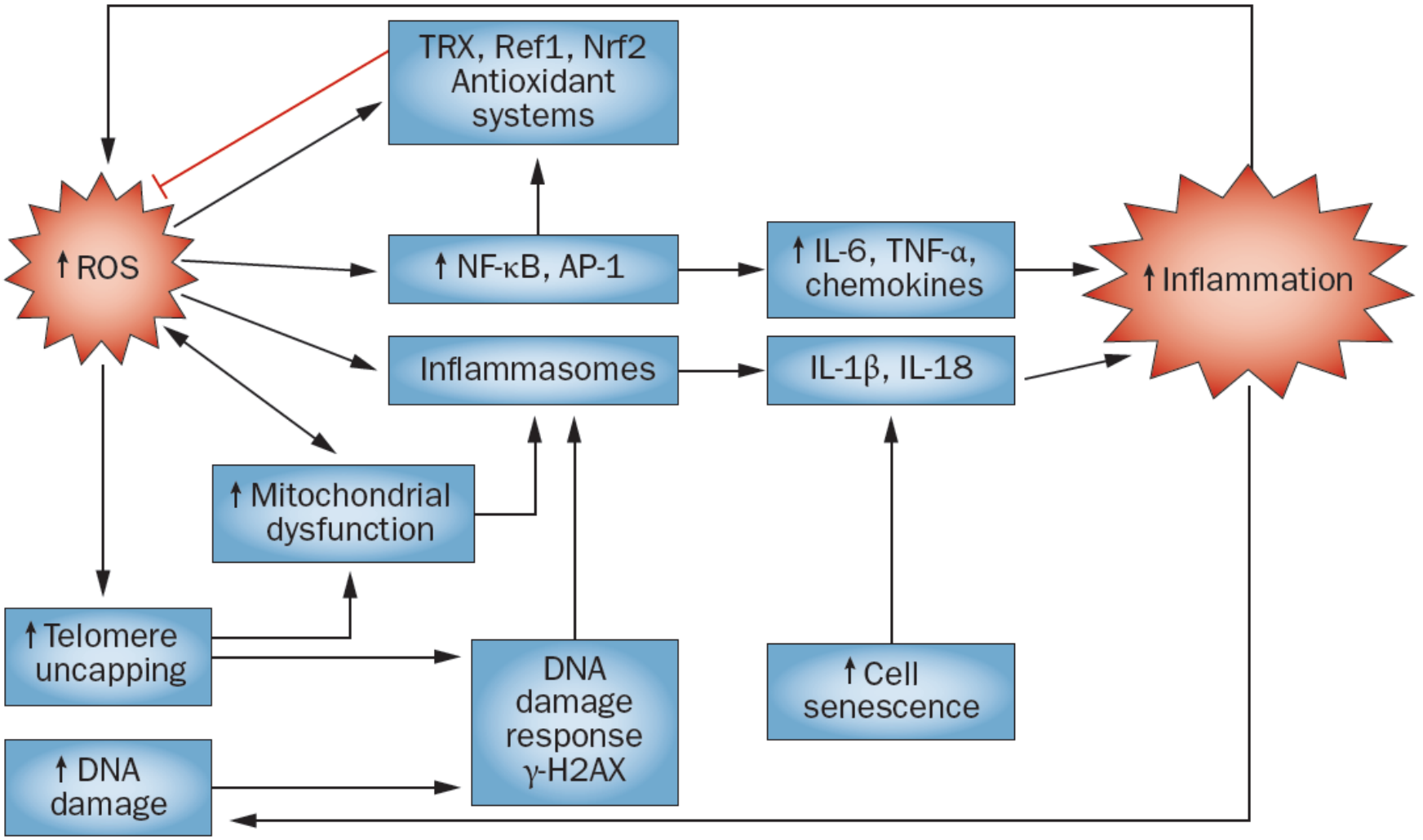
Macrophage is a central cell of inflammaging



The cell firstly described by E. Mechnikov

Franceschi et al., 2000

Mechanisms underpinning INFLAMMAGING



Vitale, Salvioli and Franceschi, Nat Rev Endocrinol, 2013

Aging is the single most important risk factor for all major ARDs and GSs

Leading Edge
Commentary

GEROSCIENCE SUMMIT
NIH, Bethesda Oct-Nov 2013

Cell

Geroscience: Linking Aging to Chronic Disease

ARDs= Age-Related Diseases
GSs= Geriatric Syndromes

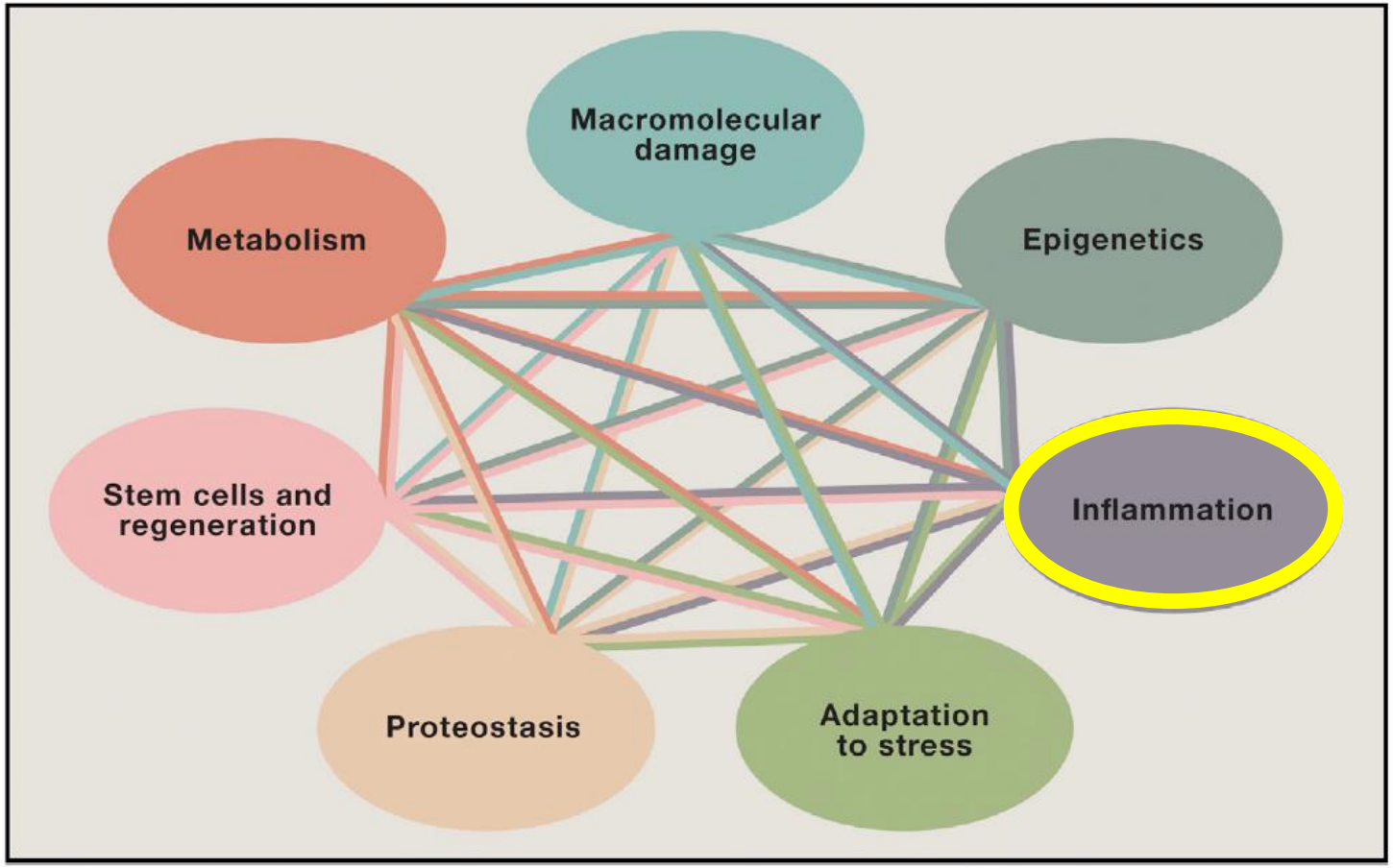
Brian K. Kennedy,[1,*] Shelley L. Berger,[2,3] Anne Brunet,[4,5] Judith Campisi,[1,6] Ana Maria Cuervo,[7,8] Elissa S. Epel,[9] Claudio Franceschi,[10,11,12] Gordon J. Lithgow,[1] Richard I. Morimoto,[13] Jeffrey E. Pessin,[14] Thomas A. Rando,[5,15,16] Arlan Richardson,[17,18] Eric E. Schadt,[19] Tony Wyss-Coray,[15,16] and Felipe Sierra[20]

Cell *159*, November 6, 2014

To combat aging in order to combat ARDs and GSs all together and not one by one

1466 citations 24/09/2022

Aging and Age-Related Diseases share few highly connected mechanistic pillars



Kennedy et al., Cell 2014

GEROSCIENCE
and the accompanying paper on Inflammaging

Advances in Geroscience: Impact on Healthspan and Chronic Disease Perspective

Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases

Claudio Franceschi[1,2] and Judith Campisi[3,4]

[1]DIMES, Department of Experimental, Diagnostic and Specialty Medicine and CIG, Interdepartmental Center "Luigi Galvani", University of Bologna, Italy.
[2]IRCCS Institute of Neurological Sciences, and CNR-ISOF, Bologna, Italy.
[3]Buck Institute for Research on Aging, Novato, California.
[4]Life Sciences Division, Lawrence Berkeley National Laboratory, California.

Address correspondence to Claudio Franceschi, MD, DIMES, Department of Experimental, Diagnostic and Specialty Medicine and CIG, Interdepartmental Center "Luigi Galvani", University of Bologna, Via S. Giacomo 12, 40126 Bologna, Italy. Email: claudio.franceschi@unibo.it

J Gerontol A Biol Sci Med Sci 2014 June;69(S1):S4–S9

2747 citations (24/09/2022)

A change of paradigm:
the enemy from within

Trends in Endocrinology & Metabolism 2017

Review

Inflammaging and 'Garb-aging'

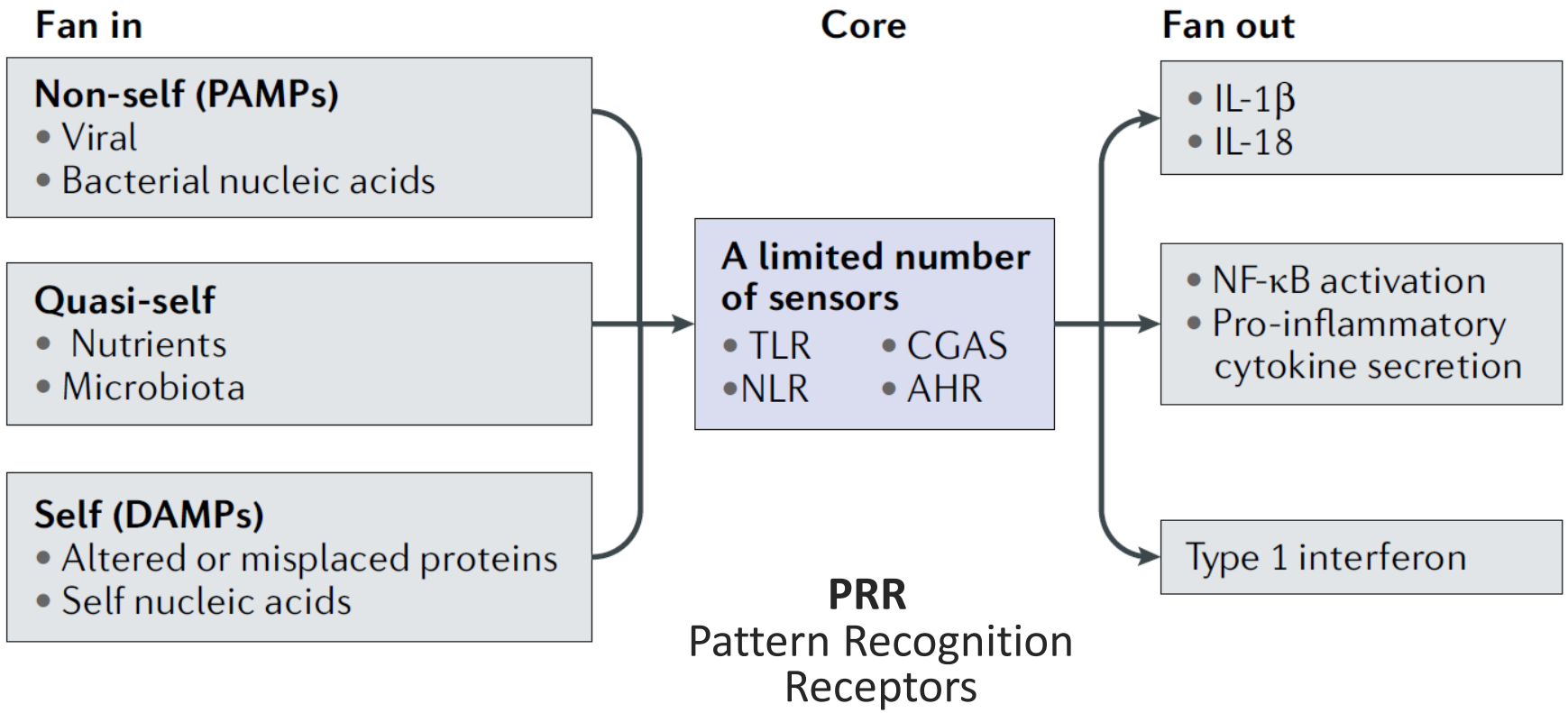
Claudio Franceschi,[1] Paolo Garagnani,[2,3] Giovanni Vitale,[4,5] Miriam Capri,[2,3,‡,*] and Stefano Salvioli[2,3,‡]

CELLULAR AND MOLECULAR GARBAGE: cell debris (resulting from cell death), misplaced/ altered/oxidized molecules, Gut Microbiota products , internal exposome, among others

Spazzatura molecolare endogena/self

- Nel corpo umano muoiono ogni giorno circa **50-70 miliardi di cellule.**
- Se la morte avviene per **NECROPTOSI** o **PIROPTOSI** si producono grandi quantità di **DAMPs**.
- Il nostro metabolismo produce centinaia/migliaia di composti potenzialmente “tossici” **(EXPOSOMA ENDOGENO)**
- Ad essi si aggiungono i prodotti batterici derivanti dal MICROBIOTA INTESTINALE e quelli dell’**EXPOSOMA ESOGENO**
- La rimozione/neutralizzazione di tale spazzatura è cruciale !

Molecular garbage converges on a limited number of DANGER/DAMAGE SENSORS characterized by a high degree of "DEGENERACY"



Franceschi et al., Nat Rev Endocrinol, 2018

INFLAMMAGING and the Theory of Antagonistic Pleiotropy

REVIEWS

Inflammaging: a new immune–metabolic viewpoint for age-related diseases

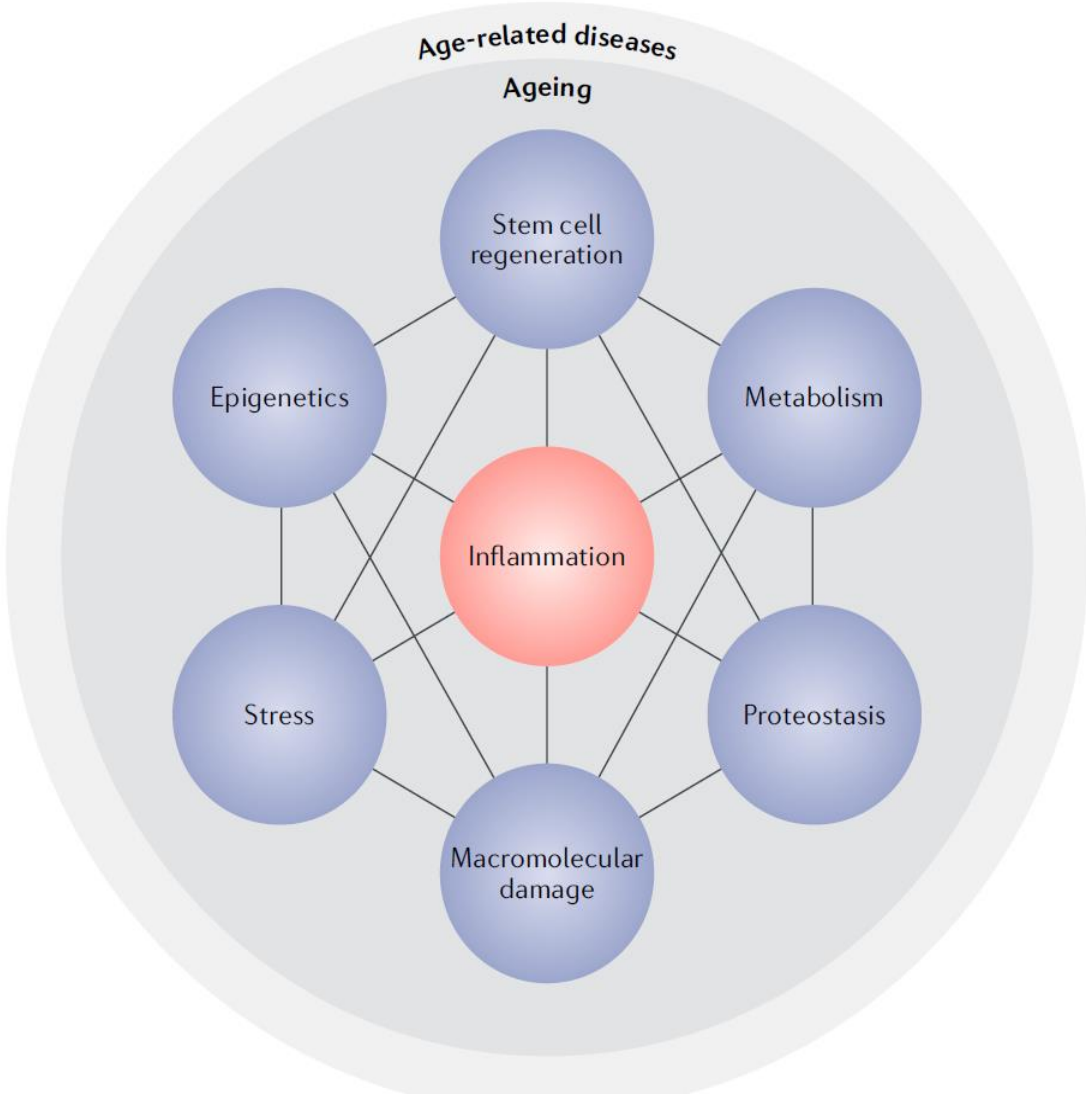
Claudio Franceschi[1,8], Paolo Garagnani[2,3,4,5,8], Paolo Parini[3], Cristina Giuliani[6,7] and Aurelia Santoro[2,7]*

