Toward precision interventions and metrics of inflammaging

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Abstract

Inflammaging describes a chronic, systemic, low-grade inflammatory state recognized as a major risk factor for age-related diseases (ARD) and a pivotal convergence point of multiple biological mechanisms involved in aging. Here, we discuss the heterogeneity of inflammaging, proposing that it emerges as a consequence of each individual's lifelong exposures to inflammatory stimuli, shaped by a unique combination of genetics, lifestyle, socioeconomic conditions and environmental factors such as infections and pollution. Through this lens, we then discuss measuring inflammaging, describing the development of inflammatory clocks which quantify inflammatory age and show strong associations with ARD incidence, as well as how other aging clocks intersect with inflammaging. Finally, we consider interventions that may counteract inflammaging, including nutritional interventions, physical activity and gerotherapies including senolytics. We propose that deepening our knowledge of the individual nature of inflammaging stands to enhance our understanding of personalized aging trajectories and inform precision interventions.

1. The underlying drivers of personalized inflammaging

The concept of inflammaging, i.e. the chronic, low-grade inflammation occurring even in the lack of any infection or chronic conditions deeply involved in aging and age-related diseases (ARDs), has evolved significantly since its inception twenty-five years ago[1]. The variety of stimuli responsible for and the complexity of the mechanisms underpinning inflammaging are illustrated in **Figure 1**. Inflammaging underscores the intricate interplay between aging, metabolism and the immune system[2,3], and can be described as a continuous, dynamic remodeling of the immune system, intimately tied to the concept of immunosenescence, the gradual decline in immune function occurring with age[4]**.** A possible conceptualization of this complex scenario (the intriguing relationship between inflammaging and the aging of the immune system) would suggest that they likely start as two distinct phenomena that eventually interact, deeply influence and drive each other, positively or negatively[5,6]. A detailed discussion of key features of immunosenescence and inflammaging is out of the purpose of this review, but we like to emphasize that in each person a different, peculiar and personal combination of these two phenomena and mechanisms is involved. Inflammaging is a lifelong process, suggested to begin *in-utero*[7], continuing through infancy, adulthood and into old age[8]**,** that can preferably be viewed as an adaptive, rather than a solely detrimental process[9]. Thus, aging is not merely a universal process but also an intensely individual experience. Indeed, no two individuals age in precisely the same way, including monozygotic twins[10]. The related concept of immunobiography, which tracks the lifelong interactions between an individual's immune system and his/her historical, geographical, and socio-economic (SES) status, emphasizes that this interplay is unique to each person[11]. Drawing on the "Principium Individuationis"[12] and the concept of immunobiography, data suggest that a major characteristic of the immune system is its largely adaptive nature which is at the basis of the individual patterns of immunological aging[13,14]. A plethora of individually unique internal and external sources of inflammaging have been identified (**Figure 1**)[15 3,16]. The accumulation with age, in most organs and systems, of senescent cells with their SASP, i.e. senescence-associated secretory phenotype, is considered as a major source of inflammatory stimuli. Senescent cells have a highly heterogeneous distribution and phenotype[17], but their characterization at the individual level is still lacking. Another major role in inflammaging is played by SES. Several studies have shown inverse associations between SES and biomarkers such as CRP and IL-6[18]. SES deprivation is lifelong associated with abnormal immune and neuroendocrine activity, depending on individual-compositional factors[19]. A recent study showed that individuals experiencing social disadvantage had an increased risk of 66 age-related diseases, and that the main enriched pathway involved the upregulation of the pro-inflammatory regulator NF-κB and its

downstream factor interleukin-8[20] Early life appears to be a sensitive period in which low SES shapes the inflammatory phenotype in adulthood[21]. Growing evidence suggests SES inequalities in mid-life contribute to the prevalence of cardiovascular, metabolic, and neurocognitive disorders in later life[22]. Additionally, lower SES and neighborhood socioeconomic conditions have been linked to increased exposure to infections and immunosenescence[23,24]. Addressing inflammaging through socioeconomic interventions could improve public health and reduce healthcare costs[25]. Future research must explore how socioeconomic disadvantage shape inflammaging across the lifespan. Accordingly, in this review we pursue the concept of "individualized inflammaging", within the framework of "Personalized Medicine", emphasizing how a unique combination of exposures can drive individual trajectories of inflammaging, and that for the first time we start having tools to quantify and modulate the heterogeneous processes of inflammaging at a person level.

1.1 Garbaging and Anti-inflammaging. The age-related decrease of physiological barriers integrity[26] and the lifelong exposure to damage, entail an increase in internal "garbage" such as endogenous, misplaced, or altered molecules resulting from damaged and/or dead cells and organelles (cell debris) and loss of gut intestinal barrier integrity[27]. This "garbage" represents a major source of inflammatory stimuli, resulting in the expression of inflammaging factors, notably pro-inflammatory cytokines which gradually accumulate and lead to tissue damage and systemic inflammation[27]. Moreover, since 2000 a number of observations suggested that inflammaging may be continuously buffered by a variety of emerging, still largely unexplored (particularly at the individual level) compensatory anti-inflammatory mechanisms, likely reflecting the ongoing adaptation of the body to the gradual increase of inflammatory stimuli with aging[28]. Thus, pro-inflammatory mediators such as cytokines accumulate over time, leading to tissue damage and systemic inflammation but anti-inflammatory molecules are also concomitantly produced as a likely compensatory mechanism suggesting that the body is actively engaged in preserving its functionality[29]. Within this adaptive framework, inflammaging can be seen as both a driver of ARDs[30] and an attempt of the body to maintain homeostasis[31], where inflammation acts as both a friend and a foe**.** Indeed, healthy centenarians largely free from ARDs exhibit a mild inflammaging counteracted by a consistent anti-inflammaging[28,32,33]. In summary, a major issue is the lack of longitudinal studies to confirm the cause-and-effect relationship between level of inflammaging and healthy longevity.

1.2 Inflammaging in men and women. Men and women differ regarding a variety of features potentially impacting on inflammaging, primarily differences in immune function[4,34,35]. Men exhibit higher inflammatory status and a weaker response against acute stimuli, as well as a higher production of ROS and less efficient antioxidant mechanisms[36]. Women generally exhibit lower infection rates

than men for various pathogens but face up to a fourfold higher risk of autoimmune diseases, especially during reproductive life[37]. Longitudinal studies revealed that higher IL-6 levels are associated with a faster decline in intrinsic capacity, defined as the physical and mental capacities that an individual can draw on at any point in time, for men but not for women[37,38]. Men and women differ in the rate at which they produce or clear senescent cells, thus resulting in different rates at which senescent cells accumulate in various tissues[29,39]. Vasculature is an important target of inflammaging that exhibit significant sex differences, influencing how aging-related pathologies (cardiovascular, metabolic and cerebrovascular diseases) develop and respond to treatment differently in men and women[40,41]. In general, women live longer than men but are more prone to frailty and have worse health at the end of life. This apparent paradox can be largely explained by different age-related trends of inflammaging observed in men and women, fuelled by complex interactions between sex-related differences in genetic factors, including maternally inherited mitochondrial DNA genetic variants, age-related X chromosome inactivation skewing, hormonal changes (menstrual cycle, pregnancy, menopause), peculiar environmental exposure and the microbiome, among others[35,37].

In summary, we suggest that it is important to go further regarding the expected large individuality of inflammaging within each sex or gender[42], taking into account the limited number of available studies largely non-longitudinal, and thus likely noisy.

2. How to measure Inflammaging

2.1 The development of clocks

Inflammaging was first quantified using a cross-sectional limited number of inflammatory factors such as interleukin-6 (IL-6), IL-1, tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP) in peripheral blood[43]. It became increasingly clear that this limited set of markers is insufficient to capture the complexity of inflammaging, so that new soluble proteins are emerging as reliable biomarkers. However, translating the biomarkers of inflammaging into clinical settings puts some technical aspects. Methylation markers are more stable but specific expertise is required to translate methylation analysis into a clinical context. As inflammaging associates with the development of ARDs, developing biological clocks, built from a larger and possibly longitudinal pool of inflammaging factors, could provide personalized insights into immune aging and disease risk and monitor the efficacy of interventions. In this area, machine learning and AI tools are proving useful in the construction of clocks, and explainable AI (XAI, **cf. Box.1**) approaches offer the possibility of unveiling, in each person, the contribution of each inflammaging factor to his/her predicted

inflammatory age[44] . In summary, we note the consensus on employing multidimensional data for clocks, and the dichotomy of the choice of data, the ease of measurement (even at bedside) confronting the stability of measured signals.

2.2 Inflammatory clocks and their explainability

An immune aging score (IMM-AGE) correlated with age and predictive of all-cause mortality was proposed in[45]. Unlike the majority of clock models regressed on chronological age, it employed the longitudinal immune cell composition and cytokine profiling to build a non-branched multi-dimensional trajectory that described the change of the immune system over time. The longitudinal approach aided noise buffering. Next, a guided autoencoder deep learning network was used to build iAge clock based on 50 cytokines, chemokines and growth factors with the mean average error (MAE, the performance metrics of clocks) of 15.2 years[33]. Remarkably, CXCL9, a chemokine modulating multiple genes implicated in inflammation, cellular senescence and vascular aging, manifested the most significant age association iAge and displayed association with multimorbidity, frailty and longevity. The age prediction accuracy of the next inflammatory clocks named ipAge was modified and improved regarding two characteristics[46], based on another lineage of 38 chemokine and cytokine markers and a linear regression model. CXCL9 remained top significant, although the next significant markers of ipAge were different. Further, SImAge clock based on the deep learning FT-Transformer model reduced the number of required inflammatory markers to 10 and MAE to 6.94 years[47]. The "black-box" of SImAge neural network was disclosed by the SHAP-value eXplainable AI method, providing explainability for the model in general, and for each particular participant (**Figure 2**)[47]. Another cytokine clock (CyClo), based on LASSO regression and 24 blood immune protein concentrations, predicted age with MAE 6 years, and exhibited significant correlation with the default mode, limbic, and dorsal attention networks assessed by MRI[48]. Intersection between the top biomarkers of iAge, SImAge and CyClo clocks is very limited: iAge and SImAge have only CXCL9 in common (**Table 1**), iAge and CyClo share EOTAXIN, and SImAge and CyClo overlap in VEGF, IL6 and CXCL10. This could be both due to the moderate overlap of the markers assessed by different panels used in the studies, and the limited cohort sizes (several hundred to a thousand) and geographical diversity (US and Russia). Developing an inclusive and expectantly more informative panel for inflammatory clocks remains a clear challenge. In any case, as the different clocks work apparently well despite including different sets of inflammatory biomarkers, these results suggest that the components of inflammaging are much more numerous and their interaction more complex than previously thought. It will be crucial to disentangle the informative importance of the single components of these clocks for the purpose of the personalized approach to inflammaging. Efforts

have to be undertaken to ensure a worldwide coverage and a more balanced representation of included subjects, with respect to ethnicity, climate, socio-economic status and other environmental factors. Addressing the issue, SImAge was used to study inflammatory profile in the Yakutian population, living in an extremely cold climate[47]. Although a statistically significant SImAge acceleration in comparison with the Central Russia population was not detected, more than a half of its entries demonstrated a significant difference, suggesting a trend towards an increased inflammaging in Yakuts. Expanding the factors on which inflammatory clocks are built may also yield improvements, for example, including IL-11 based on its role as a regulatory hub of inflammaging[49]. In summary, it isalready possible to estimate the inflammatory age of a person even if the current iAge, SImAge and CyClo clocks show little overlap, likely due to current limitations of different assays measuring only several dozens of inflammatory markers, cross-sectional nature of data, cohort sizes and geographical diversity. We envisage that this approach, which can be early applied even to adult persons before clinical manifestation of increased inflammatory age, can help to increase the healthspan of older adults, which is lagging compared to the lifespan.

2.3 The contribution of aging clocks to inflammaging signature

The broader screening of plasma proteome produced a number of promising, albeit not inflammaging-specific proteomic clocks. In particular, both linear and nonlinear age dependencies were identified in the levels of 529 plasma proteins[50]**,** as the base for a set of clocks produced by LASSO regression[51]. The recently proposed ProtAge clocks based on the gradient boosting LightGBM AI model makes use of the levels of 204 proteins, has MAE of 4.1 years and is associated with the incidence of 18 major chronic diseases, multimorbidity and all-cause mortality risk[52]. Instructively, the inflammation-related CXCL9, GDF15 and CXCL17 are among the top important markers identified by XAI SHAP. Finally, AI can accurately predict Parkinson disease up to 7 years to the onset of motor phase based on just eight inflammation-related proteins[53]**.**

Despite the plethora of epigenetic clocks, and the known disagreement between them, they exhibit sensitivity to various pathologies, including those related to the immune system[54–56]. The lack of their specificity to inflammation can be addressed by inferring the levels of circulating proteins by means of DNA methylation data (DNAm). In particular,[57] identified associations of DNAm with some of the key proteins of the immune system, such as CD48, CD163, CXCL10, CXCL11, LAG3, FCGR3B, and B2M. Stevenson et al., [58,59] built DNAm scores that estimate the levels of C-reactive protein and IL-6, and demonstrated their sensitivity to cognitive abilities, in contrast to their original protein counterparts. Later EpiScores, elastic-net-based DNAm estimators for 109 plasma proteins, were developed[60]. The selected list proved to be enriched for IS pathways and therefore appears promising

for characterizing inflammation-related morbidities. GrimAge and EpiScore composite variables were incorporated to construct epigenetic chronological and biological age estimators by elastic net with MAE 2.3 years[61]. All these proteomic and hybrid proteomic-epigenetic clocks have the potentiality to measure aging and inflammaging, and thus to identify different types of aging patterns in different individuals, a phenomenon defined as "*ageotype*"[62,63].

Recently, it was demonstrated that it is possible to generate biological clock using MicroRNA (miRNA) profiles, to predict biological age-related to human blood[64,65] or skin[66]. Several settings of miRNAs have been proposed as potential biomarkers of inflammaging, even if an inflammatory-related miRNAs-specific clock has not been developed yet. In summary, we like to stress that the major aim of the inflammatory clocks is not to predict chronological age, but to quantify the possible difference between the chronological age of a person (assumed an objective reference point) and his/her inflammatory age, and even more in the specific composition and ranking of his/her personal inflammatory clock.

3. How to treat Inflammaging

Inflammaging is fueled by a complex interaction of genetic, lifestyle and environmental factors. Research has increasingly focused on ways to mitigate or delay inflammaging with particular attention to interventions at relatively low cost and with great potential feasibility involving nutrition and lifestyle, such as Mediterranean Diet[67] and physical activity[68] (**Figure 3)**. These interventions not only have the capability to reduce inflammation, but they may also foster healthy aging by improving gut microbiota composition, influencing gene expression and promoting epigenetic rejuvenation[69–71]. At the same time, a new class of drugs, called geroprotectors, including senolytics, emerged as compounds able to prolong the lifespan and healthspan of organisms by mitigating specific targets of inflammaging such as metabolism, oxidative stress and cell senescence[72]. In summary, two major points emerge from the available literature related to such interventions: in general, the individual variability regarding the effect of the intervention on inflammatory parameters is not reported and longitudinal studies are lacking.

3.1 Inflammaging and Nutrition

Nutrition represents a pervasive tool able to finely modulate the pro- and anti-inflammaging balance, and thus the phenotype, throughout life[73]. A diet rich in anti-inflammatory compounds can help to lower the risk of chronic diseases, improve immune function, and potentially decelerate the aging process[74]. Processed foods, high in sugar and saturated fats, are known to trigger inflammatory pathways, while whole foods, abundant in vitamins, minerals, and antioxidants, help to counteract

these effects[75]. Over the past decade, nutritional science has highlighted several promising dietary strategies for extending healthspan and addressing the aging process[76]. Caloric restriction, intermittent fasting and time-restricted eating[77], have demonstrated significant effects on metabolic health, inflammation and lifespan across various species[78], although their relevance to humans is still under investigation[79].

In summary, recent clinical trials have positioned the Mediterranean diet as a promising dietary intervention to modulate inflammaging[80,81]

3.1.1 Mediterranean Diet and Anti-Inflammaging

The Mediterranean diet has been associated with a reduced risk of chronic diseases and improved metabolic health [82], although its direct impact on longevity remains to be fully elucidated. It has also been suggested as a potential anti-inflammaging strategy due to its anti-inflammatory dietary profile[83], although evidence from clinical trials, such as the PREDIMED study, relies on a limited set of inflammatory markers (e.g., CRP, IL-6). In clinical settings, the Mediterranean diet is typically defined by a high intake of plant-based foods (vegetables, fruits, legumes, nuts, and whole grains), frequent use of extra virgin olive oil as the main fat source, moderate consumption of fish, poultry, dairy, and red wine[67] and limited intake of red meat, processed foods, and sweets while also acknowledging that variations in dietary patterns exist across different Mediterranean populations[84]. Key benefits of the Mediterranean diet include enhancement of satiety, reduced postprandial glycemia and controlled insulin secretion due to its focus on low-glycemic-index carbohydrates and abundant dietary fiber. While these features have been linked to improved health outcomes and reduced inflammation, their classification as anti-aging interventions remains speculative and subject to ongoing research. Our group coordinated the NU-AGE study (clinicaltrials.gov: NCT01754012), a randomized control trial aimed at reducing inflammaging by a 1-year Mediterranean diet intervention[85] in a gender-balanced cohort of 1200 participants over the age of 65 from five European countries[86]. Compared with half of the randomly chosen participants who continued their habitual diet, people of the other half who underwent Mediterranean diet rejuvenated the epigenetic age (measured by DNAm clock) [69]. Moreover, the high adherence to the Mediterranean diet counselling significantly improved many other parameters such as intake of nutrients (macro and micro)[87,88], cognitive status[89], osteoporosis and frailty[90,91]. Of particular interest is that the Mediterranean diet induced health and inflammatory improvement (decrease of CRP and IL-17) while increasing the abundance of specific gut microbiome taxa negatively associated with pro-inflammatory markers[71,92]. Indeed, inflammaging appears to be related to a specific signature of gut microbiome in the older

adults[93]. Moreover, gut microbiome regulates immunosenescence[94] being at the center of a functional network including many organs and systems such as brain, liver, kidney and muscle. Targeting the gut microbiome has therefore emerged as a promising strategy to counteract inflammaging. In particular, specific probiotic strains (e.g., *Lactobacillus plantarum*, *Bifidobacterium longum*) have been shown to reduce systemic inflammation and modulate immune responses in aged mice and older adult subjects[95,96]. Prebiotic interventions such as inulin or fructooligosaccharides have also been shown to enhance short-chain fatty acid (SCFA) production and reduce pro-inflammatory cytokines[97]. Clinical evidence from the ELDERMET and NU-AGE studies supports the link between gut microbial composition, diet, and inflammatory status in older adults [71,98]. Additionally, early-phase trials on faecal microbiota transplantation in older adult individuals have demonstrated feasibility and potential immunomodulatory effects[99,100], though further studies are needed. Interestingly, the NU-AGE trial revealed variations across participants from the five countries and between genders, as well as a large heterogeneity of responsiveness to the Mediterranean diet at the individual level[101,102]. This heterogeneity highlights the importance of personalized nutritional approaches as genetic factors, baseline inflammatory status and microbiome composition may all influence the individual's response to dietary interventions, paving the way for future personalized recommendations. On the whole, available data suggest that Mediterranean diet is capable of fine-tuning the balance between pro- and anti-inflammaging, delaying age-related diseases, likely acting as a form of chronic hormesis[31,67]. Hormesis assumes that extremely low doses of poisonous compounds such as those present in most eatable vegetables can exert a mild stress that in turn would enhance the body cellular and molecular defense mechanisms. Indeed, the Mediterranean diet contains bioactive compounds, or "hormetins," such as resveratrol, quercetin and phenolic antioxidants, which activate pathways like Nrf2, NF-κB, mTOR, and sirtuins. Interestingly, certain hormetins are also considered geroprotectors and senolytics (**see sections 3.4 and 3.5**). In summary, Mediterranean diet can be considered an anti-inflammatory diet, but future trials are needed to evaluate efficacy at individual level.