NATURE REVIEWS | ENDOCRINOLOGY
2018 July 25

1201 citations (23/09/2022)

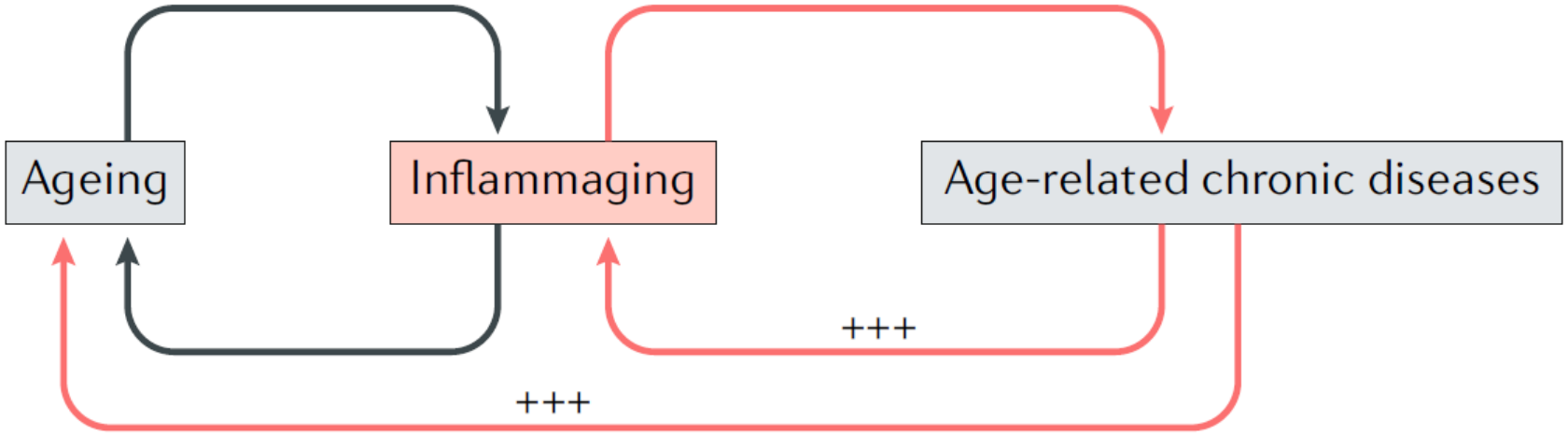
Inflammaging within Geroscience

most molecular dysfunctions converge on inflammation



Franceschi et al.,
Nat Rev Endocrinol, 2018

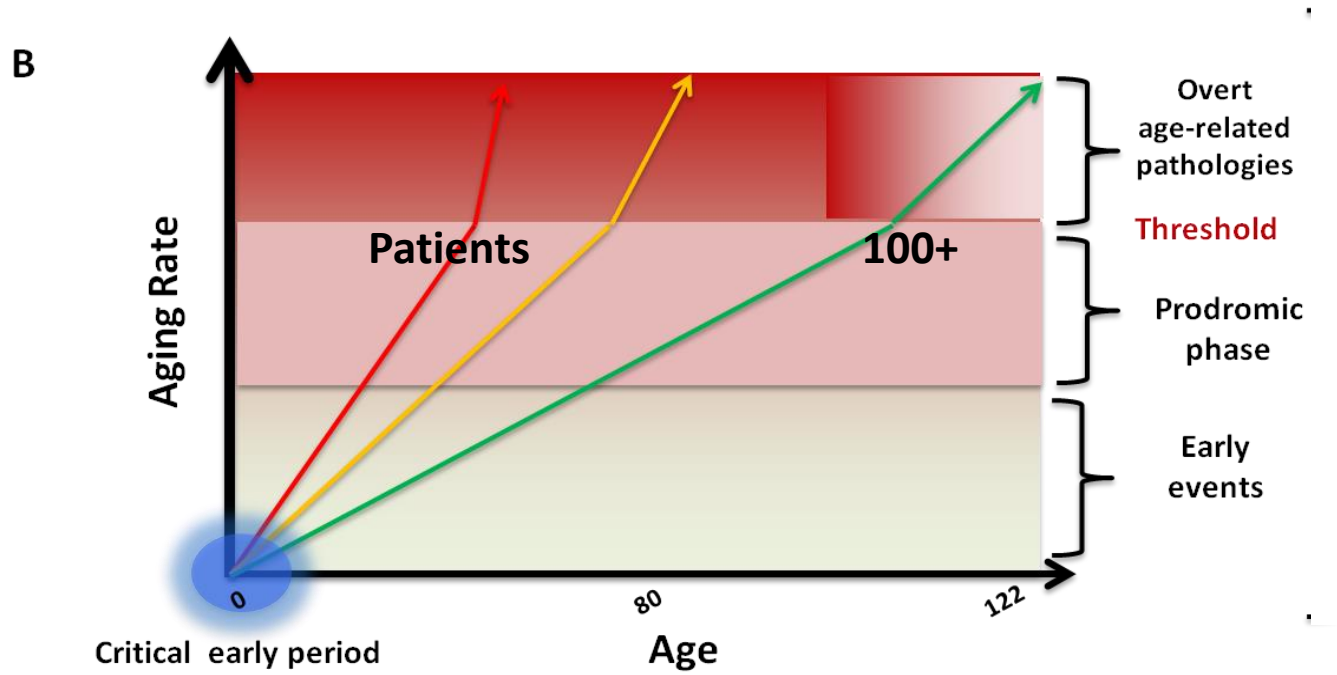
Inflammaging can be a cause and a consequence of ARDs



In turn ARDs accelerate inflammaging and aging

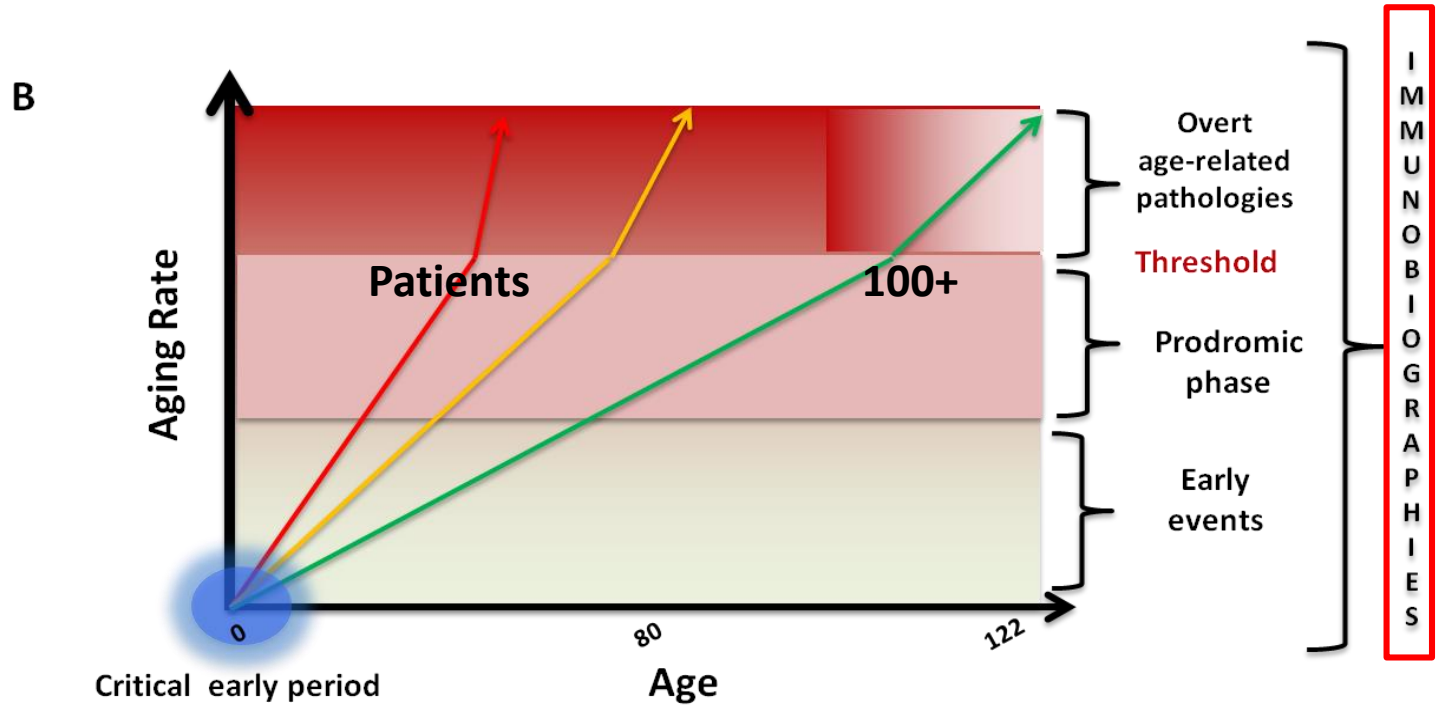
Franceschi et al., Nat Rev Endocrinol, 2018

Se un individuo seguirà una traiettoria di invecchiamento accelerato o decelerato dipenderà dalla sua **genetica** che interagisce continuamente con **fattori ambientali, incluso lo stile di vita**.



Franceschi et al., Nat Rev Endocrinol, 2018

Se un individuo seguirà una traiettoria di invecchiamento accelerato o decelerato dipenderà dalla sua **genetica** che interagisce continuamente con **fattori ambientali, incluso lo stile di vita**.



Franceschi et al., Nat Rev Endocrinol, 2018

frontiers in Immunology

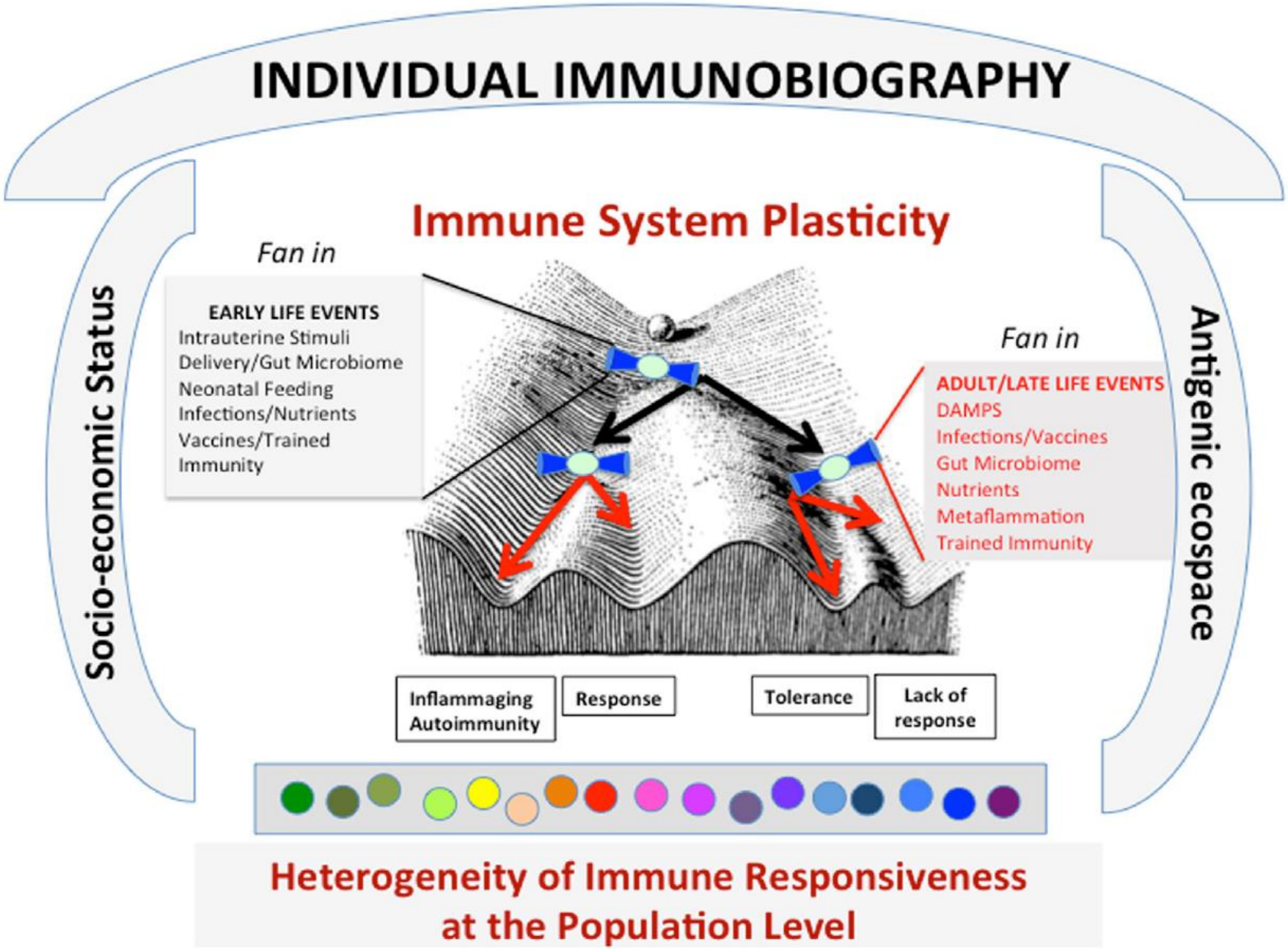
REVIEW
published: 15 August 2017
doi: 10.3389/fimmu.2017.00982

Why
such an increase
of heterogeneity
with age?

Immunobiography and the Heterogeneity of Immune Responses in the Elderly: A Focus on Inflammaging and Trained Immunity

Claudio Franceschi[1†], Stefano Salvioli[2,3†], Paolo Garagnani[2,3], Magda de Eguileor[4], Daniela Monti[5‡] and Miriam Capri[2,3‡]*

Aging/Inflammaging
beyond chronological age



nceschi et al.,
Front Immunol 2017

Mechanisms of Ageing and Development 191 (2020) 111316

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Lack of consensus on an aging biology paradigm? A global survey reveals an agreement to disagree, and the need for an interdisciplinary framework

Alan A. Cohen[a,*], Brian K. Kennedy[b,c,d,e], Ulrich Anglas[f,g], Anne M. Bronikowski[h], Joris Deelen[i,j], Frédérik Dufour[a], Gerardo Ferbeyre[k], Luigi Ferrucci[l], Claudio Franceschi[m,n,o], Daniela Frasca[p], Bertrand Friguet[q], Pierrette Gaudreau[k,r], Vadim N. Gladyshev[s], Efstathios S. Gonos[t], Vera Gorbunova[u], Philipp Gut[v], Mikhail Ivanchenko[w], Véronique Legault[a], Jean-François Lemaître[x], Thomas Liontis[f,g], Guang-Hui Liu[y], Mingxin Liu[a], Andrea B. Maier[z,A], Otávio T. Nóbrega[B,C], Marcel G.M. Olde Rikkert[D], Graham Pawelec[E,F], Sylvie Rheault[G,H], Alistair M. Senior[I,J], Andreas Simm[K], Sonja Soo[f,g], Annika Traa[f,g], Svetlana Ukraintseva[L], Quentin Vanhaelen[M], Jeremy M. Van Raamsdonk[f,N,O], Jacek M. Witkowski[P], Anatoliy I. Yashin[L], Robert Ziman[a], Tamàs Fülöp[Q,R]

"The final impression from the symposium is a **marked disagreement** on the most fundamental questions in the field, and **little consensus** on anything other than the **heterogeneous nature of aging processes"**.

"…the fundamental heterogeneity of **Inflammaging**…"

MAD, 2020

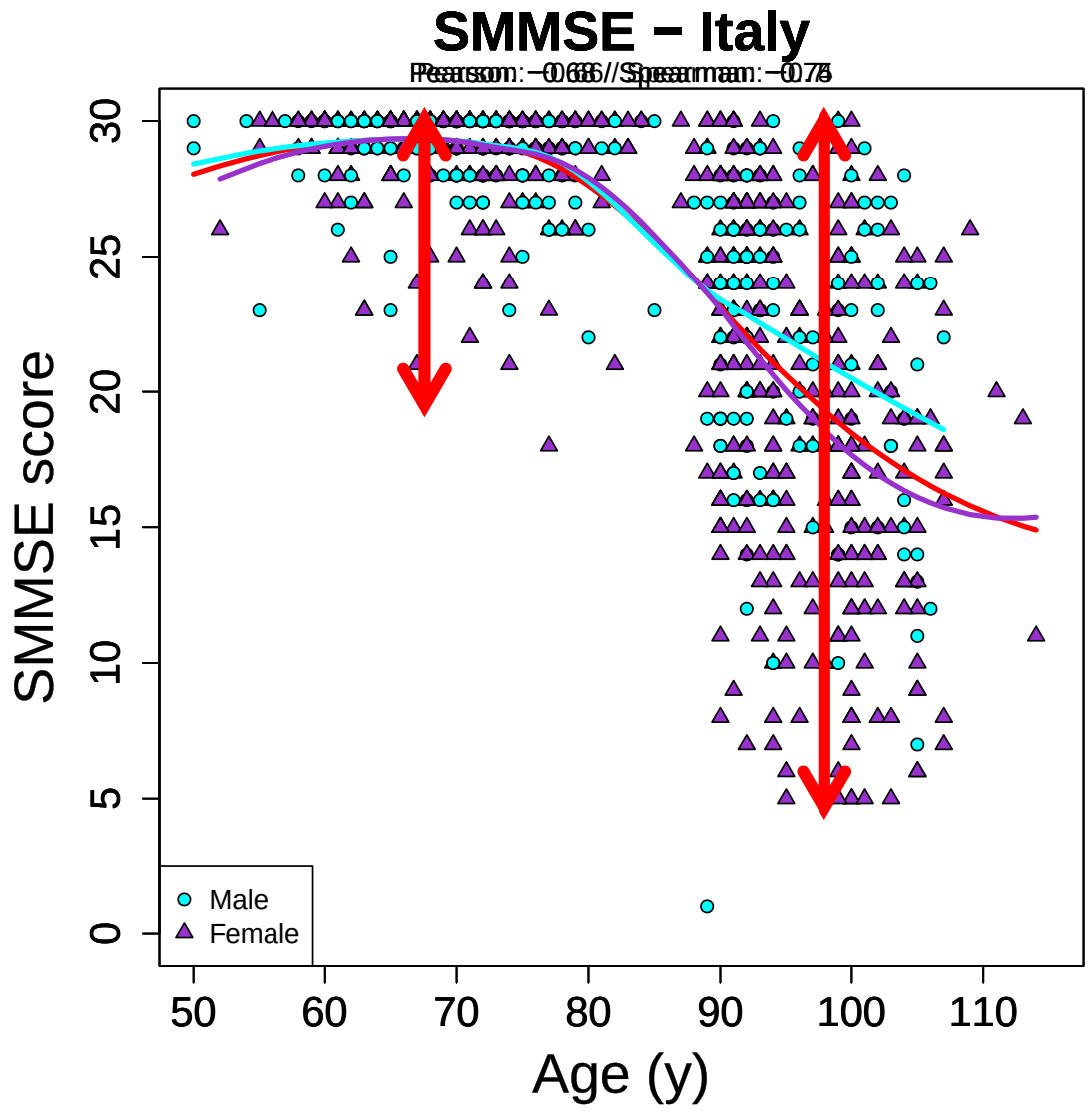
Major Characteristic of AGING:

Increased Heterogeneity & Individual Variability

The urgent need to go beyond chronological age

Standardised Mini-Mental State Examination (SMMSE) in elderly and centenarians

Accumulating heterogeneity with age

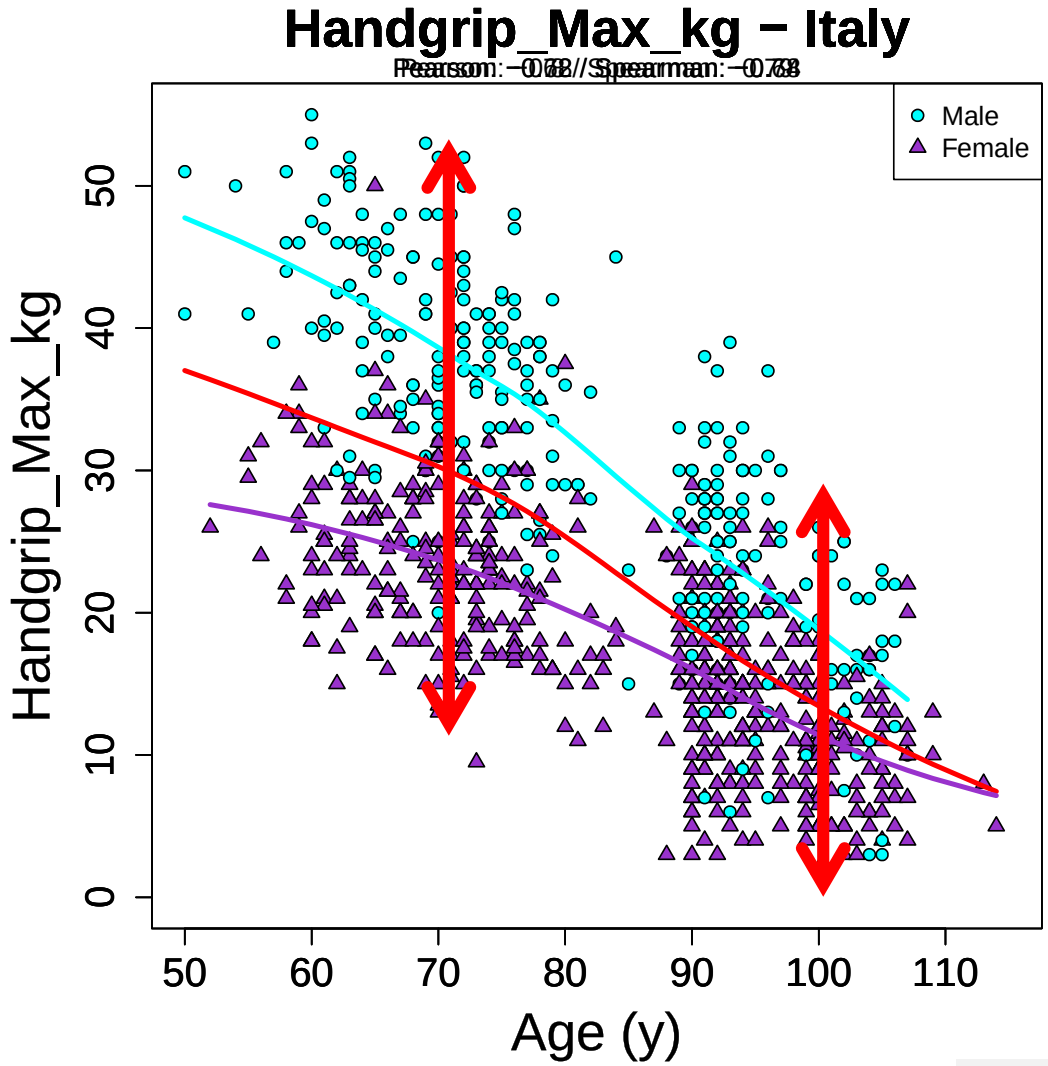


Increased Stochasticity?

Decrease of the Strength Natural Selection?

Handgrip in elderly and centenarians

Accumulating heterogeneity with age

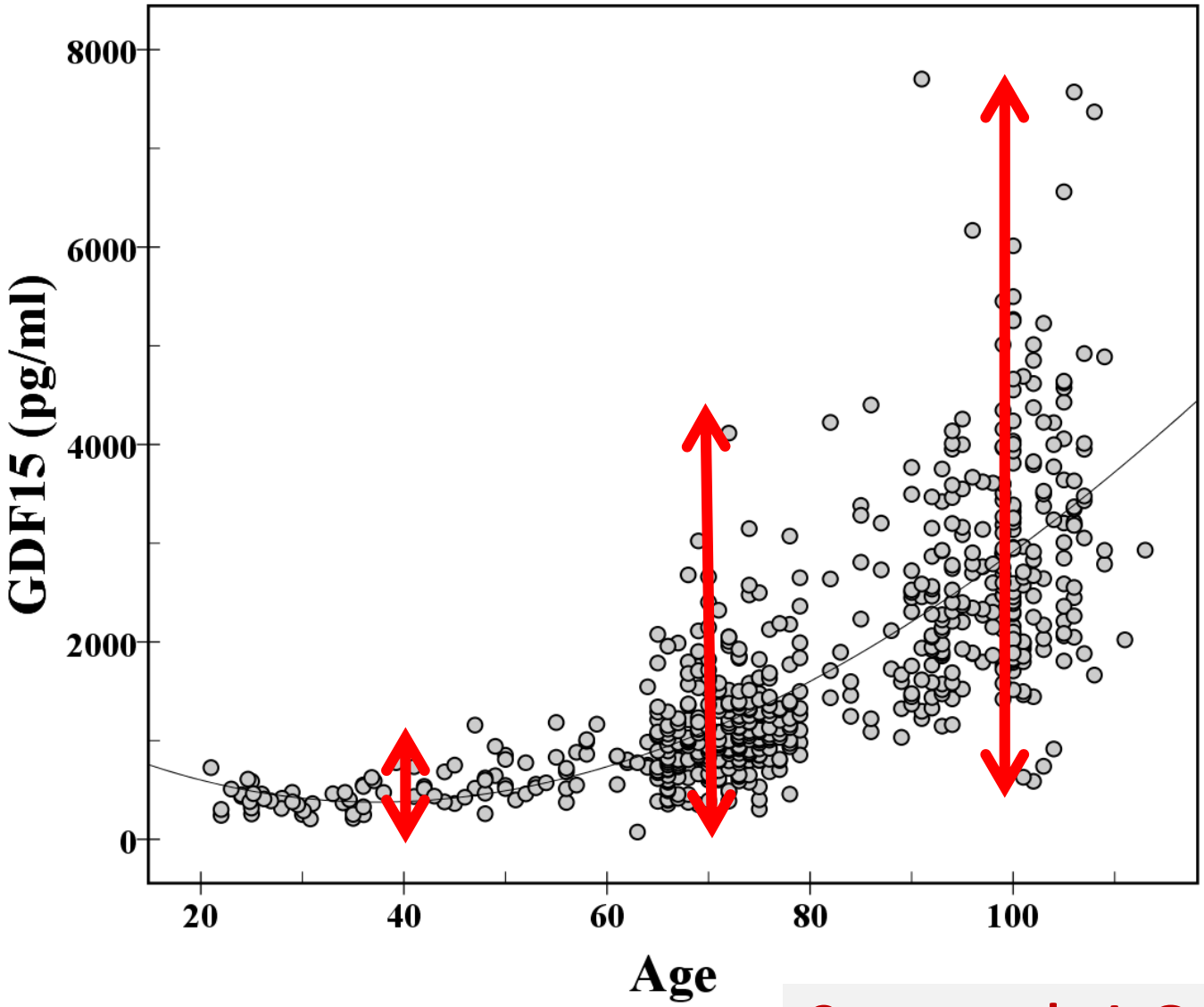


Increased Stochasticity?

Decrease of the Strength Natural Selection?

Bologna 100+ Study

Heterogeneity of GDF15 plasma levels increases with age in 693 healthy subjects of different age (21-113 years)



Conte et al., J. Gerontol 2019

Remodelling → Heterogeneity →
the Continuum between Aging & Diseases

frontiers in Medicine

REVIEW
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Check for updates

The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates

Claudio Franceschi[1], Paolo Garagnani[2,3,4,5], Cristina Morsiani[2], Maria Conte[2], Aurelia Santoro[2,6], Andrea Grignolio[7], Daniela Monti[8], Miriam Capri[2,6†] and Stefano Salvioli[2,6†]*

[1] Institute of Neurological Sciences, University of Bologna, Bellaria Hospital, Bologna, Italy, [2] Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy, [3] Clinical Chemistry, Department of Laboratory Medicine, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden, [4] Applied Biomedical Research Center (CRBA), S. Orsola-Malpighi Polyclinic, Bologna, Italy, [5] CNR Institute of Molecular Genetics, Unit of Bologna, Bologna, Italy, [6] Interdepartmental Center "L. Galvani" (CIG), University of Bologna, Bologna, Italy, [7] Unit and Museum of History of Medicine, Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy, [8] Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy

The continuum ➡ is aging a disease?

L'invecchiamento, le malattie età-correlate (ARDs) e le sindromi geriatriche (GSs) quali Fragilità e Sarcopenia, sono parte di

UN CONTINUUM SENZA LIMITI PRECISI

dove gli estremi sono rappresentati da:

i) i **centenari** (invecchiamento decelerato)

ii) i **pazienti** affetti da ARDs/GSs

Franceschi et al., Front Med 2018

Remodelling → Heterogeneity →
the Continuum between Aging & Diseases

Le malattie età-correlate (ARD)

e le sindromi geriatriche (GS)

possono essere concettualizzate come

manifestazioni di invecchiamento accelerato

The basic heterogeneity of Inflammaging

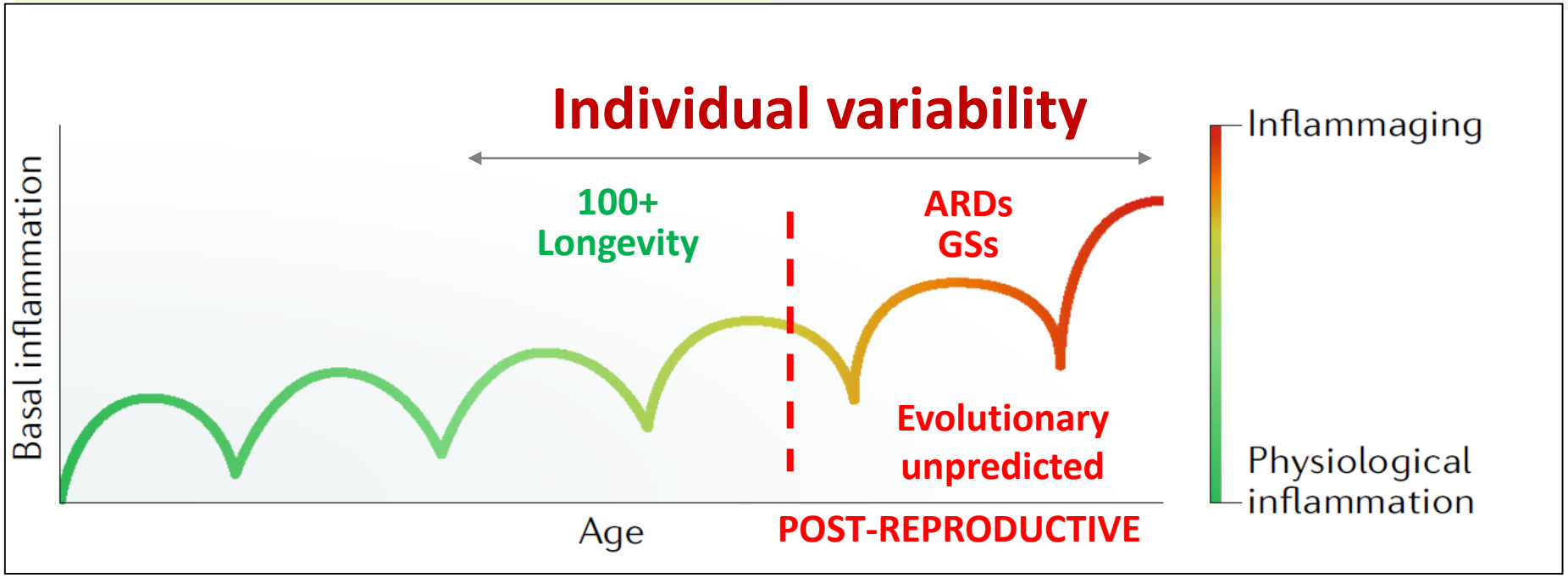
Mild/Adaptive/Beneficial

Strong/Detrimental

Inflammaging fits the Antagonistic Pleiotropy Theory of Aging

Inflammation (acute) is the most important/beneficial, adaptive, evolutionary-conserved response to «damage stimuli», and is crucial for repair/survival

When overstimulated, particularly in the post-reproductive period of life, inflammation can become chronic and detrimental



Franceschi et al., Nat Rev Endocrinol, 2018

INFLAMMAGING:
an example of
adaptation/remodeling
centered on
an ancestral cell type (macrophage)
and immune response (innate immunity)

Available online at www.sciencedirect.com

ScienceDirect

Physics of Life Reviews 38 (2021) 107–110

PHYSICS of LIFE reviews

www.elsevier.com/locate/plrev

Comment

Aging, Inflammaging and Adaptation
Comment on "Dynamic and thermodynamic models of adaptation" by A.N. Gorban et al.

Claudio Franceschi

Department of Applied Mathematics, Mathematics of Future Technologies Center, Laboratory of Systems Medicine of Healthy Aging, Lobachevsky University, Nizhny Novgorod 603950, Russia

Received 8 July 2021; accepted 8 July 2021
Available online 15 July 2021
Communicated by L. Perlovsky

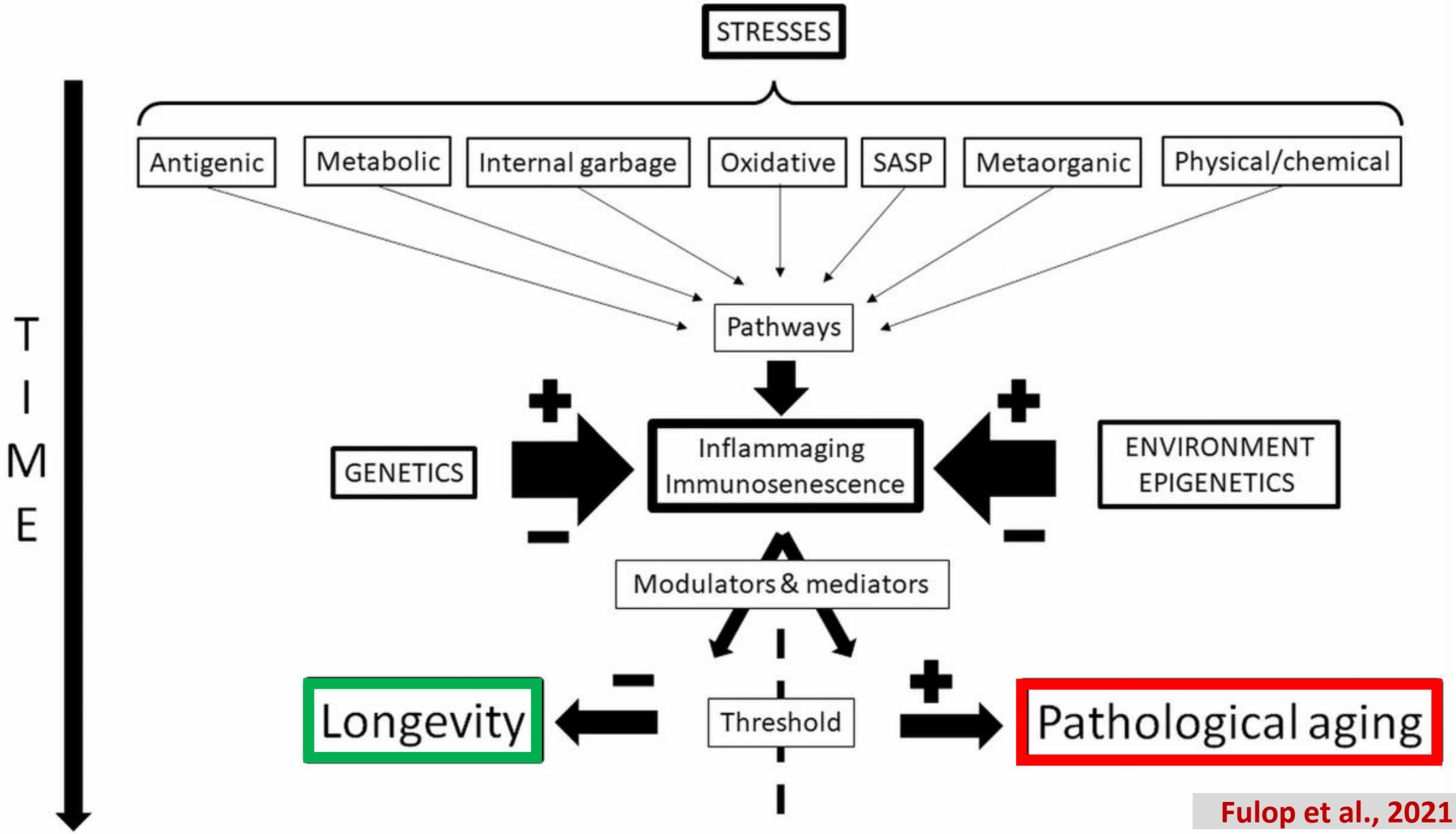
Immunology of Aging: the Birth of Inflammaging

T. Fulop[1] · A. Larbi[2] · G. Pawelec[3,4] · A. Khalil[1] · A. A. Cohen[5] · K. Hirokawa[6] · J. M. Witkowski[7] · C. Franceschi[8,9]

Clin Rev Allergy Immunol. 2021 Sep 18:1-14.