3.2 Inflammaging and Physical Activity

Physical activity is a cornerstone for healthy aging, combating inflammaging and immunosenescence with systemic and cellular benefits[103]. Sarcopenia, strongly linked to frailty, is highly correlated with inflammaging[104]. The urgent need for a personalized approach regarding evidence-based exercise prescriptions that align with individual health profiles and conditions, moving beyond generic activity guidelines, has been recently stressed. Indeed, tailored and structured exercise prescription sequence for older adults are highly recommended[105]. Regular aerobic exercise reduces systemic inflammation,

though its effectiveness depends on factors such as age, type, duration, and intensity of training[68,106]. The efficacy of exercise in reducing inflammaging appears to be highly individual, influenced not only by sex differences but also by genetic factors, baseline inflammatory status, age of exercise initiation and pre-existing health conditions, suggesting the need for personalized exercise prescriptions integrating strategies that align dietary and exercise interventions to support healthy and active aging[107] Exercise initially induces pro-inflammatory cytokine production from muscle contraction but later triggers anti-inflammatory molecules, with a systemic involvement of the immune system and other organs such as liver, adipose tissue and gut, benefitting trained individuals through a long-term systemic effect. Anti-inflammatory effects of exercise are partly mediated by myokines (also known as "exerkines"), such as IL-6, IL-10, and IL-15, which counteract inflammation by promoting anti-inflammatory molecules like IL-1ra and IL-10[108–111]. To this regard, in order to explain why trained older adults show lower circulating IL-6 levels our group hypothesized also in this case an hormetic effect, where continuous, mild exercise is able to induce adaptive, beneficial responses[112]. Lifelong running has been shown to reduce inflammaging and extend healthspan in mice[113]. Human studies indicate that moderate aerobic exercise and high-intensity interval training lower IL-6 and CRP levels in older sedentary men[114]. Resistance training also reduces muscle TNF-α expression in older adults, further decreasing inflammation[68,115]. Regular exercise can also modify body composition and respiratory fitness, improving muscle mass, reducing visceral fat tissue (a source of pro-inflammatory signals)[116–118] and enhancing antioxidant defense mechanisms[116]. However, sex differences exist, with women experiencing less pronounced anti-inflammatory benefits from lifelong aerobic exercise compared to men[119,120]. Finally, exercise has been found to interact with gut microbiota, highlighting a bidirectional link between skeletal muscle and gut microbiota: the muscle–gut axis. Exercise fosters beneficial microbial species, while gut-derived metabolites like SCFAs enhance muscle metabolism and reduce inflammation. On the other hand, dysbiosis contributes to muscle atrophy and metabolic dysfunction[121] while the increased abundance of *Christensenellaceae, Porphyromonadaceae*, and *Rikenellaceae* correlates with lower visceral adiposity[122]. Interestingly, protein supplementation with exercise further reduces inflammation[123] and regular exercise paired with Mediterranean diet supports cardiovascular health, mental well-being[124].In summary, combining exercise with proper nutrition appears to amplify its benefits, providing a holistic strategy to combat inflammaging and promote healthy aging reducing malnutrition, preserving muscle mass, cognitive function and quality of life.

3.3 Inflammaging and Sleep quality

Emerging evidence highlights that sleep disturbances, such as insomnia and obstructive sleep apnea (OSA), exacerbate inflammaging. Sleep deprivation increases pro-inflammatory cytokines and CRP, contributing to chronic conditions such as heart disease and diabetes[125]. Conversely, good sleep quality reduces age-related inflammation, and higher sleep efficiency correlates with lower IL-6 levels[126,127]. Sleep is crucial for clearing inflammatory stimuli or "molecular garbage" produced by brain cells during normal activity[27,128]. In particular, microglial senescence, highly sensitive to aging, is a key driver of neurodegenerative progression and a promising therapeutic target[127]. Accumulating senescent microglia, essential for clearing cellular debris, accelerates brain aging, inflammaging, and susceptibility to neurodegenerative diseases. Similarly, the glymphatic system, facilitated by aquaporin-4 (AQP4) on astrocyte end-feet, clears brain metabolites and maintains homeostasis. Dysfunction of this system leads to protein accumulation (amyloid-β and Tau), neuroinflammation, and age-related diseases, sharing features with aging, including mitochondrial dysfunction, oxidative stress, and chronic inflammation[129]. A recent model predicts that insufficient sleep increases senescent glia accumulation, surpassing a critical inflammaging threshold. This progression becomes irreversible even with restored sleep, driving inflammaging further. Reversing this scenario requires reducing senescent glia below the threshold[130]. Tools like the Cognitive Clock might reflect brain inflammaging levels and correlate with age acceleration[131]. This machine learning-based Cognitive Clock is indeed able to predict, with a high accuracy, not only chronological age but also epigenetic and phenotypic ages[131].The sleep-inflammation relationship is bidirectional and mediated by the gut-brain axis[121]. Chronic inflammation disrupts sleep patterns, creating a cycle that accelerates aging. Insomnia, common among middle-aged and older adults, worsens with age, impairing quality of life and increasing risks for heart failure, neurodegenerative, and metabolic diseases[132]. Distinct gut microbiota profiles can help in stratifying insomnia types, identify at-risk individuals, and enable microbiota-based diagnostics and therapies[133,134].

In summary, prioritizing sleep hygiene and addressing sleep disorders are critical for reducing inflammation and promoting healthy aging.

3.4 Geroprotectors Targeting Inflammaging

Unlike nutraceuticals, which are dietary supplements that maintain physiological functions without necessarily affecting aging mechanisms, geroprotectors are compounds targeting the fundamental causes of aging and ARDs, their primary criterion being to extend longevity while preserving physiological function and health-related quality of life[135]. Accordingly, the present review is focused on major geroprotectors and few nutraceuticals sharing characteristics with geroprotecors. Geroprotectors can be classified by their mechanisms of preventing macromolecular

damage or slowing aging-related gene activity, and work through multiple pathways including mTOR, NF-kB, stress-response factors (FOXO3a, AMPK, NRF2, HIF1, HSF1), mitochondrial function improvement, and epigenetic mechanisms[72], all targets mechanistically linked to inflammation regulation (**Table 2**). Anti-inflammatory drugs like aspirin and ibuprofen have shown life-extending properties in various organisms[136,137]. Natural geroprotectors such as vitamin D, curcumin, resveratrol, polyphenols, and terpenoids influence inflammaging predominantly through indirect mechanisms rather than direct anti-inflammatory action[138–140].These compounds primarily modulate upstream cellular pathways including NRF2, AMPK, SIRT1, and FOXO3 signaling, which subsequently lead to downregulation of inflammatory processes. This distinction is important when considering personalized approaches to inflammaging, as individual variations in these primary target pathways may account for the heterogeneous responses observed in clinical studies. Understanding these indirect mechanisms helps explain why geroprotector efficacy may vary substantially among individuals and why biomarker profiles reflecting specific cellular pathway activity might better predict treatment response than general inflammatory markers alone. Transcriptomic data from major geroprotective interventions suggests inflammation reduction as a core anti-aging mechanism[141]. Currently, several clinical studies are underway, where the effectiveness of potential geroprotectors is studied using inflammaging markers. For example, metformin is employed by TAME (Targeting Aging with Metformin) trial with a comprehensive inflammaging biomarker panel, including classical inflammatory markers (IL-6, TNFα-receptor I or II, CRP) alongside novel anti-aging factors such as GDF15[142]. Both pre-clinical and clinical results indicate metformin's effectiveness in reducing IL-6 and CRP levels[143]. Rapamycin, an mTOR inhibitor, extends lifespan in *D. melanogaster*[144] and mice[145]. In humans, clinical investigations of rapamycin have incorporated comprehensive immunological analyses, including assessment of immune cell senescence markers and inflammatory mediators in peripheral blood samples[146]. A randomized, double-blind multicenter trial of rapamycin (2 mg/m2/day or 1 mg/m2/day vs placebo) in 63 patients with amyothrophic lateral sclerosis[147] demonstrated anti-inflammatory effects through decreased IL-18 expression (both mRNA and protein levels) and beneficial changes in immune cell populations. Finally, spermidine ameliorates colitis via induction of anti-inflammatory macrophages and prevention of intestinal dysbiosis[148].

The effectiveness of geroprotectors likely varies between individuals due to differences in their inflammaging mechanisms and baseline inflammatory profiles. Future research should focus on identifying biomarkers that can predict individual responsiveness to specific geroprotector compounds.

In summary, research on inflammaging-targeted geroprotectors demonstrated their potential in delaying aging processes, promoting healthspan and reducing disease severity, and we suggest that future studies may benefit from using the inflammaging clocks discussed above. However, challenges such as the lack of a unified theory of aging, complex classifications, discrepancies in mechanisms, and difficulties in translating findings to human applications need to be addressed. Further research and well-designed clinical trials are essential to fully realize the potential of these interventions in combating inflammaging and promoting healthy aging.