Abstract

The inflammaging concept was introduced in 2000 by Prof. Franceschi. This was an evolutionary or rather a revolutionary conceptualization of the immune changes in response to a lifelong stress. This conceptualization permitted to consider the lifelong proinflammatory process as an adaptation which could eventually lead to either beneficial or detrimental consequences. This dichotomy is influenced by both the genetics and the environment. Depending on which way prevails in an individual, the outcome may be healthy longevity or pathological aging burdened with aging-related diseases. The concept of inflammaging has also revealed the complex, systemic nature of aging. Thus, this conceptualization opens the way to consider age-related processes in their complexity, meaning that not only the process but also all counter-processes should be considered. It has also opened the way to add new concepts to the original one, leading to better understanding of the nature of inflammaging and of aging itself. Finally, it showed the way towards potential multimodal interventions involving a holistic approach to optimize the aging process towards a healthy longevity.



Fulop et al., 2021

Chronic inflammation in the etiology of disease across the life span

David Furman[1,2,3,4*], Judith Campisi[1,5], Eric Verdin[1], Pedro Carrera-Bastos[6], Sasha Targ[4,7], Claudio Franceschi[8,9], Luigi Ferrucci[10], Derek W. Gilroy[11], Alessio Fasano[12], Gary W. Miller[13], Andrew H. Miller[14], Alberto Mantovani[15,16,17], Cornelia M. Weyand[18], Nir Barzilai[19], Jorg J. Goronzy[20], Thomas A. Rando[20,21,22], Rita B. Effros[23], Alejandro Lucia[24,25], Nicole Kleinstreuer[26,27] and George M. Slavich[28]

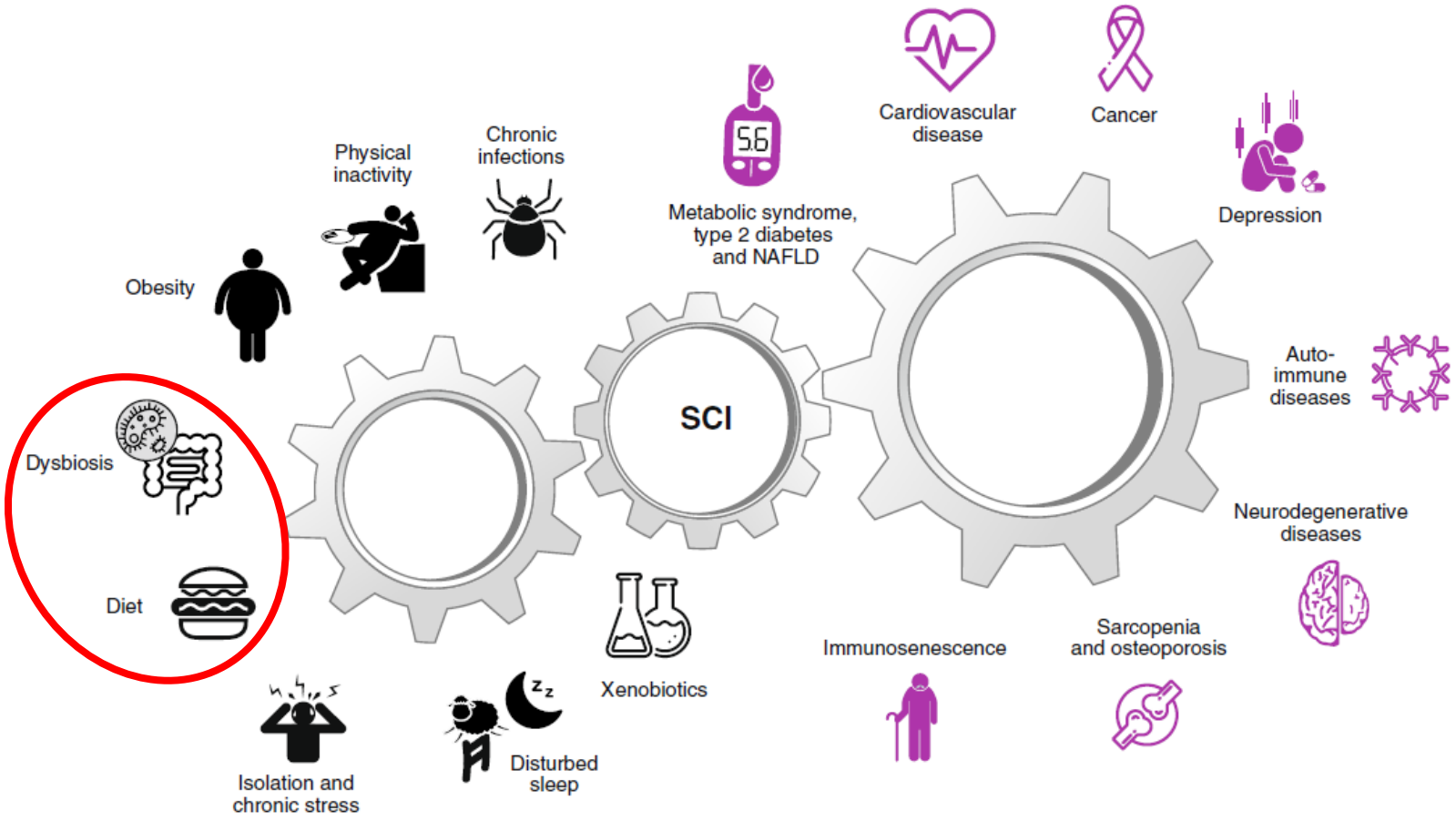
Although intermittent increases in inflammation are critical for survival during physical injury and infection, recent research has revealed that certain social, environmental and lifestyle factors can promote systemic chronic inflammation (SCI) that can, in turn, lead to several diseases that collectively represent the leading causes of disability and mortality worldwide, such as cardiovascular disease, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease and autoimmune and neurodegenerative disorders. In the present Perspective we describe the multi-level mechanisms underlying SCI and several risk factors that promote this health-damaging phenotype, including infections, physical inactivity, poor diet, environmental and industrial toxicants and psychological stress. Furthermore, we suggest potential strategies for advancing the early diagnosis, prevention and treatment of SCI.

NATURE MEDICINE | VOL 25 | DECEMBER 2019 | 1822–1832 |

1383 citations (23/10/2022)

SCI = Systemic Chronic Inflammation/Inflammaging

A variety of causes/triggers & a variety outcomes/multimorbidity

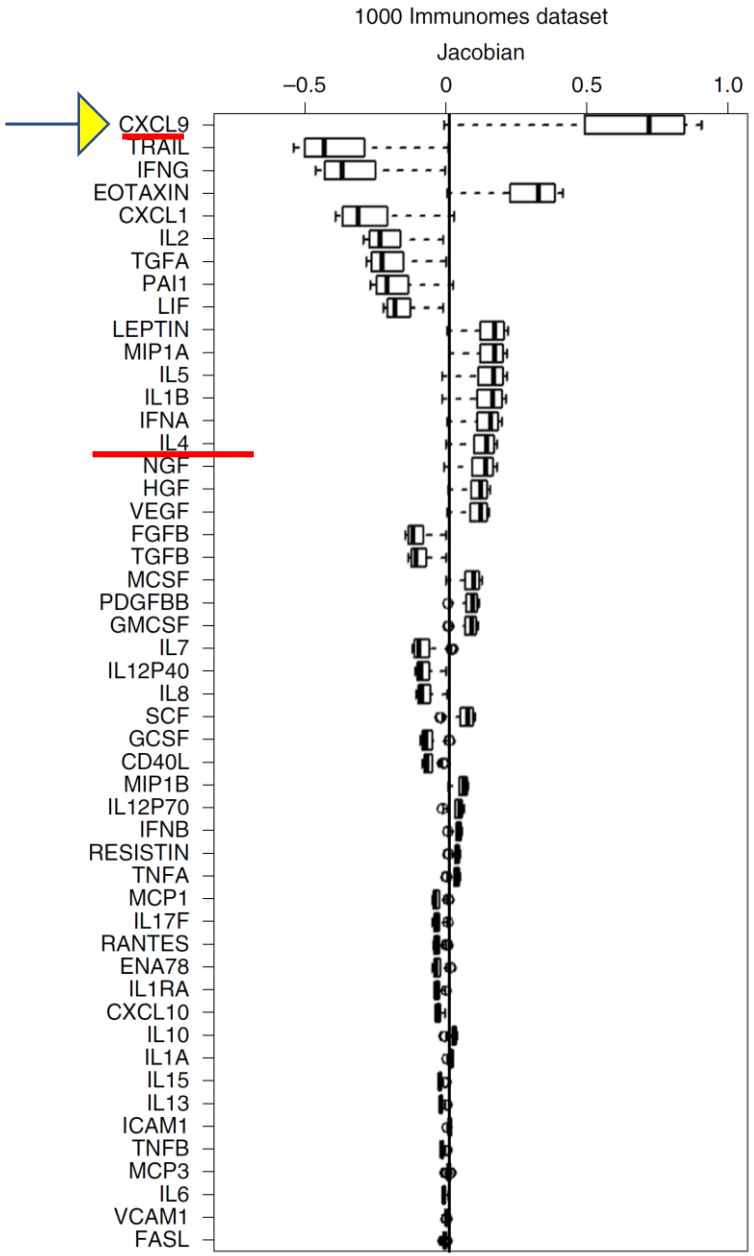


Furman et al., Nature Medicine 2019

ARTICLES
https://doi.org/10.1038/s43587-021-00082-y
nature aging

An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging

Nazish Sayed[1,2,3,24], Yingxiang Huang[4,24], Khiem Nguyen[4], Zuzana Krejciova-Rajaniemi[5], Anissa P. Grawe[4], Tianxiang Gao[6], Robert Tibshirani[7], Trevor Hastie[7], Ayelet Alpert[8], Lu Cui[9], Tatiana Kuznetsova[10], Yael Rosenberg-Hasson[11], Rita Ostan[12], Daniela Monti[13], Benoit Lehallier[14], Shai S. Shen-Orr[8], Holden T. Maecker[11], Cornelia L. Dekker[15,16], Tony Wyss-Coray[14,17], Claudio Franceschi[18], Vladimir Jojic[5,19], François Haddad[2], José G. Montoya[20], Joseph C. Wu[2,21], Mark M. Davis[1,16,22] and David Furman[1,4,5,23] ✉



The top 15 most variable jacobians contributing to **the inflammatory index (iAGE)** are:

1. positive contributors: CXCL9, EOTAXIN, Mip-1α, LEPTIN, IL-1β, IL-5, IFN-α and IL-4;
2. negative contributors TRAIL, IFN-β, CXCL1, IL-2, TGF-α, PAI-1 and LIF.

NATURE AGING | VOL 1 | JULY 2021 | 598–615 |

news & views

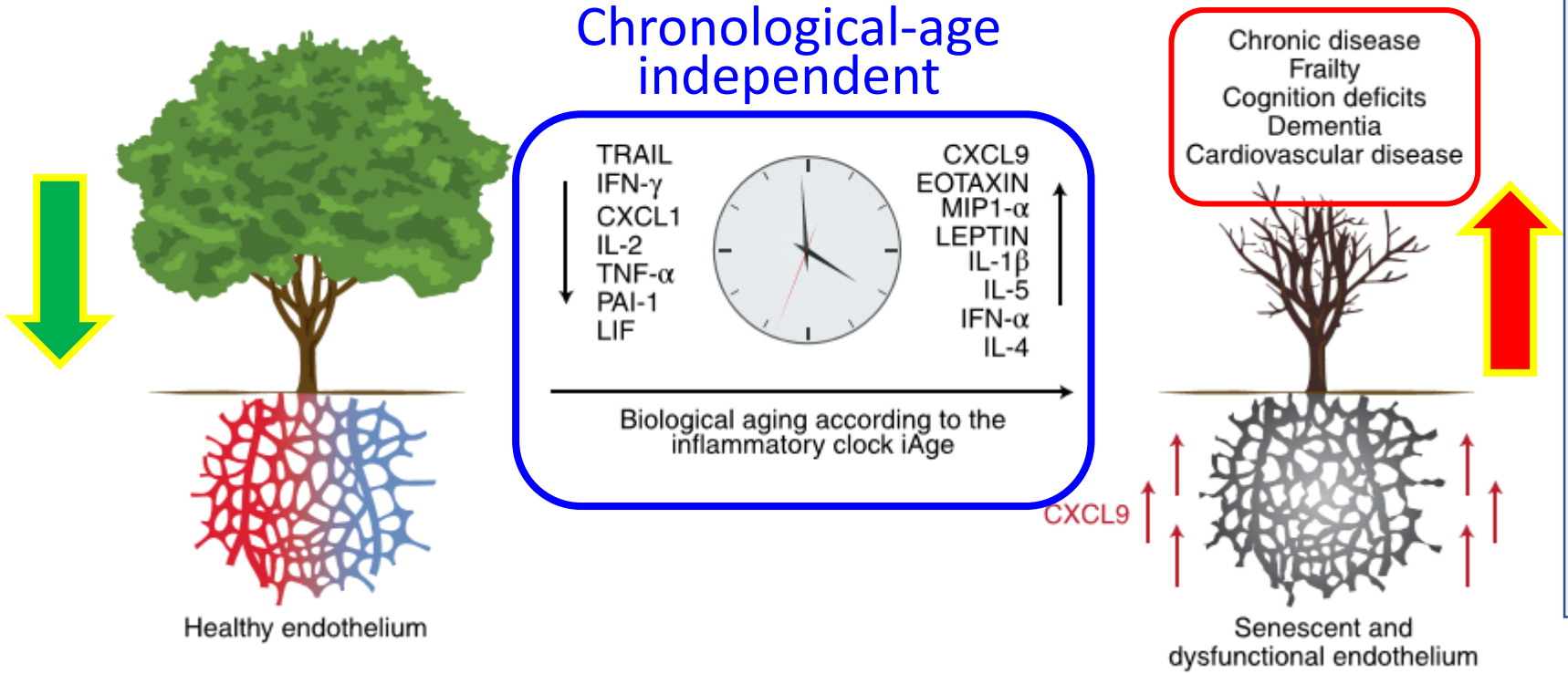
INFLAMMAGING

An inflammatory clock for healthy aging

Inflammation is known to be elevated with progressive age. In this issue, Sayed et al. identify a group of circulating cytokines that correlate with health decline in aging, particularly the chemokine CXCL9. The findings offer a new understanding of how wellbeing and biological resilience are independent from chronological age.

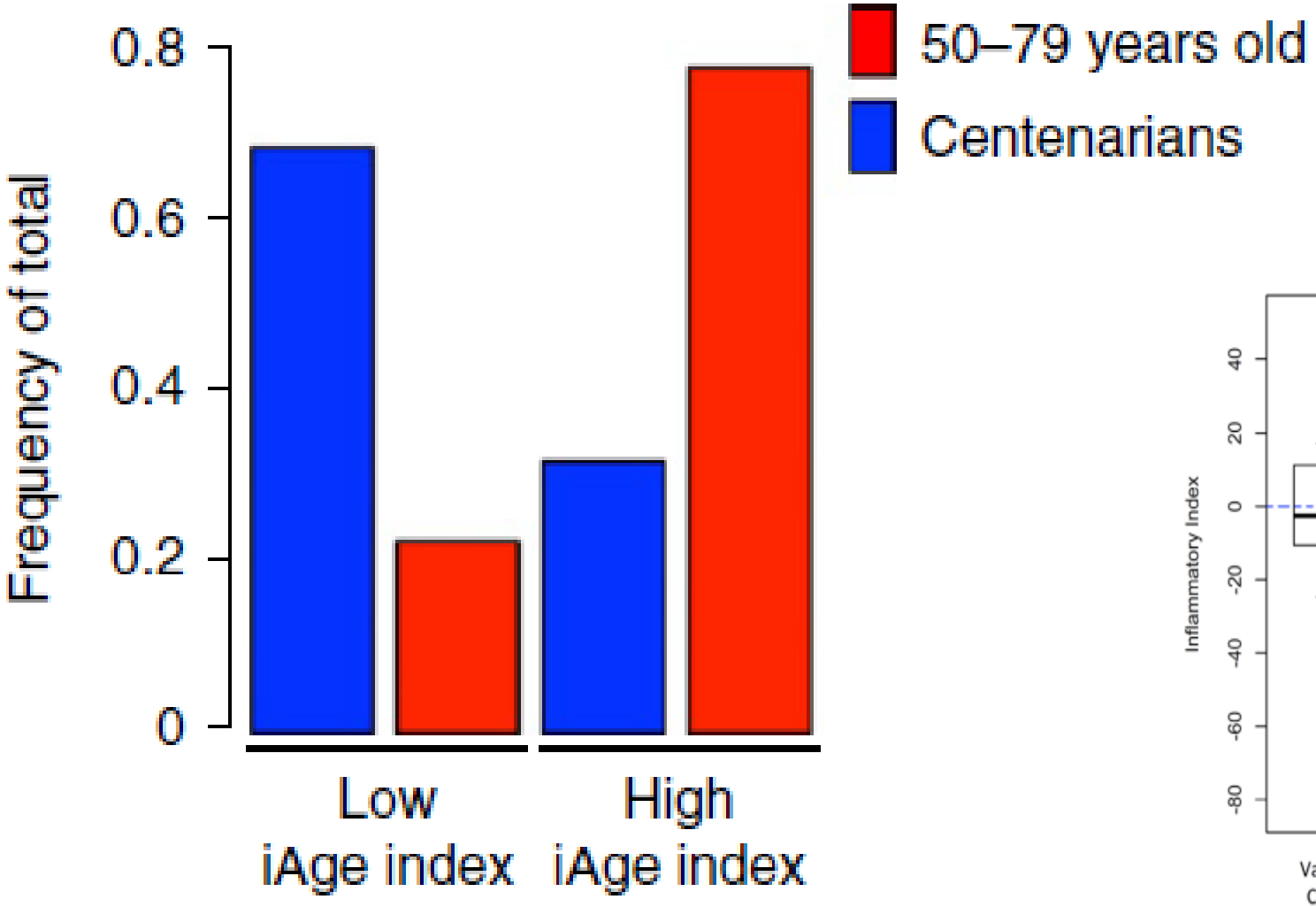
M. Luisa Iruela-Arispe

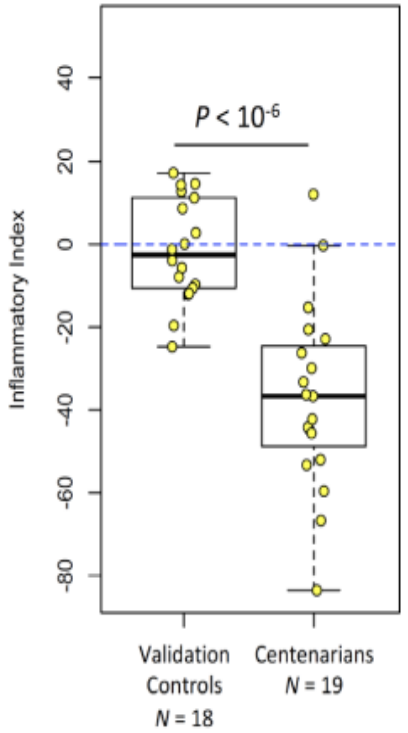
NATURE AGING | VOL 1 | JULY 2021 | 574–575 |



The strongest contributor to iAge was **the chemokine CXCL9** which is involved in cardiac aging, adverse cardiac remodeling and poor vascular function.
iAge is also associated with exceptional longevity in centenarians.

NATURE AGING | VOL 1 | JULY 2021 | 574–575 |



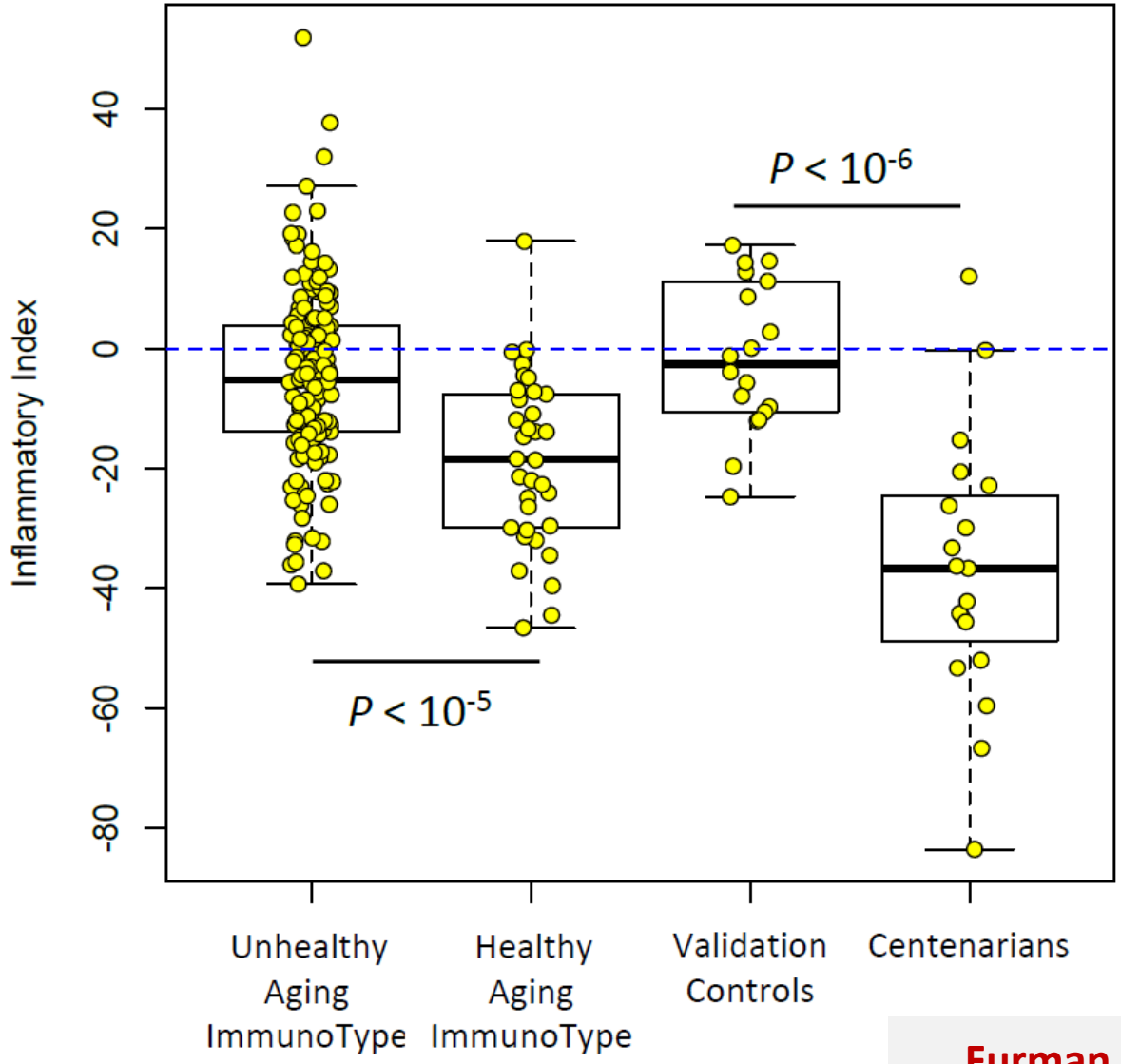


Centenarians have a low inflammatory index

Nature Aging, in press

Inflammatory Index

(inflammatory age minus chronological age)



Furman et al., 2021

Centenarians (100+) in Italy (59.2 mln) an increasing population

Women outnumber men:
at January 1st 2021, 100+ were 17.177
and 83% were women

Semi-supercentenarians (105+) were 1.111

Supercentenarians (110+) were 17 & all women
(the oldest was 112 years old)

Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans

Claudio Franceschi [a,b,c,e,*], Miriam Capri [a], Daniela Monti [d], Sergio Giunta [e], Fabiola Olivieri [e], Federica Sevini [b], Maria Panagiota Panourgia [b], Laura Invidia [a], Laura Celani [b], Maria Scurti [b], Elisa Cevenini [b], Gastone C. Castellani [b,f], Stefano Salvioli [a,b,c]

[a] *Department of Experimental Pathology, University of Bologna, via S. Giacomo 12, 40126 Bologna, Italy*
[b] *Centro Interdipartimentale "L. Galvani", University of Bologna, via S. Giacomo 12, 40126 Bologna, Italy*
[c] *ER-GenTech laboratory, via Saragat 1, 44100 Ferrara, Italy*
[d] *Department of Experimental Pathology and Oncology, University of Florence, Viale Morgagni 50, 50134 Florence, Italy*
[e] *I.N.R.C.A., Department of Gerontological Sciences, via Birarelli 8, 60121 Ancona, Italy*
[f] *DIMORFIPA, University of Bologna, Via Tolara di Sopra 50, 40064 Ozzano dell'Emilia, Italy*

Mechanisms of Ageing and Development 128 (2007) 92–105

Centenarians are inflamed but the data suggest that the increase of pro-inflammatory molecules is accompanied by a corresponding adaptive increase of anti-inflammatory molecules

2017 citations (24/09/2022)

Fulvia, 109 years

We surmised
that a possible main reason why
most 100+ succeed in attaining
100 years is because they
continuously reach
AN OPTIMAL BALANCE
between
pro- (CRP, IL-6, TNFα)
& anti-(TGFβ, Cortisol, IL-1RA,
Adiponectin)
Inflammatory molecules

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pro- (CRP, IL-6, TNFα)
& anti-(TGFβ, Cortisol, IL-1RA, Adiponectin)
Inflammatory molecules

But...

?

At present, we have only circumstantial evidence that **inflammaging is** different, and likely **milder and more adaptive in women**, but a lot of research is needed to clarify the underpinning basic molecular mechanisms (**gut microbiome** ?...)

MAJOR INFLAMMATORY STIMULI

Non Self

- Virus, Bacteria, Parasites and their products
- Pollutants

Quasi Self

- Nutrients & Gut Microbiota and their products

Self

- SELF Cell debris , RAGEs
- SELF Misplaced/Misfolded/Modified Proteins
- SELF Misplaced Nucleic Acids

Genetics of Human Longevity Within an Eco-Evolutionary Nature-Nurture Framework

Cristina Giuliani, Paolo Garagnani, Claudio Franceschi

Circulation Research 2018;123:745-772.

September 14, 2018

Longevity = G x E lifelong

G = 3 = Nuclear and Mitochondrial genomes + Microbiomes

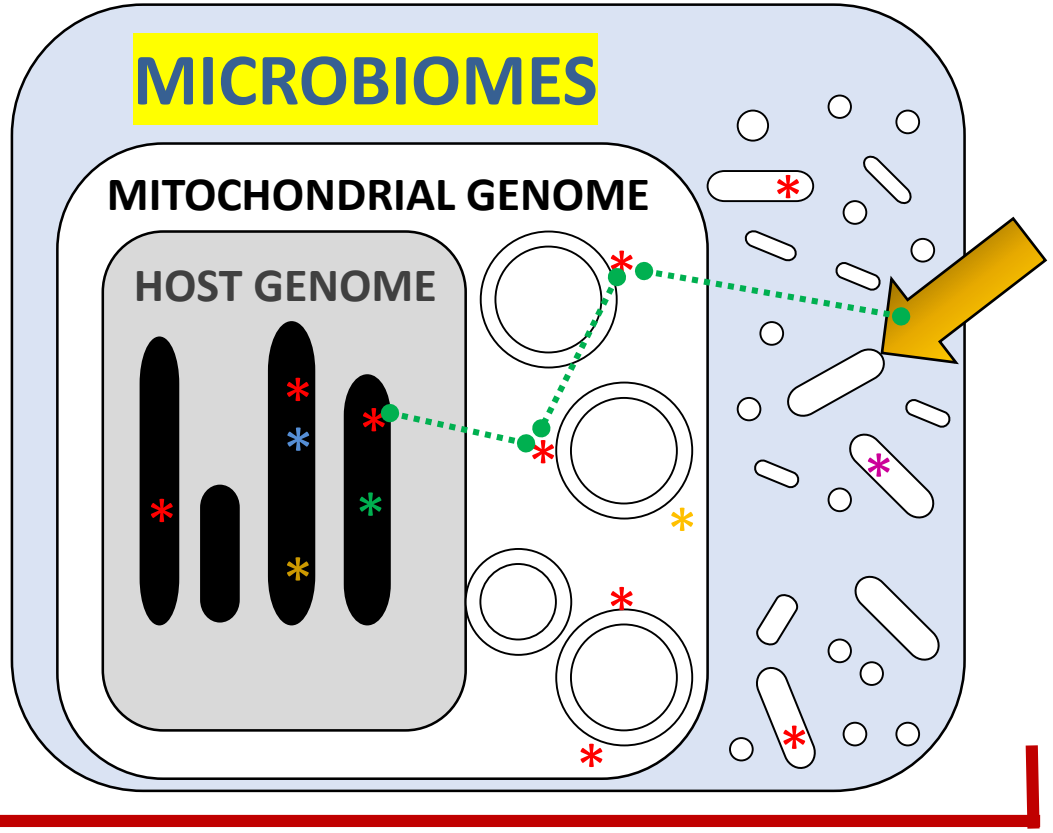
The capability to reach the extreme decades of human lifespan seems to be the result of an intriguing mixture of gene-environment interactions. Accordingly, the genetics of human longevity is here described as a highly context-dependent phenomenon, within a new integrated, ecological, and evolutionary perspective, and is presented as a dynamic process, both historically and individually. The available literature has been scrutinized within this perspective, paying particular attention to factors (sex, individual biography, family, population ancestry, social structure, economic status, and education, among others) that have been relatively neglected.

Circ Res. 2018;123:745-772.

Holobiont and metaorganism are terms coined within the framework of ecology, evolution and zoology

H. sapiens as HOLOBIONT/METAORGANISM

EVOLUTIONARY SETTLED INTERACTIONS



The 3 genomes of *Homo sapiens*

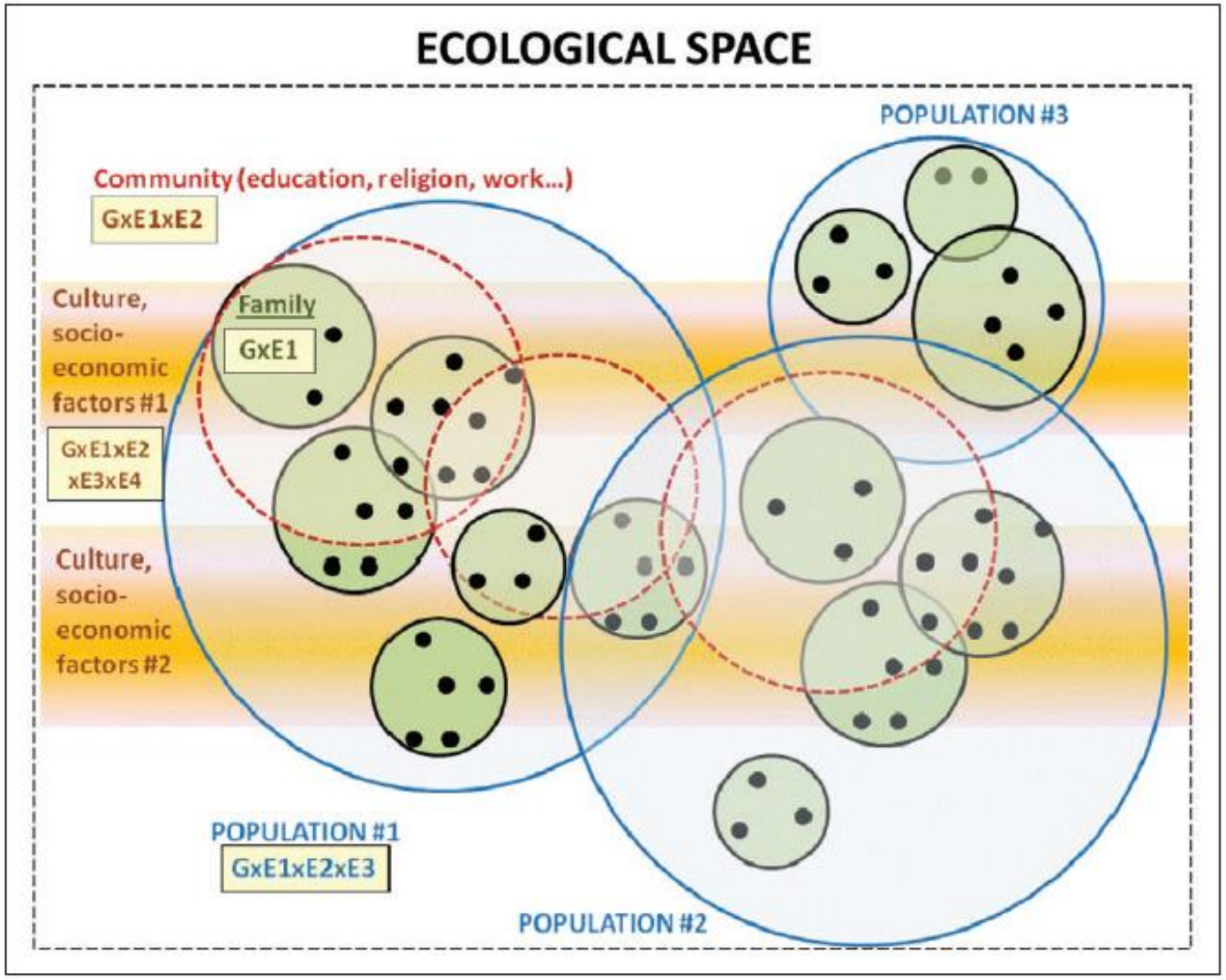
GM is 100x larger than the human genome and **MODIFIABLE** by Diet, Lifestyle Drugs… and environment-dependent

The genetics of longevity depends on the interaction among the **3 genomes** of *H. sapiens* as a metaorganism, interacting **lifelong** with the environment

Giuliani, Garagnani & Franceschi, Circulation Res, 2018

Any change of the
gut microbiome (GM) composition
can be assumed as a
“genetic” change
(the number of genes of GM is about 100 times that of *H. sapiens* genome)

The complexity of GxE interactions in humans



Human longevity is highly context- & population-dependent

Giuliani, Garagnani & Franceschi, *Circulation Res*, 2018

THE GUT MICROBIOTA CONTRIBUTES TO INFLAMMAGING

OPEN ACCESS Freely available online

PLoS one

Through Ageing, and Beyond: Gut Microbiota and Inflammatory Status in Seniors and Centenarians