3.5 Senolytics Targeting Inflammaging

A vast and growing literature, using a variety of biological clocks and markers suggests that aging is malleable, and that the aging rate can be not only delayed but also reversed. The same considerations can be applied to inflammaging. Cellular reprogramming has demonstrated rejuvenating effects both *ex vivo* and *in vivo*, potentially by deactivating stress signals from damaged cells, which can reduce inflammation[149]. Heterochronic parabiosis, involving the joining of circulatory systems between young and old organisms, can reduce systemic inflammation by diluting pro-inflammatory mediators in old blood or introducing youthful anti-inflammatory factors, as well as by reducing the burden of senescent cells in the older organism[150]. Senolysis, the selective elimination of senescent cells through senolytic agents, reduces inflammaging, distinct from senomorphic compounds which attenuate the senescence-associated secretory phenotype through modulation rather than removal of senescent cells[151]. Senolytics are synthetic or natural compounds that induce apoptotic cell death in senescent cells by affecting several pro-survival pathways[152]. This mechanism is crucial because senescent cells, despite high levels of DNA damage, evade apoptosis and contribute to the pro-inflammatory environment characteristic of inflammaging[153]. As with other inflammaging interventions, individuals may respond differently to senolytic treatments based on their unique senescent cell burden, tissue distribution and inflammatory signature, highlighting the importance of personalized approaches to senolytic therapy. Senolytics like dasatinib, navitoclax, and venetoclax have demonstrated anti-inflammatory effects, ameliorating chronic inflammation[154]. Clinical trials are currently underway to assess the therapeutic efficacy of senolytics in mitigating various age-related morbidities, including diabetes, idiopathic pulmonary fibrosis, Alzheimer's disease, COVID-19, osteoarthritis, osteoporosis, eye diseases, bone marrow transplant, and conditions affecting childhood cancer survivors[155]. Preliminary results from these trials are promising, suggesting that senolytics can decrease senescent cell numbers, reduce inflammation, and alleviate frailty[155]. Report from a clinical trial of dasatinib plus quercetin in individuals with diabetic

kidney disease showed a reduction in circulating SASP factors including IL-1α, IL-6 and metalloproteinases MMP-9 and MMP-12[156].

On the whole, senolytics have been shown to delay, prevent, or alleviate various age-related conditions, including frailty, cancers, cardiovascular and neuropsychiatric, liver, kidney, musculoskeletal, lung, eye, hematological, metabolic, and skin disorders. Despite these encouraging findings, the use of senolytics is not without risks. A primary concern is the potential for off-target effects, as senolytics target pathways also present in non-senescent cells. For example, inhibition of BCL-2 family proteins can lead to unintended apoptosis in healthy cells, potentially causing adverse effects[157]. Furthermore, the long-term effects of senolytic therapy remain unclear, necessitating further extensive clinical trials to thoroughly evaluate the safety and efficacy of these agents. Targeting inflammaging is complex, as immune responses must be carefully modulated to avoid exacerbating inflammation or causing further tissue damage[104].

In conclusion, senolytics represent a promising avenue for treating age-related dysfunctions and diseases by targeting and eliminating senescent cells, potentially improving healthspan and lifespan. However, thorough investigation into the long-term safety and efficacy of these drugs is imperative to ensure their safe application in humans. Moreover, the possible predicted marked heterogeneity in individual burden and distribution of senescent cells, and response to senolytics underscores the need for personalized approaches to such anti-inflammaging treatment (see **Figure 3**).

4. Conclusions and perspectives

The present review suggests that inflammaging appears to be highly individualized, particularly in humans, owing to the complexity and intricacy of factors that characterize the aging of *H. sapiens* and that emerging approaches - such as the use of inflammaging-specific biological clocks - could enable more personalized strategies for managing inflammaging in the future. Indeed, the results of the inflammatory clocks, and particularly of the one using XAI, show that: a) inflammaging is different among individuals, being the stratification of the components peculiar of each person; b) the inflammatory age can be poorly related to chronological age, as it happens for many other biological clocks, being rather a function of exposure to a “personal inflammatory load”. Thus, cross-sectional inflammaging data should be considered preliminary owing to their possible high noise, and longitudinal studies in the same person are urgently needed to check their temporal reliability. Another related factor to consider is that soluble proteins such as those measured in the inflammatory clocks are technically easy to measure, even in a clinical setting, yet their biological stability shows high fluctuation.

There is an urgent need to address the heterogeneity of inflammaging, particularly as it may vary across different populations, especially those outside of affluent, high-income groups. Geographic and demographic evidence suggests that aging and longevity are influenced by a complex interplay of genetics, environment, and chance, and these factors differ significantly across regions and time. Therefore, we can expect inflammaging to manifest in peculiar ways in different populations, underscoring the need for studies that include diverse ethnic and environmental backgrounds. This is especially important for native populations, as for example those in Brazil[158], Yakutia[44], Bolivia and Malaysia[159], where distinct patterns of inflammaging are emerging and warrants closer investigations[47,158].

Another key point is that the majority of current data on inflammaging in older individuals, including centenarians, often lacks personalized information, as most studies report aggregated data that do not account for individual differences. This limits the potential for tailored interventions. In particular, it remains largely unknown how particular interventions like diet, exercise, geroprotectors, and senolytics will intersect with the individualized factors driving inflammaging to modulate its phenotype. Looking ahead, it will be crucial to quantify inflammaging at systems and organ level, providing essential information for physicians to implement more targeted, early, and personalized interventions. Since the degenerative diseases of aging start years before they manifest clinically[160] it could be worthwhile measuring inflammaging in adults who are still seemingly healthy to identify individuals at risk of these conditions. To this regard, a significant challenge remains the lack of methodologies to quantify number, anatomical distribution and type of senescent cells in individuals as they are considered a major source of inflammaging. Understanding the role of senescent cells in inflammaging across different organs and time points is a crucial area for future research.

The use of anti-inflammatory monoclonal antibody (mAb) alone or in combinations could be envisaged to counteract inflammaging at individual level on the basis of the results of the personalized inflammatory profile[161]. Nevertheless, the long-term safety, immunosenescence risk, and economic viability of such interventions remain critical areas for further investigation. On a short-term perspective, there is an urgent need to establish a consensus on a standardized set of inflammaging markers for first-line screening, which could be used routinely in large populations of adults and older individuals. This strategy could eventually be followed by more specific and expensive assessments if needed. Such an approach would complement initiatives like the transdisciplinary Clin-STAR group on inflammaging[162], fostering a broader, more inclusive approach to understand and address inflammaging. This two-step strategy could also be instrumental in exploring new, previously

unrecognized situations where inflammaging plays a role, expanding our knowledge of its impact and potential interventions[163].

On a longer-term perspective a pervasive application of personalized, and possibly organ-specific, inflammaging clocks could offer a cost-effective, preventative public health strategy. Moreover, by integrating these tools with other clocks, like the brain clocks and the most advanced epigenetic clocks, it should be possible to reach a remarkable level of precision in quantifying the individual risk of specific ARD, paving the way to early targeted interventions. Ultimately, we envision large, individualized, longitudinal studies where inflammaging clocks, possibly tailored to specific organs, and combined with other clocks, are measured at multiple time points across a person's lifespan offering an unprecedented level of precision in aging research.

Figure Legends:

Figure 1. **Main sources and mechanisms underlying personalized inflammaging.** A systematic representation of the main internal and external sources fuelling inflammaging and of the main mechanisms and pathways underlying personalized inflammaging. Figure was modified from[164]. ANS (Autonomous Nervous System), ECM (Extra Cellular Matrix).

Figure 2. Local explainability of AI-based SImAge clock illustrated by waterfall plots. The plots are visualizations of the results of[165] SHAP values in year units provide specific contributions of inflammatory clock variables to individual age acceleration: participants from the control group with (a) positive (chronological age 66.8 years, inflammatory age 56.9 years), (b) negative (chronological age 56.0 years, inflammatory age 66.8 years) and (c) negligible (chronological age 55.7 years, inflammatory age 56.0 years) age acceleration, and (d) an end-stage renal disease patient (chronological age 60.0 years, inflammatory age 86.9 years), exemplifying high- and low-inflammation, balanced and pathological individual profiles.

Figure 3. Personalized anti-inflammaging treatments. The main strategies to mitigate or delay inflammaging in single individual are illustrated. Particular attention is payed to general feasibility and low cost.

Figure 4. Personalized explainable inflammaging clocks. Recent progresses in the field make it desirable and feasible large, individualized, longitudinal studies where inflammaging clocks, possibly organ-specific, are measured in the same person at different time points in the lifespan. The measure in the same subject of blood-based inflammaging clocks and routine parameters aided by the last generation of epigenetic clocks, should improve the early quantification of the aging rate at the individual level.

TABLES:

Table 1. SImAge and iAge Markers of inflammaging according to their relevance to chronic diseases and cost

Marker	Relevance to Age-Related Diseases	Cost*	Routine blood test
IL-6	Key proinflammatory cytokine, associated with multiple age-related diseases and mortality	Moderate	Yes
IL-1β	Proinflammatory cytokine, linked to systemic inflammation	Moderate	Yes

LEPTIN	Adipokine, associated with metabolic disorders and inflammation	Moderate	No
PAI-1	Fibrinolysis regulator, linked to thrombosis and aging	Moderate	No
CSF1	Macrophage regulator, linked to inflammation and metabolic disorders	High	No
PDGFA	Growth factor, associated with fibrosis and vascular disorders	High	No
CXCL10	Chemokine, marker of immune activation and inflammation	High	No
CXCL9	Chemokine, reflects T-cell activation and chronic inflammation	High	No
CCL22	Chemokine, linked to immune regulation and inflammation	High	No
PDGFB	Growth factor, involved in tissue remodeling and fibrosis	High	No
VEGFA	Vascular growth factor, associated with angiogenesis and inflammation	High	No
EOTAXIN	Chemokine, linked to allergic inflammation and immune aging	High	No
MIP-1α	Chemokine, reflects immune cell activation	High	No
IL-5	Cytokine, regulates eosinophils and allergic reactions	High	No
IFN-α	Antiviral cytokine, associated with autoimmunity	High	No
IL-4	Regulatory cytokine, influences immune response	High	No
TRAIL	Cytokine, linked to cell death and inflammation	High	No
IFN-γ	Proinflammatory cytokine, marker of T-cell activation	High	No
CXCL1	Chemokine, attracts neutrophils during inflammation	High	No
IL-2	Cytokine, regulates T-cell proliferation	High	No
TGF-α	Growth factor, associated with tissue remodeling	High	No
LIF	Cytokine, influences cell differentiation and inflammation	High	No
IL27	Cytokine, pro- and anti-inflammatory effects, regulating T-helper cell development	High	No
CD40LG	Cytokine, expressed on the surface of T cells, regulating B cell function by engaging CD40 on the B cell surface	High	No