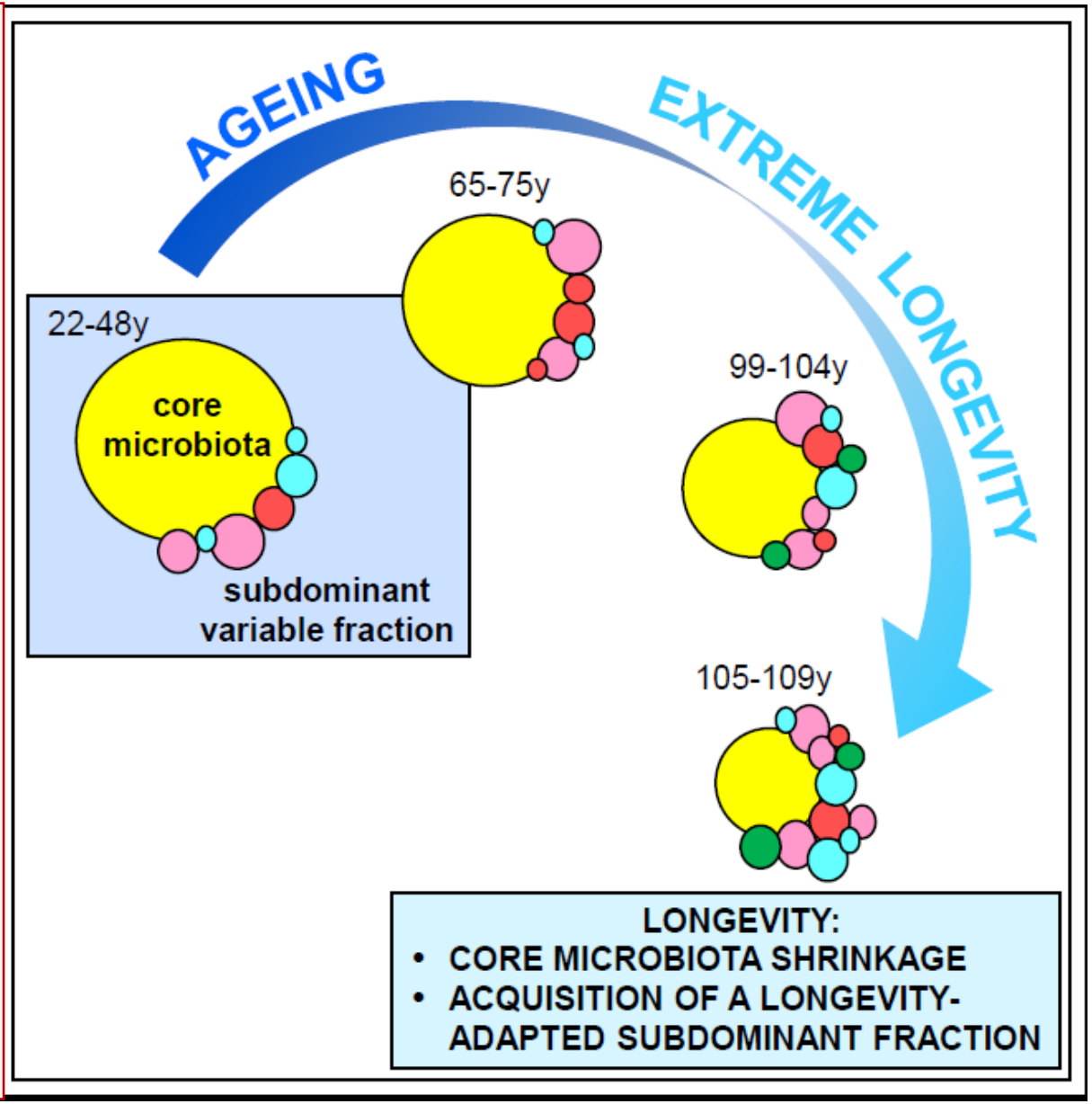
Elena Biagi[1]*, Lotta Nylund[2,3], Marco Candela[1], Rita Ostan[4], Laura Bucci[4], Elisa Pini[4], Janne Nikkïla[3], Daniela Monti[5], Reetta Satokari[2], Claudio Franceschi[4], Patrizia Brigidi[1], Willem De Vos[3,6]

PLoS ONE |May 2010 | Volume 5 | Issue 5 | e10667

- Abbiamo ricostruito **la più lunga traiettoria del microbiota intestinale oggi disponibile,** analizzando le **feci di persone da 20 fino a 110 anni.**
- **9% della variabilita' del GM e' correlata ai livelli di citochine infiammatorie**

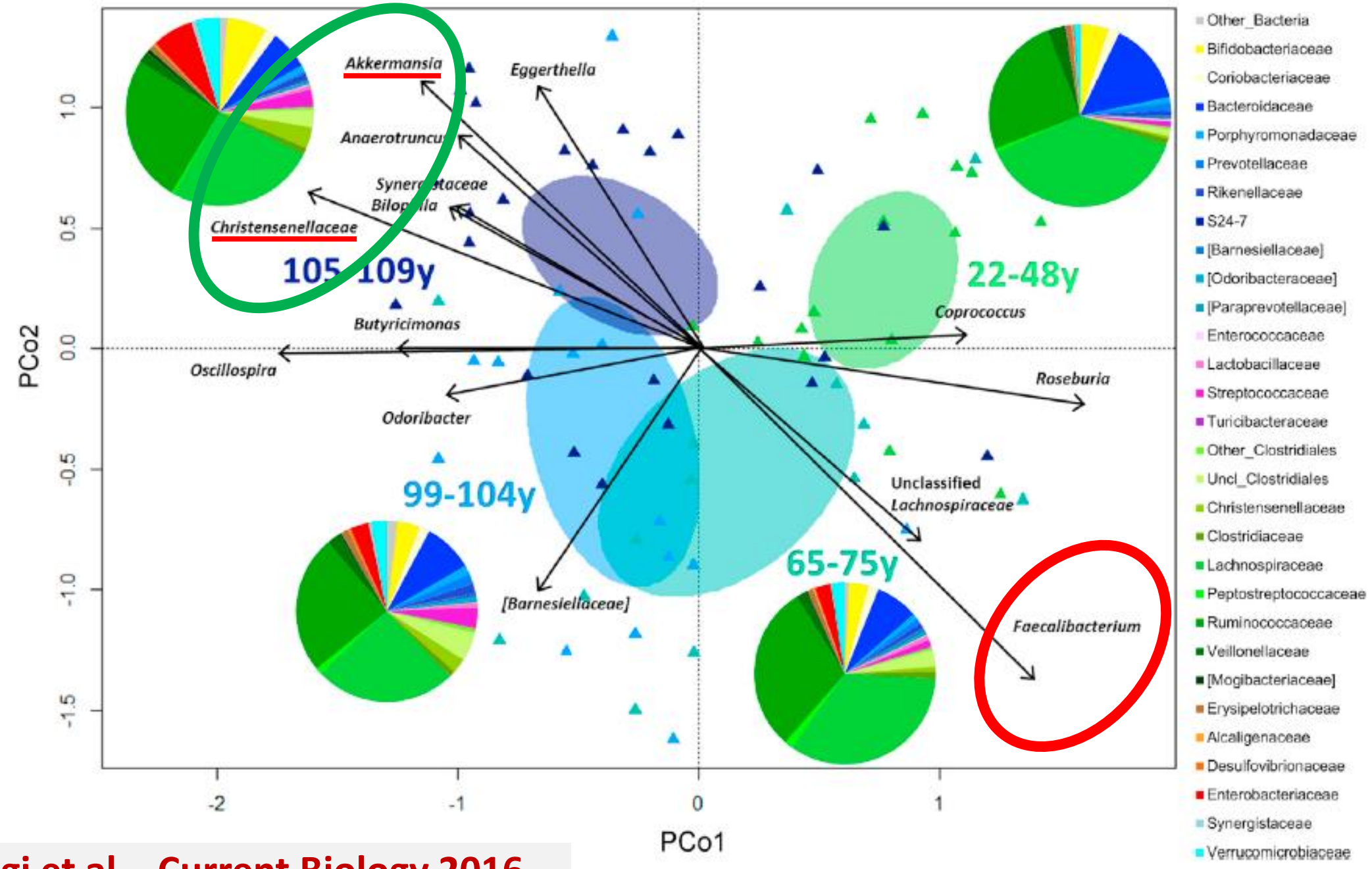
1383 citations (24/09/2022)

Adaptive, balanced pro- & anti-inflammatory remodeling of GM with age from 22 to 109 years



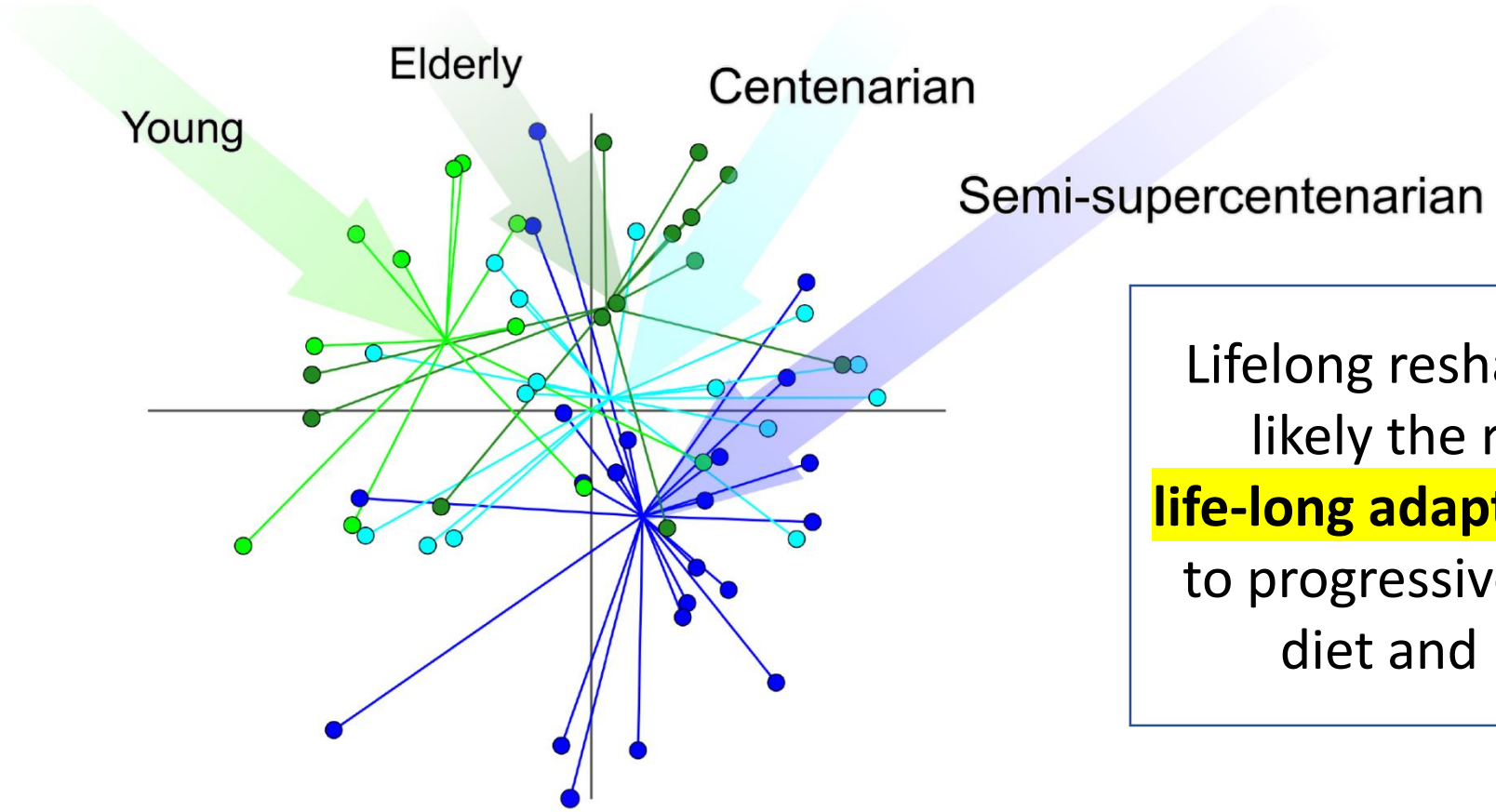
551 citations (24/09/2022)

Biagi et al., *Curr Biol* 2016



Biagi et al., Current Biology 2016

Shotgun metagenomics of the fecal microbiome of 62 individuals of different ages



Lifelong reshaping of GM likely the result of a **life-long adaptive response** to progressive changes in diet and lifestyle.

Rampelli et al., mSystems 2020

Unexpected INCREASE of GM DIVERSITY in Italian, Chinese and Japanese centenarians

Diversity	GM diversity in Centenarians according to:			
	Biagi et al., 2016	Wang et al., 2015	Kong et al., 2016	Odamaki et al., 2016
Simpson reciprocal index of diversity	↑			
Alpha diversity (Chao index)	↑	↑	↑	↑
Shannon index	↑	=	↑	↑

In chronic age-associated diseases the GM diversity decreases

Santoro *et al.*, 2017

Si può contrastare Inflammaging?

Can we modulate the Gut Microbiota by diet in the elderly?

Human intervention study

NU-AGE ⊣ **MedDiet**

inflammaging

«New dietary strategies addressing the specific needs of the elderly population for healthy aging in Europe»

Coordinator: **Prof. Claudio Franceschi,** University of Bologna

Start-End: **May 2011- April 2016**

Funded with 9 million €

BASIC HYPOTHESIS & RATIONALE

An *ad hoc* fortified MedDiet will decrease INFLAMMAGING

N. 1294 NON frail and **PRE-FRAIL** (Fried) **volunteers aged 65-79 years**

from Italy, France, The Netherland, UK and Poland

29 papers published between 2014-2022

EU-wide diet intervention

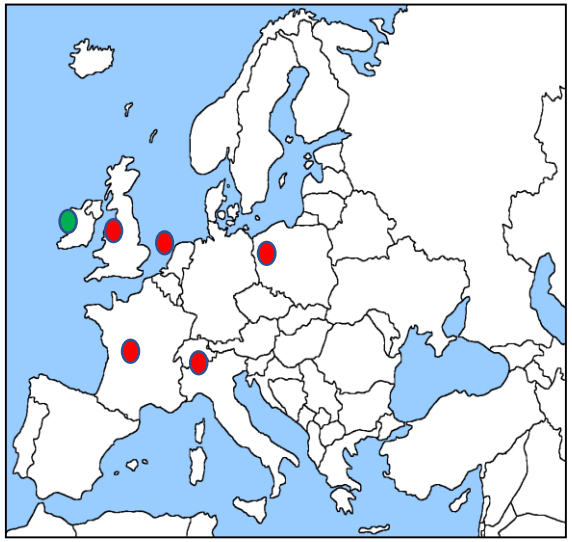
- 1. Alma Mater Studiorum Università di Bologna Research institution
- 2. University of East Anglia Research institution
- 3. Wageningen Universiteit Research institution
- 4. Institut National de la Recherche Agronomique Research institution
- 5. Spread European Safety Geie Stakeholder
- 6. University College Cork, Nat. Univ. of Ireland, Cork Research institution
- 7. Institute of Food Research Research institution
- 8. Szkola Glowna Gospodarstwa Wiejskiego Research institution
- 9. Confederation des Industries Agro-Alimentaires de L'UE Stakeholder
- 10. European Food Information Council Aisbl Stakeholder
- 11. Maa Ja Elintarviketalouden Tutkimuskeskus Research institution
- 12. Ethniko Idryma Erevnon Research institution
- 13. Straticell Screening Technologies SME
- 14. The University of Reading Research institution
- 15. Karolinska Institutet Research institution
- 16. Valio Enterprise
- 17. Orebro University Research institution
- 18. Lesieur Enterprise
- 19. Villani S.p.A. Enterprise
- 20. Pancrazio S.p.A. SME
- 21. Newsol SME
- 22. Wiesbauer Gourmet Gastro Gmbh Enterprise
- 23. Kanizsa Pékség Zrt. SME
- 24. VIDRERES LLET, S.L. Enterprise
- 25. Zeelandia Enterprise
- 26. MEVGAL Enterprise
- 27. Yoruk Sut Urunleri Hayvancılık Gıda San. Ve Tic. Ltd. Şti. SME
- 28. Kraft Foods R&D Inc., Zweigniederlassung München Enterprise
- 29. NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOE Research institution
- 30. CRNH Auvergne Research institution
- 31. Nestec Enterprise

NU-AGE

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

Coordinator: Prof. Claudio Franceschi

UK, NL, FR, IT, PL



Scientific Manager: Dr. Aurelia Santoro

n = 570 controls

n = 571 MedDiet

12 months

NU-AGE Randomized Volunteers (N. 1294; age range 65-79 years)

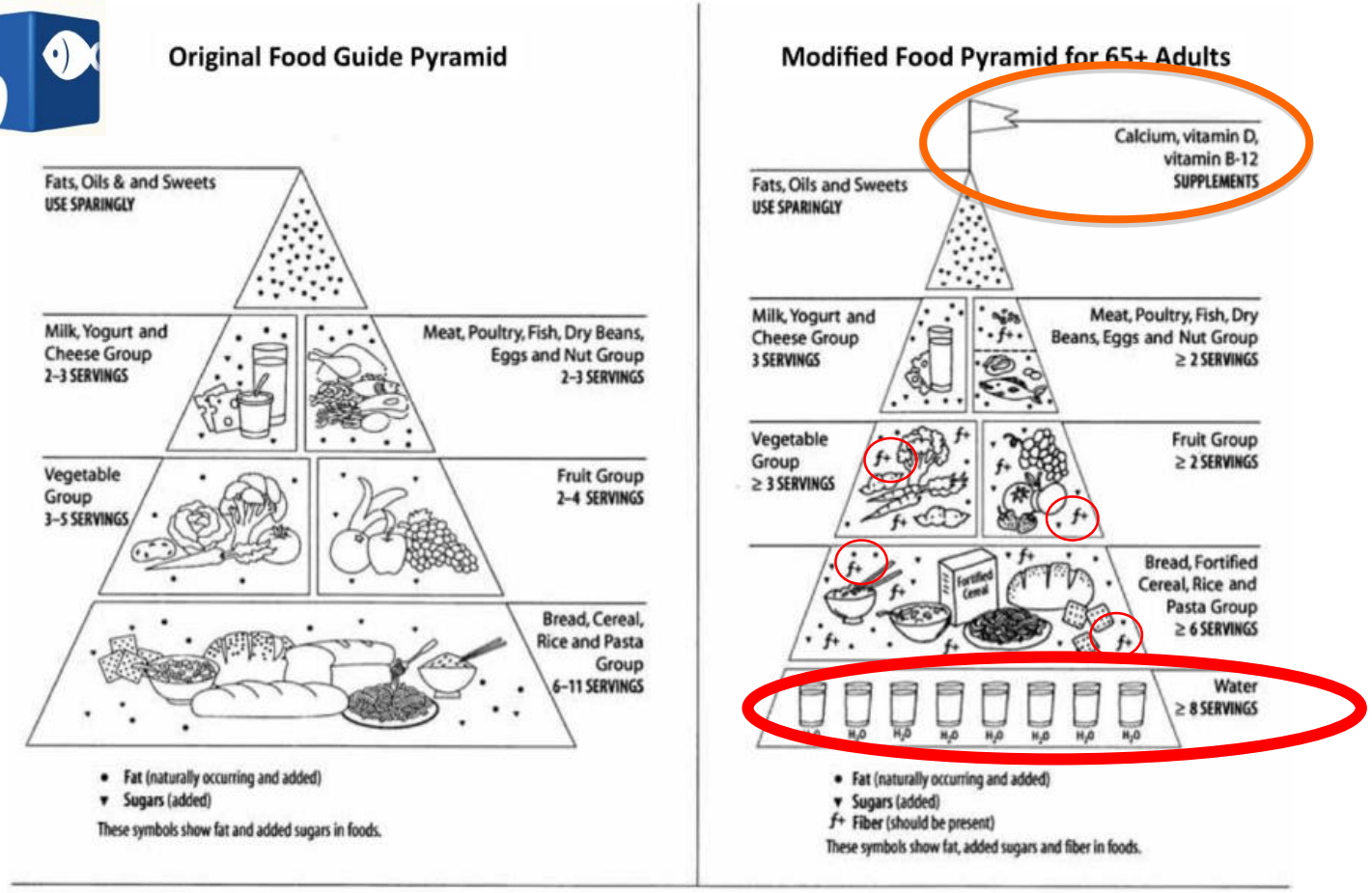
	Netherlands (%)	UK (%)	Italy (%)	France (%)	Poland (%)	Total (%)
Pre-frail	23	21	22	13	30	22
Men	44	36	49	50	43	44
65-72y	64	74	54	71	58	64