*Moderate cost estimated on current pricing: < 10 dollars; High cost >10 dollars

Table 2: Geroprotectors and senolytics targeting inflammation

Geroprotector	Model Organisms	Health Condition	Readouts and Endpoints	Key Findings	Reference
Rapamycin	Mice	Genetically heterogeneous healthy aging	Lifespan, age-related pathologies	Extended lifespan even when administered late in life	145
	Drosophila melanogaster	Healthy	Survival	Improved survival	144

	Humans	Amyotrophic lateral sclerosis (ALS)	IL-18 expression, immune cell populations	Decreased IL-18 expression, beneficial changes in immune cell populations	147
	Humans	Healthy adults	Immune cell senescence markers, inflammatory mediators	Results pending (referenced as ongoing clinical investigation)	146
Metformin	Humans	Polycystic ovary syndrome	Serum CRP and IL-6 levels	Reduction in inflammatory markers	166
	Humans	Various (TAME trial)	Multiple inflammaging biomarkers including IL-6, TNFα-receptor, CRP, GDF15	Trial in progress	142
Ibuprofen	Yeast	Healthy	Longevity, tryptophan import	Enhanced longevity through inhibition of tryptophan import	136
	Drosophila melanogaster	Healthy	Longevity	Extended lifespan	137
Acarbose	Humans	Adults (meta-analysis of RCTs)	Inflammatory cytokines and adipokines	Reduction in inflammatory markers	167
Spermidine	Mice	Colitis model	Macrophage phenotype, intestinal microbiota	Ameliorated colitis via induction of anti-inflammatory macrophages and prevention of intestinal dysbiosis	148
Terpenoids (Natural geroprotectors)	Various (review paper)	Healthy and disease models	NRF2, AMPK, SIRT1 activation	Potential geroprotective effects through multiple pathways	140
Polyphenols (Natural geroprotectors)	Various (review paper)	Healthy and disease models	NRF2, AMPK, SIRT1, FOXO3 activation	Potential geroprotective effects through multiple pathways	139

Dasatinib + Quercetin (Senolytics)	Aged rats	Normal aging	Cognitive abilities, inflammation, hippocampal synaptic plasticity, histone H3 methylation	Improved cognitive abilities, alleviated inflammation, changes in hippocampal synaptic plasticity and histone methylation profile	152
	Humans	Diabetic kidney disease	Circulating SASP factors (IL-1α, IL-6, MMP-9, MMP-12)	Reduction in senescence-associated secretory phenotype factors	156
	Mice	Aging model	Adipose tissue inflammation, metabolic function	Attenuated adipose tissue inflammation, improved metabolic function	168
Navitoclax and Venetoclax (Senolytics)	Zebrafish	Chronic inflammation models	Anti-inflammatory effects	Senescence-independent anti-inflammatory activity	154

BOXES:

BOX 1: eXplainable Artificial Intelligence

Advanced AI models show much promise in biomedical research and clinical practice, but are often poorly interpretable and act as "black boxes" that undermines contestability of AI decisions, the possibility to identify and correct mistakes, and, after all, trustworthiness and security of deployment. These concerns led to the development of XAI that aim at disclosing the grounds beyond AI decision-making, and building logically interpretable solutions, despite the nonlinearity and complex architectures of deep models[169]. Global explainability methods disclose the contribution of each feature to the model output in general ("on average"), whereas Local explainability disentangles specific decisions of AI. Both issues present major challenges for AI-based biological clocks to meet the needs of (i) understanding the general mechanisms and processes behind age acceleration, and (ii) delivering personalized reports on the patient's aging profile and associated risk factors. Approaches like SHAP and GNN Explainer, among others, can be adapted to almost any type of input

data (tables, images, time series), different AI models, and provide both global and local explainability, thus having the potential to become a gold-standard use in AI-based biological clocks[47].

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Author contributions

CF and AS conceived the review and wrote the first draft of the manuscript. FO, AM and MI provided constructive input and wrote additional sections in subsequent revisions of the manuscript. All authors approved the final version of the article, tables, boxes and figures.

Conflict of interests

Authors have no conflict of interests to declare.

REFERENCES

1. FRANCESCHI, C. *et al.* Inflamm-aging: An Evolutionary Perspective on Immunosenescence. *Ann N Y Acad Sci* **908**, 244–254 (2000).
2. Franceschi, C., Garagnani, P., Parini, P., Giuliani, C. & Santoro, A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* **14**, 576–590 (2018).
3. Fulop, T. *et al.* Immunology of Aging: the Birth of Inflammaging. *Clin Rev Allergy Immunol* **64**, 109–122 (2021).
4. Santoro, A., Bientinesi, E. & Monti, D. Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? *Ageing Res Rev* **71**, 101422 (2021).
5. Franceschi, C. *et al.* The network and the remodeling theories of aging: historical background and new perspectives. *Exp Gerontol* **35**, 879–896 (2000).
6. Fulop, T., Witkowski, J. M., Olivieri, F. & Larbi, A. The integration of inflammaging in age-related diseases. *Semin Immunol* **40**, 17–35 (2018).
7. Kerepesi, C., Zhang, B., Lee, S.-G., Trapp, A. & Gladyshev, V. N. Epigenetic clocks reveal a rejuvenation event during embryogenesis followed by aging. *Sci Adv* **7**, (2021).
8. Franceschi, C., Ostan, R. & Santoro, A. Nutrition and Inflammation: Are Centenarians Similar to Individuals on Calorie-Restricted Diets? *Annu Rev Nutr* **38**, 329–356 (2018).
9. Fulop, T. *et al.* Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? *Front Immunol* **8**, (2018).
10. Remondini, D. *et al.* Identification of a T cell gene expression clock obtained by exploiting a MZ twin design. *Sci Rep* **7**, 6005 (2017).
11. Franceschi, C. *et al.* Immunobiography and the Heterogeneity of Immune Responses in the Elderly: A Focus on Inflammaging and Trained Immunity. *Front Immunol* **8**, (2017).
12. Audi, R. *The Cambridge Dictionary of Philosophy* . (Cambridge University Press., Cambridge , 1999).
13. Brodin, P. & Davis, M. M. Human immune system variation. *Nat Rev Immunol* **17**, 21–29 (2017).
14. Brodin, P. *et al.* Variation in the Human Immune System Is Largely Driven by Non-Heritable Influences. *Cell* **160**, 37–47 (2015).
15. Lyons, C. E. *et al.* Chronic social stress induces p16-mediated senescent cell accumulation in mice. *Nat Aging* (2024) doi:10.1038/s43587-024-00743-8.
16. Marfella, R. *et al.* Microplastics and Nanoplastics in Atheromas and Cardiovascular Events. *New England Journal of Medicine* **390**, 900–910 (2024).
17. Kwiatkowska, K. M. *et al.* Heterogeneity of Cellular Senescence: Cell Type-Specific and Senescence Stimulus-Dependent Epigenetic Alterations. *Cells* **12**, 927 (2023).
18. Muscatell, K. A., Brosso, S. N. & Humphreys, K. L. Socioeconomic status and inflammation: a meta-analysis. *Mol Psychiatry* **25**, 2189–2199 (2020).
19. Hamilton, O. S. & Steptoe, A. Socioeconomic determinants of inflammation and neuroendocrine activity: A longitudinal analysis of compositional and contextual effects. *Brain Behav Immun* **107**, 276–285 (2023).
20. Kivimäki, M. *et al.* Social disadvantage accelerates aging. *Nat Med* (2025) doi:10.1038/s41591-025-03563-4.
21. Natale, B. N. *et al.* Systemic Inflammation Contributes to the Association Between Childhood Socioeconomic Disadvantage and Midlife Cardiometabolic Risk. *Annals of Behavioral Medicine* **57**, 26–37 (2023).
22. Gireesh, A., Sacker, A., McMunn, A. & Cadar, D. Role of inflammation in the socioeconomic inequalities of neurocognitive disorders. *Brain Behav Immun* **113**, 203–211 (2023).

23. Noppert, G. A., Stebbins, R. C., Dowd, J. B. & Aiello, A. E. Socioeconomic and race/ethnic differences in immunosenescence: Evidence from the Health and Retirement Study. *Brain Behav Immun* **107**, 361–368 (2023).
24. Ye, X. *et al.* Associations of socioeconomic status with infectious diseases mediated by lifestyle, environmental pollution and chronic comorbidities: a comprehensive evaluation based on UK Biobank. *Infect Dis Poverty* **12**, 5 (2023).
25. Tang, B., Li, Z., Hu, S. & Xiong, J. Economic Implications of Health Care Burden for Elderly Population. *INQUIRY: The Journal of Health Care Organization, Provision, and Financing* **59**, (2022).
26. Solovev, I. *et al.* Aging and physiological barriers: mechanisms of barrier integrity changes and implications for age-related diseases. *Mol Biol Rep* **51**, 917 (2024).
27. Franceschi, C., Garagnani, P., Vitale, G., Capri, M. & Salvioli, S. Inflammaging and 'Garb-aging'''. *Trends in Endocrinology & Metabolism* **28**, 199–212 (2017).
28. Franceschi, C. *et al.* Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* **128**, 92–105 (2007).
29. Olivieri, F., Prattichizzo, F., Lattanzio, F., Bonfigli, A. R. & Spazzafumo, L. Antifragility and antiinflammaging: Can they play a role for a healthy longevity? *Ageing Res Rev* **84**, 101836 (2023).
30. Furman, D. *et al.* Chronic inflammation in the etiology of disease across the life span. *Nat Med* **25**, 1822–1832 (2019).
31. Santoro, A. *et al.* Inflammaging, hormesis and the rationale for anti-aging strategies. *Ageing Res Rev* **64**, 101142 (2020).
32. Storci, G. *et al.* Genomic stability, anti-inflammatory phenotype, and up-regulation of the RNAseH2 in cells from centenarians. *Cell Death Differ* **26**, 1845–1858 (2019).
33. Sayed, N. *et al.* An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. *Nat Aging* **1**, 598–615 (2021).
34. Baker, C., Kim, M. & Benayoun, B. A. A researcher's guide to studying sex differences in immune aging. *Trends Mol Med* (2025) doi:10.1016/j.molmed.2025.01.005.
35. Márquez, E. J. *et al.* Sexual-dimorphism in human immune system aging. *Nat Commun* **11**, 751 (2020).
36. Martínez de Toda, I. *et al.* Sex differences in markers of oxidation and inflammation. Implications for ageing. *Mech Ageing Dev* **211**, 111797 (2023).
37. 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).
38. de Assunção Cortez Corrêa, L. C., Raffin, J., Vellas, B., Guerra, R. O. & de Souto Barreto, P. Sex-specific associations of neurodegeneration and inflammatory biomarkers with intrinsic capacity in older adults: Findings from the 4-year longitudinal Multidomain Alzheimer's Prevention Trial (MAPT). *Maturitas* **193**, 108191 (2025).
39. Bronikowski, A. M. *et al.* Sex-specific aging in animals: Perspective and future directions. *Aging Cell* **21**, (2022).
40. Ungvari, A. *et al.* Sex-specific mechanisms in vascular aging: exploring cellular and molecular pathways in the pathogenesis of age-related cardiovascular and cerebrovascular diseases. *Geroscience* (2025) doi:10.1007/s11357-024-01489-2.
41. Barbieri, M. *et al.* Is it time to revise the fighting strategy toward type 2 diabetes? Sex and pollution as new risk factors. *Ageing Res Rev* **99**, 102405 (2024).
42. Olivieri, F. *et al.* Sex/gender-related differences in inflammaging. *Mech Ageing Dev* **211**, 111792 (2023).
43. Tylutka, A., Walas, Ł. & Zembron-Lacny, A. Level of IL-6, TNF, and IL-1β and age-related diseases: a systematic review and meta-analysis. *Front Immunol* **15**, (2024).

44. Kalyakulina, A. *et al.* Inflammaging Markers in the Extremely Cold Climate: A Case Study of Yakutian Population. *Int J Mol Sci* **25**, 13741 (2024).
45. Alpert, A. *et al.* A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring. *Nat Med* **25**, 487–495 (2019).
46. Yusipov, I. *et al.* Accelerated epigenetic aging and inflammatory/immunological profile (ipAGE) in patients with chronic kidney disease. *Geroscience* **44**, 817–834 (2022).
47. Kalyakulina, A., Yusipov, I., Moskalev, A., Franceschi, C. & Ivanchenko, M. eXplainable Artificial Intelligence (XAI) in aging clock models. *Ageing Res Rev* **93**, 102144 (2024).
48. Markov, N. T. *et al.* Age-related brain atrophy is not a homogenous process: Different functional brain networks associate differentially with aging and blood factors. *Proceedings of the National Academy of Sciences* **119**, (2022).
49. Widjaja, A. A. *et al.* Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. *Nature* **632**, 157–165 (2024).
50. Lehallier, B. *et al.* Undulating changes in human plasma proteome profiles across the lifespan. *Nat Med* **25**, 1843–1850 (2019).
51. Lehallier, B., Shokhirev, M. N., Wyss-Coray, T. & Johnson, A. A. Data mining of human plasma proteins generates a multitude of highly predictive aging clocks that reflect different aspects of aging. *Aging Cell* **19**, (2020).
52. Argentieri, M. A. *et al.* Proteomic aging clock predicts mortality and risk of common age-related diseases in diverse populations. *Nat Med* **30**, 2450–2460 (2024).
53. Hällqvist, J. *et al.* Plasma proteomics identify biomarkers predicting Parkinson's disease up to 7 years before symptom onset. *Nat Commun* **15**, 4759 (2024).
54. Horvath, S. & Raj, K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet* **19**, 371–384 (2018).
55. Crimmins, E. M., Klopack, E. T. & Kim, J. K. Generations of epigenetic clocks and their links to socioeconomic status in the Health and Retirement Study. *Epigenomics* **16**, 1031–1042 (2024).
56. Yusipov, I., Kalyakulina, A., Trukhanov, A., Franceschi, C. & Ivanchenko, M. Map of epigenetic age acceleration: A worldwide analysis. *Ageing Res Rev* **100**, 102418 (2024).
57. Zaghlool, S. B. *et al.* Epigenetics meets proteomics in an epigenome-wide association study with circulating blood plasma protein traits. *Nat Commun* **11**, 15 (2020).
58. Stevenson, A. J. *et al.* Characterisation of an inflammation-related epigenetic score and its association with cognitive ability. *Clin Epigenetics* **12**, 113 (2020).
59. Stevenson, A. J. *et al.* Creating and Validating a DNA Methylation-Based Proxy for Interleukin-6. *The Journals of Gerontology: Series A* **76**, 2284–2292 (2021).
60. Gadd, D. A. *et al.* Correction: Epigenetic scores for the circulating proteome as tools for disease prediction. *Elife* **12**, (2023).
61. Bernabeu, E. *et al.* Refining epigenetic prediction of chronological and biological age. *Genome Med* **15**, 12 (2023).
62. Ahadi, S. *et al.* Personal aging markers and ageotypes revealed by deep longitudinal profiling. *Nat Med* **26**, 83–90 (2020).
63. Prattichizzo, F. *et al.* Organ-specific biological clocks: Ageotyping for personalized anti-aging medicine. *Ageing Res Rev* **96**, 102253 (2024).
64. Jung, A. M. *et al.* Associations Between Epigenetic Age Acceleration and microRNA Expression Among U.S. Firefighters. *Epigenet Insights* **16**, (2023).
65. Salignon, J. *et al.* Age prediction from human blood plasma using proteomic and small RNA data: a comparative analysis. *Aging* (2023) doi:10.18632/aging.204787.
66. Roig-Genoves, J. V., García-Giménez, J. L. & Mena-Molla, S. A miRNA-based epigenetic molecular clock for biological skin-age prediction. *Arch Dermatol Res* **316**, 326 (2024).
67. Martucci, M. *et al.* Mediterranean diet and inflammaging within the hormesis paradigm. *Nutr Rev* **75**, 442–455 (2017).