Criteria for Frailty Phenotype (Fried et al., 2001):

- Unintentional weight loss (4.5kg in past year)
- Self-reported exhaustion
- Weakness (grip strength)
- Slow walking speed
- Low physical activity

Non-frail: absence of the 5 criteria
Pre-frail: presence of 1 or 2 criteria

NU-AGE MEDITERRANEAN DIETARY INTERVENTION

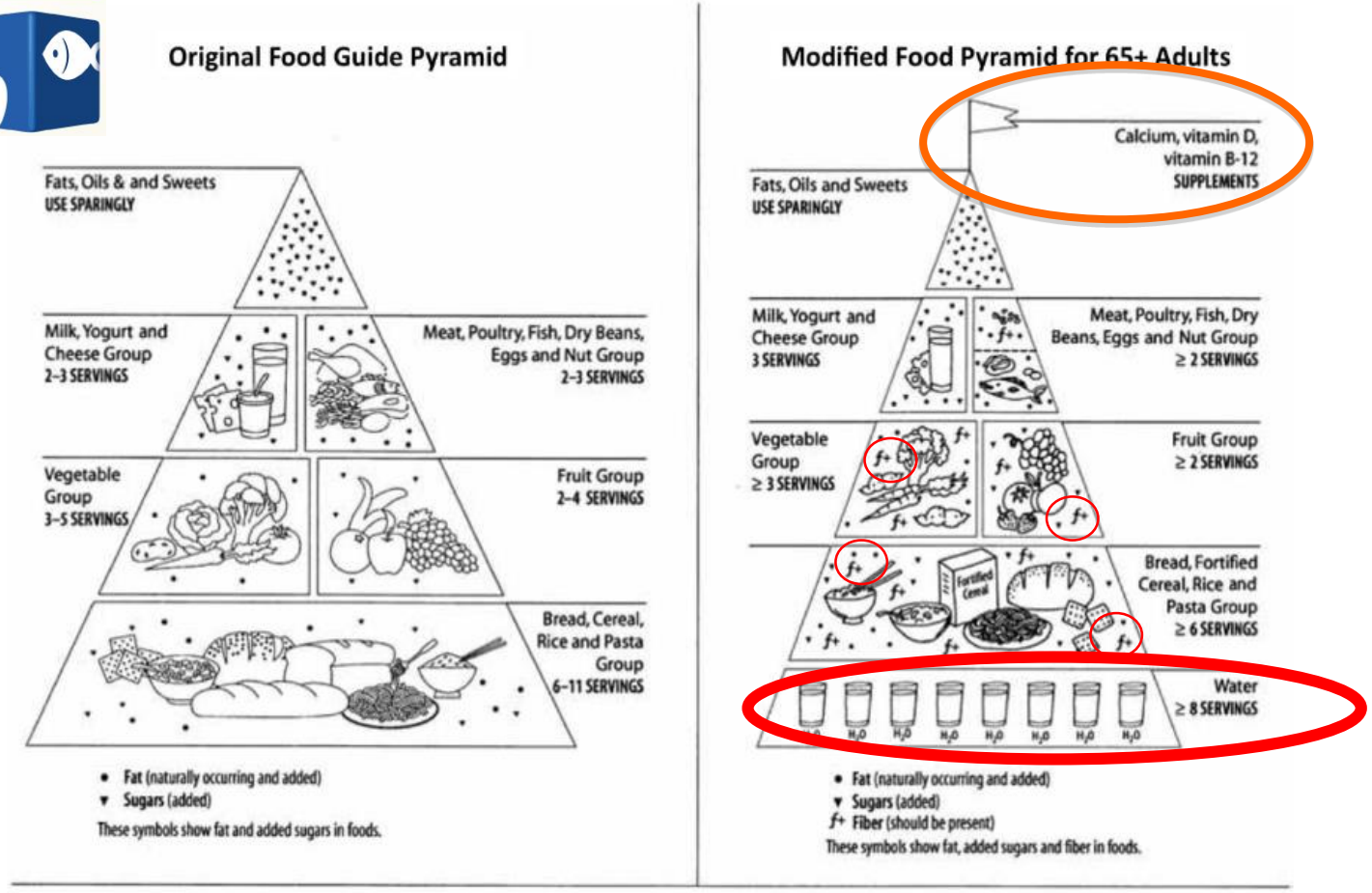


The dietary advice is aiming to meet
the **NU-AGE quantitative requirements*** by means of the
NU-AGE Food Based Dietary Guidelines* (NU-AGE FBDGs)

1383 citations (24/09/2022) *RDA's*

Berendsen et al., MAD 2014

NU-AGE MEDITERRANEAN DIETARY INTERVENTION



Water is at the basis of MedDiet as an essential component

The dietary advice is aiming to meet
the **NU-AGE quantitative requirements*** by means of the
NU-AGE Food Based Dietary Guidelines* (NU-AGE FBDGs)
RDA's

1383 citations (24/09/2022)

Berendsen et al., MAD 2014

DATABASE

QUESTIONNAIRES DATA

+

ANALYSES ON BLOOD & URINE:

- Admission 1
- Admission 2
- General T0/T1 (+ medicines)
- Interview T0/T1
- Blood, Urines & Faeces T0/T1
- Supplement T0/T1
- Energy Expenditure T0/T1
- Follow-up M4/M8/M12 (+ medicines)
- Vitamin D
- DXA (body composition)
- Nutrients data
- Food Groups

~ 2040 variables

Blood & Faeces

OMICS

- Metabolomics T0/T1
- Metagenomics T0/T1
- Genetics T0
- Epigenetics T0/T1
- Transcriptomics T0/T1

~ 2500 variables

For a TOTAL of
~ 4500 variables

➡ **To unraveal the molecular and cellular pathways responsible for the beneficial effects of a Med Diet pattern**

Mediterranean Diet and Inflammaging in the elderly
The European project NU-AGE

Edited by Aurelia Santoro, Patrizia Brigidi, Efstathios S. Gonos, Vilhelm A. Bohr, Claudio Franceschi

Volumes 136–137, Pages 1-162 (March–April 2014)

Mechanisms of Ageing and Development 136-137 (2014) 50–58

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Water-loss dehydration and aging☆

Lee Hooper*, Diane Bunn, Florence O. Jimoh, Susan J. Fairweather-Tait

Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich NR4 7TJ, Norfolk, UK

Highlights

- **Twenty to 30% of older people have water-loss dehydration**.
- **Dehydration is associated with increased mortality, morbidity and disability**.
- **Vulnerability to dehydration is associated with aging.**
- Relationships between fluid intake and hydration status is examined.
- Drinking and dietary patterns associated with good hydration are described

Risk of dehydration in old people

In older adults, lower muscle mass, reduced kidney function, physical and cognitive disabilities, blunted thirst, and polypharmacy all increase dehydration risk.

Strategies to increase fluid intake include identifying and overcoming individual and institutional barriers to drinking, such as being worried about not reaching the toilet in time, physical inability to make or to reach drinks, and reduced social drinking and drinking pleasure.

For older people serum osmolality appears the most appropriate gold standard for diagnosis of water-loss dehydration, but clear signs of early dehydration have not been developed.

Box 1. Serum measures of hydration status (potential gold standards for dehydration)

- Serum osmolality is measured using the freezing point of serum (mOsm/kg)
- Serum osmolarity (mOsm/L) is calculated by summing components:
  - 2Na + 2K + glucose + urea (all in mmol/L)*
- Serum tonicity (mOsm/L) (or effective osmolarity) is calculated:
  - 2Na + 2K + glucose (all in mmol/L)
- Serum sodium may be used as a proxy for osmolality or tonicity

* This is one formula for osmolarity but there are many more (Fazekas et al., 2013).

OPEN ACCESS

ORIGINAL RESEARCH

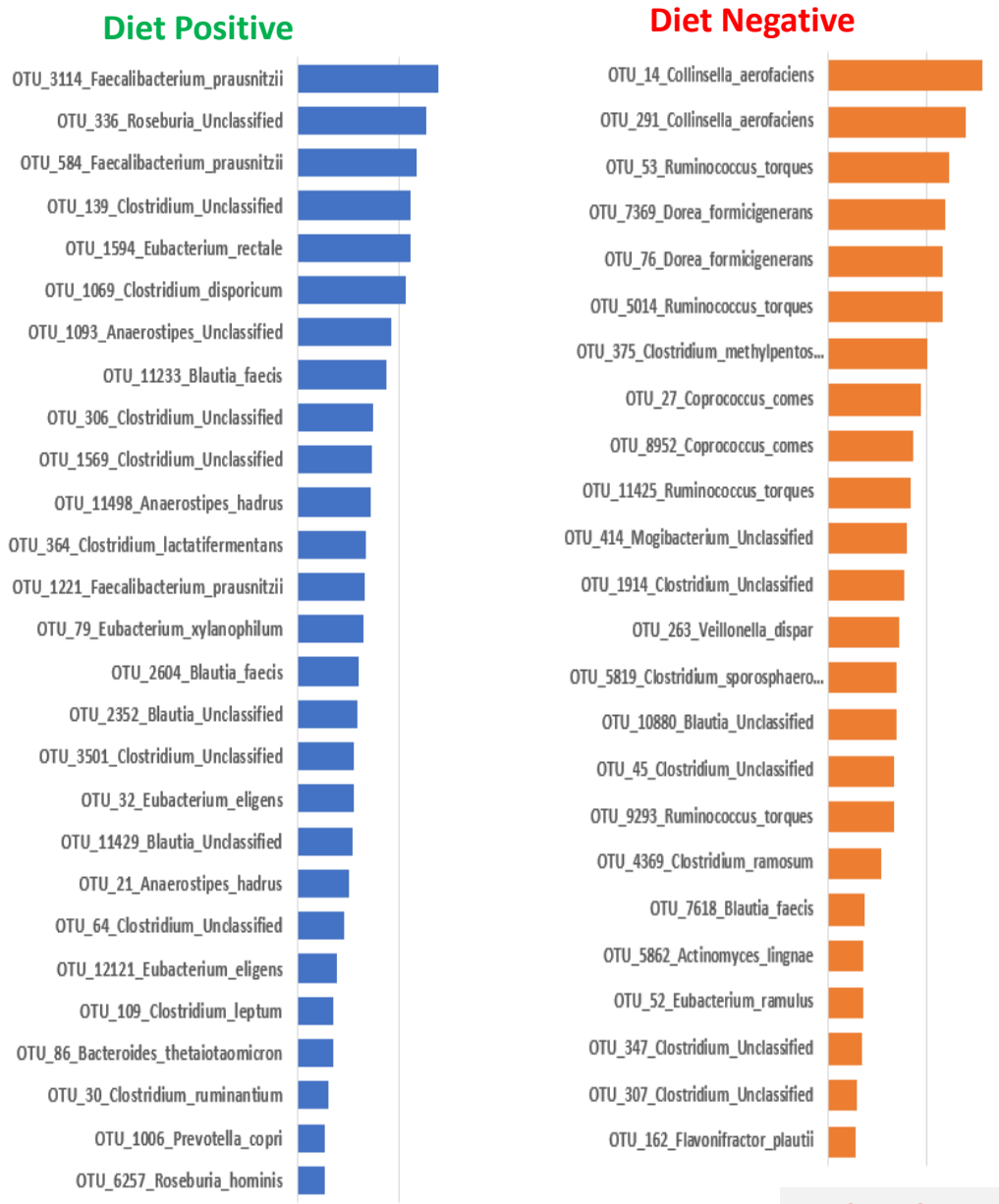
Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries

Tarini Shankar Ghosh,[1,2] Simone Rampelli,[3] Ian B Jeffery,[1,2] Aurelia Santoro,[4,5] Marta Neto,[1,2] Miriam Capri,[3] Enrico Giampieri,[4] Amy Jennings ,[6] Marco Candela,[3] Silvia Turroni,[3] Erwin G Zoetendal,[7] Gerben D A Hermes ,[7] Caumon Elodie,[8] Nathalie Meunier,[8] Corinne Malpuech Brugere,[9] Estelle Pujos-Guillot,[10] Agnes M Berendsen,[11] Lisette C P G M De Groot,[11] Edith J M Feskins,[11] Joanna Kaluza ,[12] Barbara Pietruszka ,[12] Marta Jeruszka Bielak,[12] Blandine Comte,[10] Monica Maijo-Ferre,[13] Claudio Nicoletti,[13,14] Willem M De Vos,[7,15] Susan Fairweather-Tait,[16] Aedin Cassidy,[17] Patrizia Brigidi,[18] Claudio Franceschi,[19,20] Paul W O'Toole [1,2]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2019-319654).

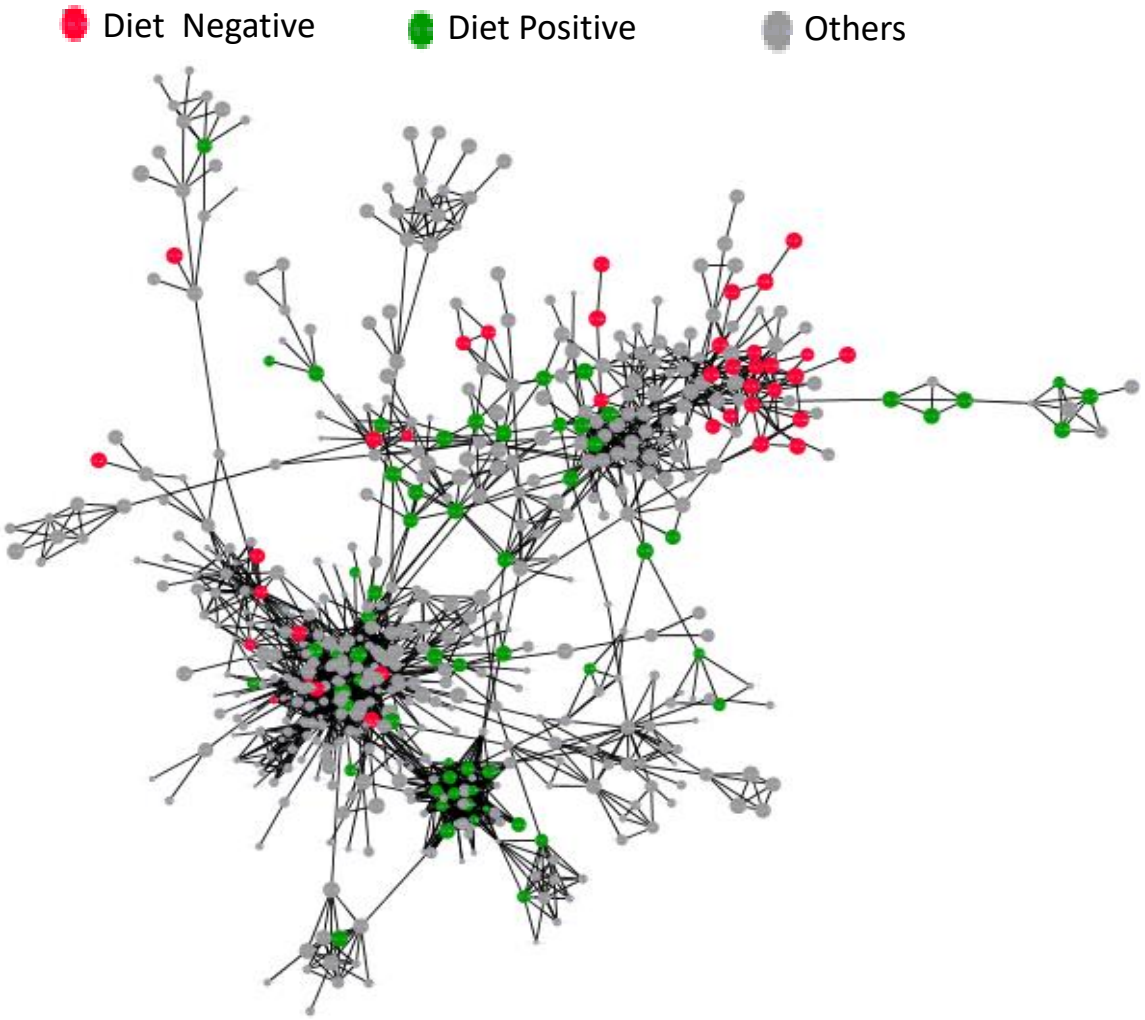
Ghosh TS, *et al*. *Gut* 2020;**69**:1218–1228.