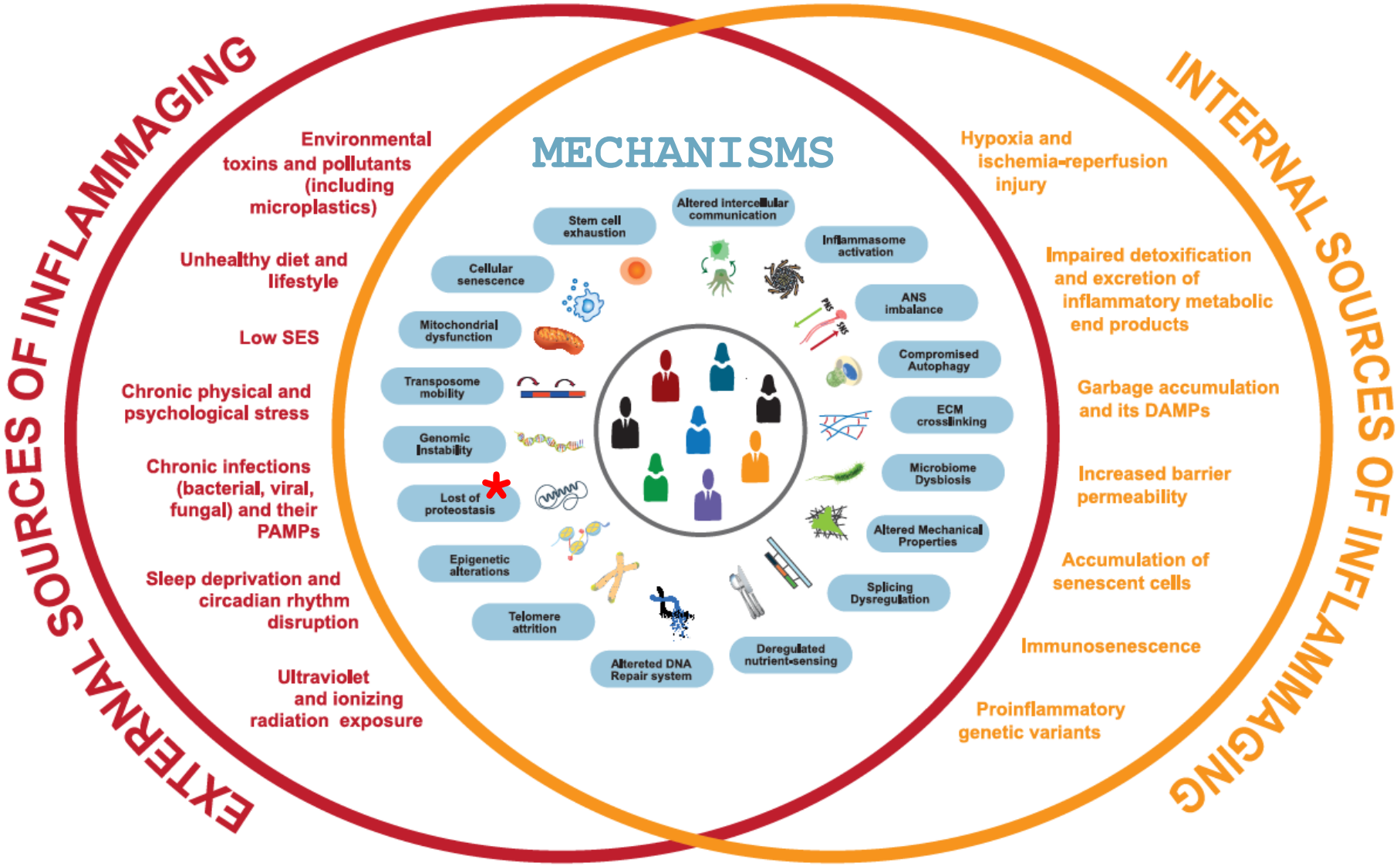
68. Izquierdo, M. *et al.* International Exercise Recommendations in Older Adults (ICFSR): Expert Consensus Guidelines. *J Nutr Health Aging* **25**, 824–853 (2021).
69. Gensous, N. *et al.* One-year Mediterranean diet promotes epigenetic rejuvenation with country- and sex-specific effects: a pilot study from the NU-AGE project. *Geroscience* **42**, 687–701 (2020).
70. Gialluisi, A. *et al.* Epidemiological and genetic overlap among biological aging clocks: New challenges in biogerontology. *Ageing Res Rev* **72**, 101502 (2021).
71. Ghosh, T. S. *et al.* 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. *Gut* **69**, 1218–1228 (2020).
72. Moskalev, A. *et al.* Targeting aging mechanisms: pharmacological perspectives. *Trends in Endocrinology & Metabolism* **33**, 266–280 (2022).
73. Di Giosia, P. *et al.* The role of nutrition in inflammaging. *Ageing Res Rev* **77**, 101596 (2022).
74. Casas, R. *et al.* The Effects of the Mediterranean Diet on Biomarkers of Vascular Wall Inflammation and Plaque Vulnerability in Subjects with High Risk for Cardiovascular Disease. A Randomized Trial. *PLoS One* **9**, e100084 (2014).
75. Firth, J. *et al.* The Effects of Dietary Improvement on Symptoms of Depression and Anxiety: A Meta-Analysis of Randomized Controlled Trials. *Psychosom Med* **81**, 265–280 (2019).
76. Longo, V. D. *et al.* Interventions to Slow Aging in Humans: Are We Ready? *Aging Cell* **14**, 497–510 (2015).
77. de Cabo, R. & Mattson, M. P. Effects of Intermittent Fasting on Health, Aging, and Disease. *New England Journal of Medicine* **381**, 2541–2551 (2019).
78. Mercken, E. M. *et al.* Calorie restriction in humans inhibits the <scp>PI</scp> 3 <scp>K</scp> / <scp>AKT</scp> pathway and induces a younger transcription profile. *Aging Cell* **12**, 645–651 (2013).
79. Kittana, M., Apostolopoulos, V. & Stojanovska, L. The Role of Calorie Restriction in Modifying the Ageing Process through the Regulation of SIRT1 Expression. in 173–181 (2024). doi:10.1007/978-3-031-66768-8_8.
80. Trichopoulou, A. *et al.* Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. *BMC Med* **12**, 112 (2014).
81. Fadnes, L. T., Økland, J.-M., Haaland, Ø. A. & Johansson, K. A. Estimating impact of food choices on life expectancy: A modeling study. *PLoS Med* **19**, e1003889 (2022).
82. Kahleova, H., Levin, S. & Barnard, N. Cardio-Metabolic Benefits of Plant-Based Diets. *Nutrients* **9**, 848 (2017).
83. Casas, R. *et al.* Long-Term Immunomodulatory Effects of a Mediterranean Diet in Adults at High Risk of Cardiovascular Disease in the PREvención con DIeta MEDiterránea (PREDIMED) Randomized Controlled Trial. *J Nutr* **146**, 1684–1693 (2016).
84. Margină, D. *et al.* Chronic Inflammation in the Context of Everyday Life: Dietary Changes as Mitigating Factors. *Int J Environ Res Public Health* **17**, 4135 (2020).
85. Berendsen, A. *et al.* A parallel randomized trial on the effect of a healthful diet on inflammageing and its consequences in European elderly people: Design of the NU-AGE dietary intervention study. *Mech Ageing Dev* **134**, 523–530 (2013).
86. Santoro, A. *et al.* Combating inflammaging through a Mediterranean whole diet approach: The NU-AGE project's conceptual framework and design. *Mech Ageing Dev* **136–137**, 3–13 (2014).
87. Ostan, R. *et al.* Cross-Sectional Analysis of the Correlation Between Daily Nutrient Intake Assessed by 7-Day Food Records and Biomarkers of Dietary Intake Among Participants of the NU-AGE Study. *Front Physiol* **9**, (2018).
88. Berendsen, A. A. M. *et al.* Changes in Dietary Intake and Adherence to the NU-AGE Diet Following a One-Year Dietary Intervention among European Older Adults—Results of the NU-AGE Randomized Trial. *Nutrients* **10**, 1905 (2018).

89. Marseglia, A. *et al.* Effect of the NU-AGE Diet on Cognitive Functioning in Older Adults: A Randomized Controlled Trial. *Front Physiol* **9**, (2018).
90. Jennings, A. *et al.* A Mediterranean-like dietary pattern with vitamin D3 (10 µg/d) supplements reduced the rate of bone loss in older Europeans with osteoporosis at baseline: results of a 1-y randomized controlled trial. *Am J Clin Nutr* **108**, 633–640 (2018).
91. Maijo, M. *et al.* One-Year Consumption of a Mediterranean-Like Dietary Pattern With Vitamin D3 Supplements Induced Small Scale but Extensive Changes of Immune Cell Phenotype, Co-receptor Expression and Innate Immune Responses in Healthy Elderly Subjects: Results From the United Kingdom Arm of the NU-AGE Trial. *Front Physiol* **9**, (2018).
92. van Soest, A. P. M. *et al.* Associations between Pro- and Anti-Inflammatory Gastro-Intestinal Microbiota, Diet, and Cognitive Functioning in Dutch Healthy Older Adults: The NU-AGE Study. *Nutrients* **12**, 3471 (2020).
93. Biagi, E. *et al.* Through ageing, and beyond: Gut microbiota and inflammatory status in seniors and centenarians. *PLoS One* **5**, (2010).
94. Golshany, H. *et al.* The gut microbiome across the lifespan: how diet modulates our microbial ecosystem from infancy to the elderly. *Int J Food Sci Nutr* 1–27 (2024) doi:10.1080/09637486.2024.2437472.
95. Lazou-Ahrén, I. *et al.* Probiotic-Reduced Inflammaging in Older Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. *Probiotics Antimicrob Proteins* (2024) doi:10.1007/s12602-024-10310-7.
96. Roberts, J. L. *et al. Bifidobacterium longum* supplementation improves age-related delays in fracture repair. *Aging Cell* **22**, (2023).
97. Wang, X., Wang, T., Zhang, Q., Xu, L. & Xiao, X. Dietary Supplementation with Inulin Modulates the Gut Microbiota and Improves Insulin Sensitivity in Prediabetes. *Int J Endocrinol* **2021**, 1–8 (2021).
98. Claesson, M. J. *et al.* Gut microbiota composition correlates with diet and health in the elderly. *Nature* **488**, 178–184 (2012).
99. Liu, T. *et al.* Hesperidin and Fecal Microbiota Transplantation Modulate the Composition of the Gut Microbiota and Reduce Obesity in High Fat Diet Mice. *Diabetes, Metabolic Syndrome and Obesity* **Volume 17**, 3643–3656 (2024).
100. Novelle, M. G., Naranjo-Martínez, B., López-Cánovas, J. L. & Díaz-Ruiz, A. Fecal microbiota transplantation, a tool to transfer healthy longevity. *Ageing Res Rev* **103**, 102585 (2025).
101. Santoro, A. *et al.* A Cross-Sectional Analysis of Body Composition Among Healthy Elderly From the European NU-AGE Study: Sex and Country Specific Features. *Front Physiol* **9**, (2018).
102. Santoro, A. *et al.* Gender-specific association of body composition with inflammatory and adipose-related markers in healthy elderly Europeans from the NU-AGE study. *Eur Radiol* **29**, 4968–4979 (2019).
103. Ribeiro, I. S. *et al.* Regular physical activity reduces the effects of inflammaging in diabetic and hypertensive men. *Exp Gerontol* **155**, 111558 (2021).
104. Antuña, E. *et al.* Inflammaging: Implications in Sarcopenia. *Int J Mol Sci* **23**, 15039 (2022).
105. Izquierdo, M. *et al.* Global consensus on optimal exercise recommendations for enhancing healthy longevity in older adults (ICFSR). *J Nutr Health Aging* **29**, 100401 (2025).
106. Duggal, N. A., Pollock, R. D., Lazarus, N. R., Harridge, S. & Lord, J. M. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. *Aging Cell* **17**, (2018).
107. Moradell, A., Casajús, J. A., Moreno, L. A. & Vicente-Rodríguez, G. Perspectives on Diet and Exercise Interaction for Healthy Aging: Opportunities to Reduce Malnutrition Risk and Optimize Fitness. *Nutrients* **17**, 596 (2025).