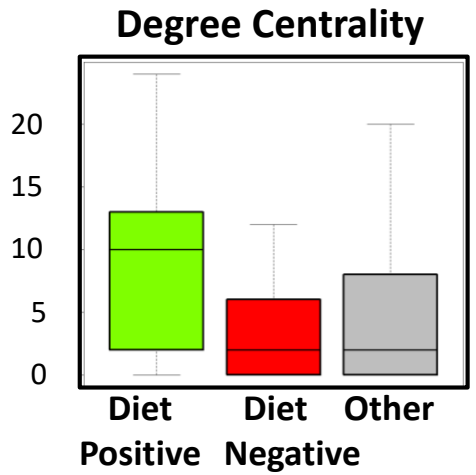
Identification of diet-responsive taxa



Ghosh et al., GUT, in press

Diet-positive taxa are keystone species at nodes of microbiome network





Reboot; Kendall correlations

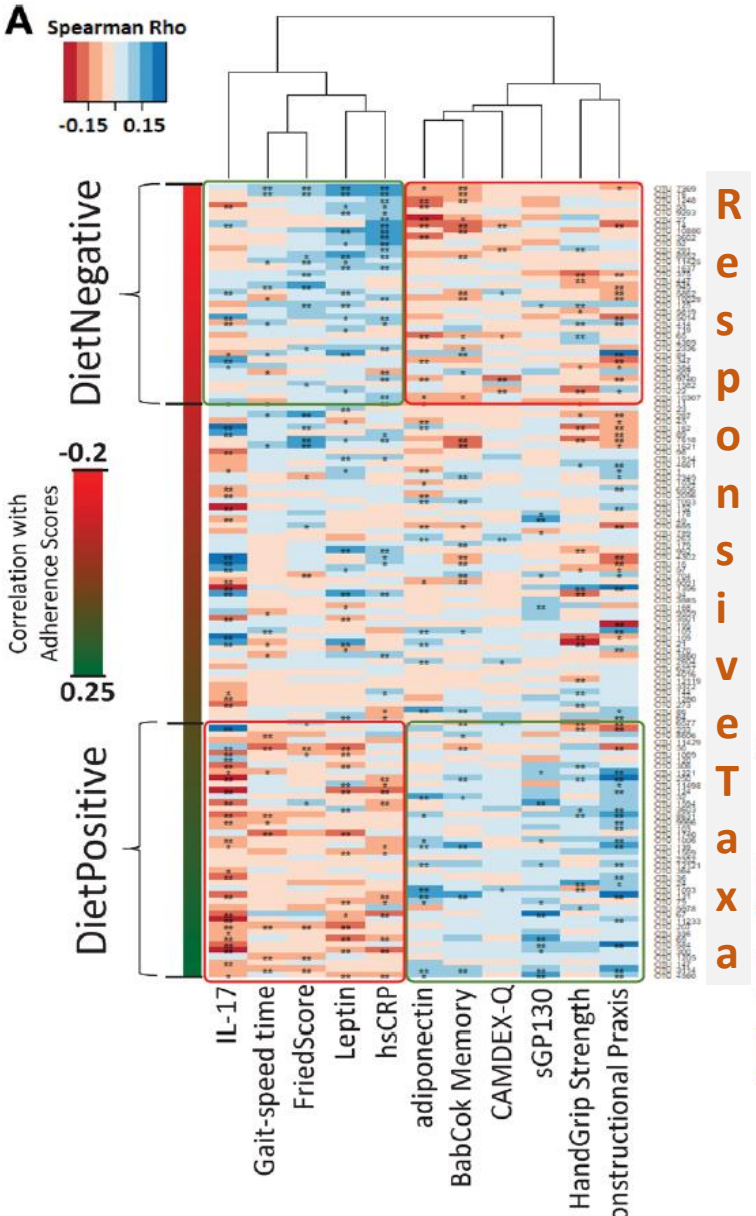
Ghosh et al., GUT, in press

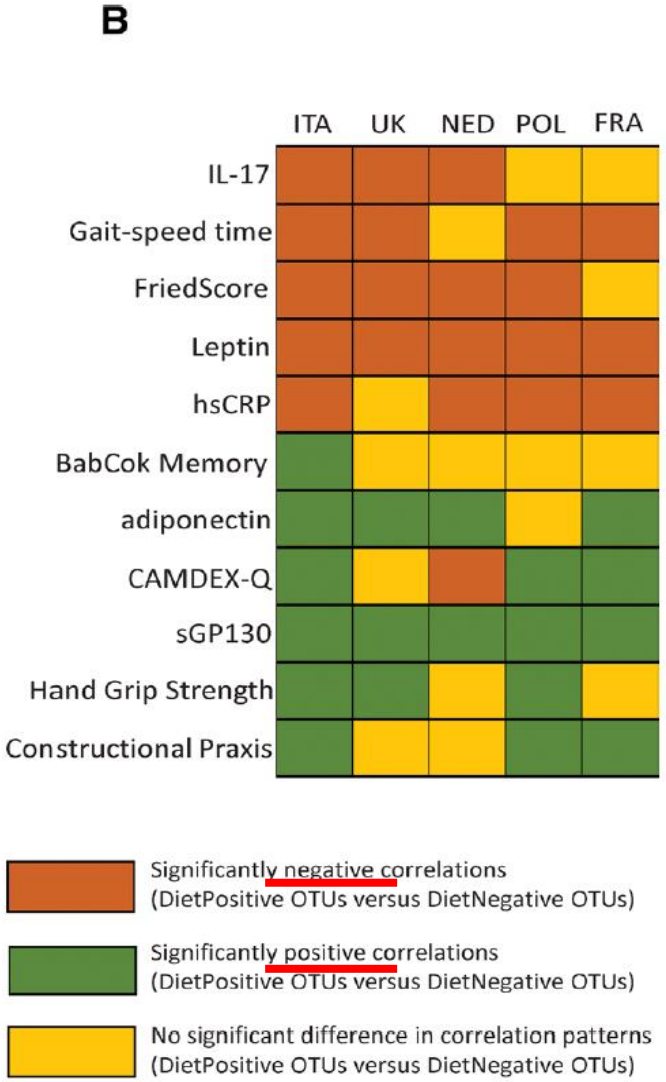
NU-AGE Med-Diet changes the GM

& has positive effects on inflammaging, frailty and cognitive function

1 year MedDiet in 570 elderly aged 65-79 years

571 age-matched controls follower their habitual diet





OTUs (Operational Taxonomic Units) are cluster of similar sequence variants of the 16S rDNA marker gene sequence

Un'unità tassonomica operativa è una definizione operativa utilizzata per classificare gruppi di individui strettamente correlati. Il termine è stato originariamente introdotto nel 1963 da Robert R. Sokal e Peter H. A.

Ghosh *et al.*, GUT 2020

GeroScience (2020) 42:687–701
https://doi.org/10.1007/s11357-019-00149-0

ORIGINAL ARTICLE

One-year Mediterranean diet promotes epigenetic rejuvenation with country- and sex-specific effects: a pilot study from the NU-AGE project

Noémie Gensous · Paolo Garagnani · Aurelia Santoro · Cristina Giuliani · Rita Ostan · Cristina Fabbri · Maddalena Milazzo · Davide Gentilini · Anna Maria di Blasio · Barbara Pietruszka · Dawid Madej · Agata Bialecka-Debek · Anna Brzozowska · Claudio Franceschi · Maria Giulia Bacalini

A one year MedDiet **reduces inflammaging** and **has rejuvenating effects** (more than 1 year, according to Horvath's clock, i.e. regarding 353 CpG across the whole genome).

A one year **MedDiet** nutritional intervention **reduces inflammaging** and promote **epigenetic rejuvenation of more than 1 year (Horvath's clock)** in the elderly.

This effect appears to be:

(1) **country-/population-specific** (anthropologic and cultural components);

(2) **sex-/gender- specific**;

(3) **individual-specific**, related to the genetic background.

Thus, MedDiet in humans , besides its strictly nutritional effects, can be assumed as a «genetic intervention» on the metagenome:

Each person have his/her individual genome + his/her personalized metagenome

An emerging role of astrocytes in aging /neuroinflammation and gut - brain axis with consequences on sleep and sleep disorders

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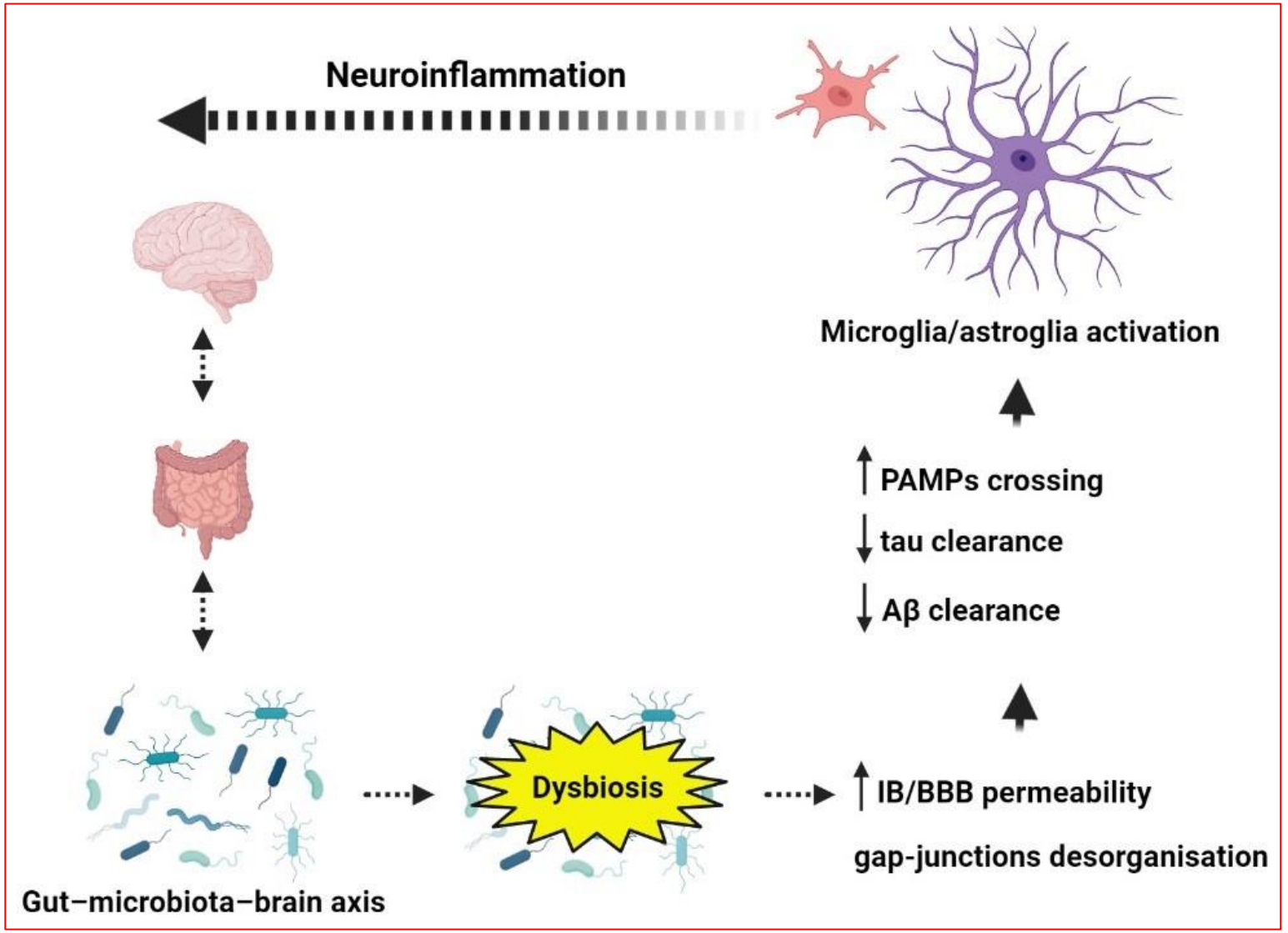
Astrocytes and the gut microbiota-brain axis

Abbreviations: PAMPs, pathogen-associated molecular patterns. IB, interstitial barrier. BBB, blood–brain barrier.



Gudkov SV... Franceschi C... et al., ARR. 2022, submitted

TAKE HOME MESSAGE: TO STUDY AGING IN YOUNG PEOPLE

Article

Cell Reports

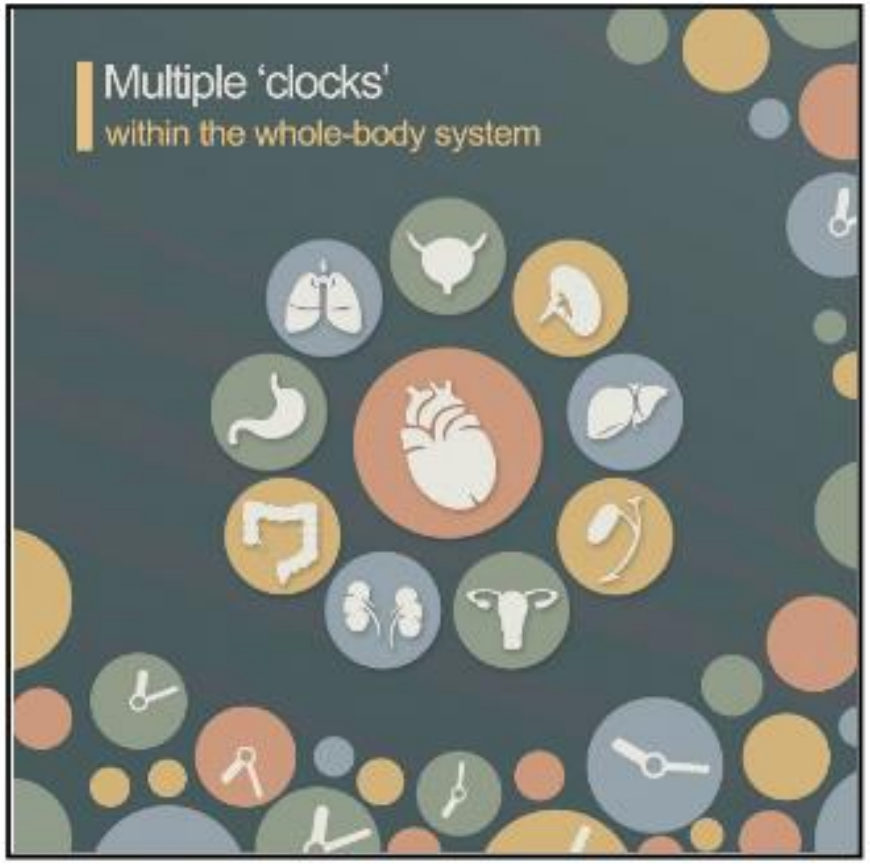
Cell Rep. 2022 Mar 8;38(10):110459

Distinct biological ages of organs and systems identified from a multi-omics study

402 features were measured

including 74 metabolomic features, 34 clinical biochemistry features, 36 immune repertoire features, 15 body composition features, 8 physical fitness features, 10 electroencephalography (EGG) features, 16 facial skin features, and 210 gut microbiome feature

Graphical abstract



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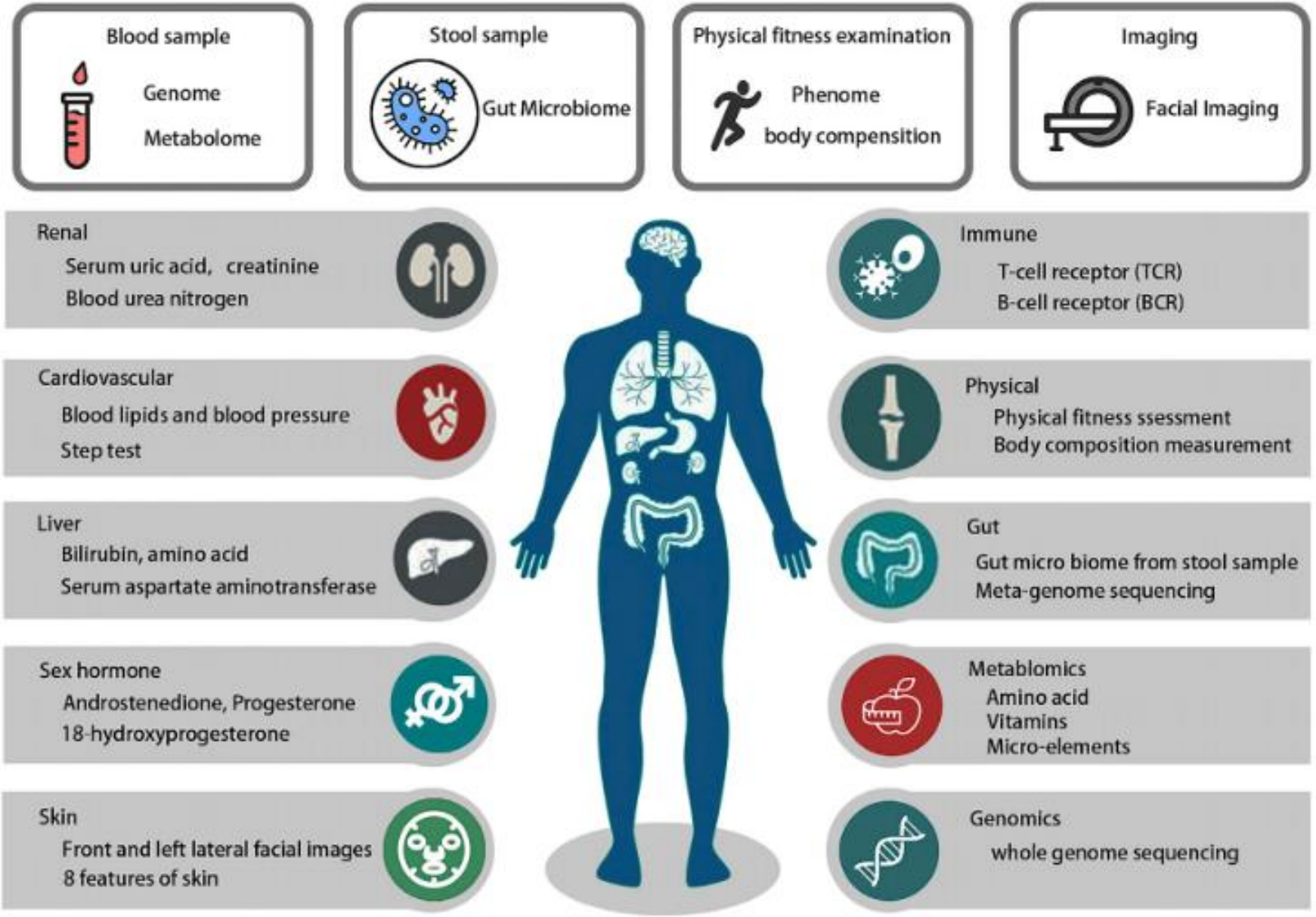
4,066 individuals aged between 20 and 45 years of age

In brief

Nie et al. estimate biological ages of organs and systems using 402 multi-omics features from 4,066 individuals and demonstrate several applications. They find that organs and systems are aging at different rates, and biological ages could be utilized for population stratification, mortality prediction, and phenotypes of genetic association studies.



Nie et al., CR 2022

Highlights

- Constructing biological ages of organs/systems using multi-omics features
- Organs and systems are aging at different rates
- Specific biological age could predict disease of corresponding organs
- Biological ages of organs and systems have diverse genetic architectures

Nie et al., CR 2022

The Biological Aging (BA) rates of organs and systems are diverse

There are multiple “clocks” within the body

The identified BA predicts:

1. Mortality in the US National Health and Nutrition Examination Survey
2. Longevity in the Chinese Longitudinal Healthy Longevity Survey

Thanks 4 your attention

BOLOGNA/UNIBO: the arcades of the oldest university in the Western world (founded in 1080)