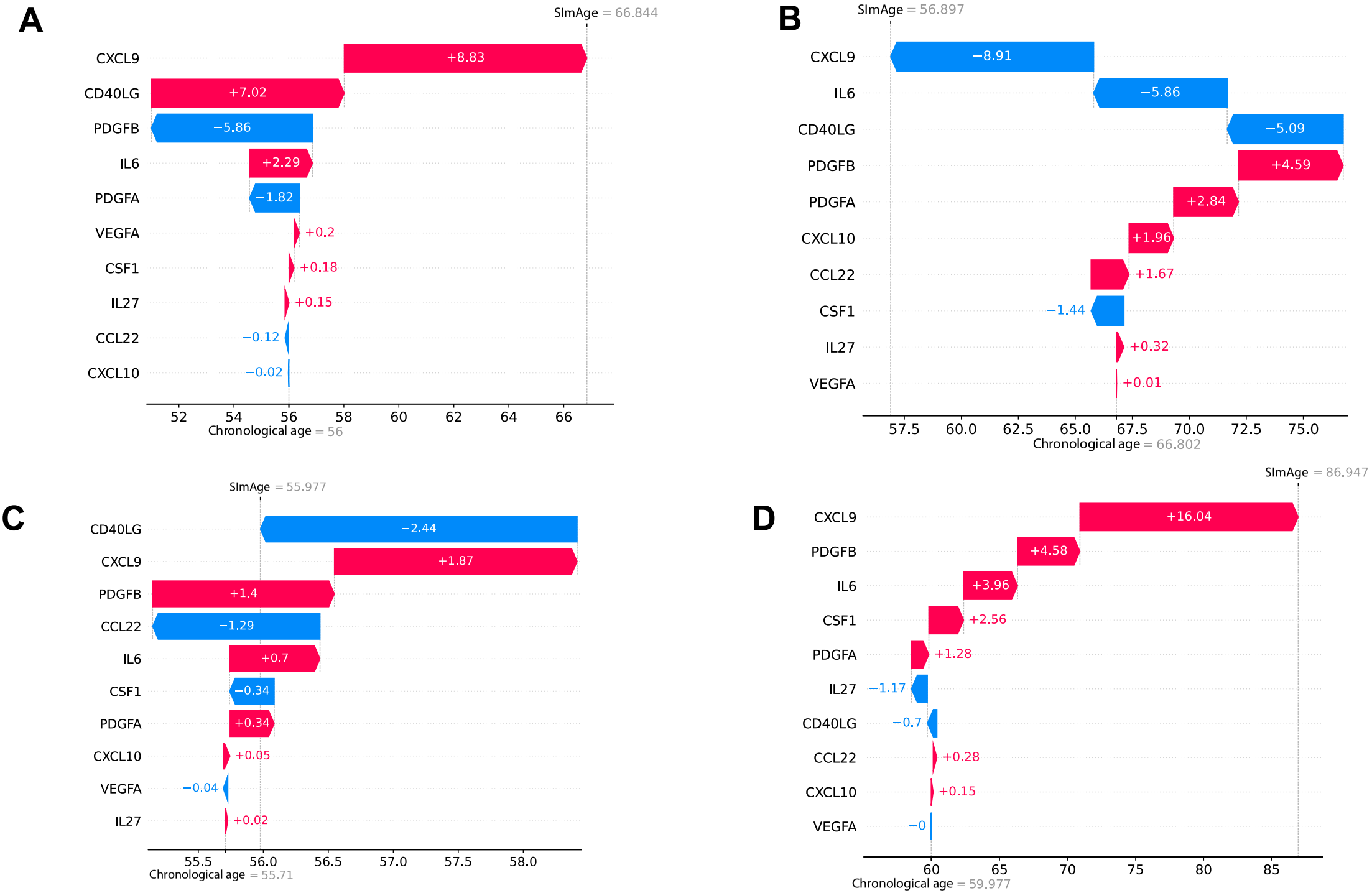
108. Petersen, A. M. W. & Pedersen, B. K. The anti-inflammatory effect of exercise. *J Appl Physiol* **98**, 1154–1162 (2005).
109. Docherty, S. *et al.* The effect of exercise on cytokines: implications for musculoskeletal health: a narrative review. *BMC Sports Sci Med Rehabil* **14**, 5 (2022).
110. Farley, M. J. *et al.* Interleukin-15 and high-intensity exercise: relationship with inflammation, body composition and fitness in cancer survivors. *J Physiol* **602**, 5203–5215 (2024).
111. Ringleb, M. *et al.* Beyond muscles: Investigating immunoregulatory myokines in acute resistance exercise – A systematic review and meta-analysis. *The FASEB Journal* **38**, (2024).
112. Forcina, L., Franceschi, C. & Musarò, A. The hormetic and hermetic role of IL-6. *Ageing Res Rev* **80**, 101697 (2022).
113. Nilsson, M. I. *et al.* Lifelong aerobic exercise protects against inflammaging and cancer. *PLoS One* **14**, e0210863 (2019).
114. Hayes, L. D., Herbert, P., Sculthorpe, N. F. & Grace, F. M. Short-Term and Lifelong Exercise Training Lowers Inflammatory Mediators in Older Men. *Front Physiol* **12**, (2021).
115. Ferreira, R. Z. *et al.* Effects of strength training with free weights and elastic resistance in older adults: A randomised clinical study. *J Bodyw Mov Ther* **41**, 48–55 (2025).
116. Sallam, N. & Laher, I. Exercise Modulates Oxidative Stress and Inflammation in Aging and Cardiovascular Diseases. *Oxid Med Cell Longev* **2016**, (2016).
117. Kolnes, K. J., Petersen, M. H., Lien-Iversen, T., Højlund, K. & Jensen, J. Effect of Exercise Training on Fat Loss—Energetic Perspectives and the Role of Improved Adipose Tissue Function and Body Fat Distribution. *Front Physiol* **12**, (2021).
118. COUVERT, A. *et al.* Effects of a Cycling versus Running HIIT Program on Fat Mass Loss and Gut Microbiota Composition in Men with Overweight/Obesity. *Med Sci Sports Exerc* **56**, 839–850 (2024).
119. Lavin, K. M. *et al.* Effects of aging and lifelong aerobic exercise on basal and exercise-induced inflammation in women. *J Appl Physiol* **129**, 1493–1504 (2020).
120. Perkins, R. K. *et al.* Effects of aging and lifelong aerobic exercise on expression of innate immune components in skeletal muscle of women. *J Appl Physiol* **136**, 482–491 (2024).
121. Saponaro, F. *et al.* Myokines and Microbiota: New Perspectives in the Endocrine Muscle–Gut Axis. *Nutrients* **16**, 4032 (2024).
122. Tavella, T. *et al.* Elevated gut microbiome abundance of *Christensenellaceae, Porphyromonadaceae and Rikenellaceae* is associated with reduced visceral adipose tissue and healthier metabolic profile in Italian elderly. *Gut Microbes* **13**, (2021).
123. Nejati Bervanlou, R., Hlaváčová, N., Figueiredo, V. C., Attarzadeh Hosseini, S. R. & Motahari Rad, M. The Impact of Exercise and Protein Intake on Inflammaging: A Meta-Analysis and Systematic Review of Randomized Controlled Trials. *Nutr Rev* (2024) doi:10.1093/nutrit/nuae169.
124. Mantzorou, M. *et al.* Mediterranean Diet Adherence Is Associated with Favorable Health-Related Quality of Life, Physical Activity, and Sleep Quality in a Community-Dwelling Greek Older Population. *Antioxidants* **12**, 983 (2023).
125. Piber, D. *et al.* Sleep disturbance and activation of cellular and transcriptional mechanisms of inflammation in older adults. *Brain Behav Immun* **106**, 67–75 (2022).
126. Singh, K. K. *et al.* Sleep and Immune System Crosstalk: Implications for Inflammatory Homeostasis and Disease Pathogenesis. *Ann Neurosci* (2024) doi:10.1177/09727531241275347.
127. Rim, C., You, M.-J., Nahm, M. & Kwon, M.-S. Emerging role of senescent microglia in brain aging-related neurodegenerative diseases. *Transl Neurodegener* **13**, 10 (2024).
128. Gudkov, S. V. *et al.* An emerging role of astrocytes in aging/neuroinflammation and gut-brain axis with consequences on sleep and sleep disorders. *Ageing Res Rev* **83**, 101775 (2023).

129. Xiong, Y. *et al.* Advances in the study of the glymphatic system and aging. *CNS Neurosci Ther* **30**, (2024).
130. Gordleeva, S., Kanakov, O., Ivanchenko, M., Zaikin, A. & Franceschi, C. Brain aging and garbage cleaning. *Semin Immunopathol* **42**, 647–665 (2020).
131. Krivonosov, M. I. *et al.* Correction to: A new cognitive clock matching phenotypic and epigenetic ages. *Transl Psychiatry* **12**, 452 (2022).
132. Brewster, G. S., Riegel, B. & Gehrman, P. R. Insomnia in the Older Adult. *Sleep Med Clin* **17**, 233–239 (2022).
133. Barone, M. *et al.* Towards a personalized prediction, prevention and therapy of insomnia: gut microbiota profile can discriminate between paradoxical and objective insomnia in post-menopausal women. *EPMA Journal* **15**, 471–489 (2024).
134. Ratiner, K., Ciocan, D., Abdeen, S. K. & Elinav, E. Utilization of the microbiome in personalized medicine. *Nat Rev Microbiol* **22**, 291–308 (2024).
135. Moskalev, A. *et al.* Developing criteria for evaluation of geroprotectors as a key stage toward translation to the clinic. *Aging Cell* **15**, 407–415 (2016).
136. He, C. *et al.* Enhanced Longevity by Ibuprofen, Conserved in Multiple Species, Occurs in Yeast through Inhibition of Tryptophan Import. *PLoS Genet* **10**, e1004860 (2014).
137. Danilov, A. *et al.* Influence of non-steroidal anti-inflammatory drugs on *Drosophila melanogaster* longevity. *Oncotarget* **6**, 19428–19444 (2015).
138. Rivero-Segura, N. A. *et al.* Exploring the Geroprotective Potential of Nutraceuticals. *Nutrients* **16**, 2835 (2024).
139. Proshkina, E. *et al.* Polyphenols as Potential Geroprotectors. *Antioxid Redox Signal* **40**, 564–593 (2024).
140. Proshkina, E. *et al.* Terpenoids as Potential Geroprotectors. *Antioxidants* **9**, 529 (2020).
141. Landsberger, T., Amit, I. & Alon, U. Geroprotective interventions converge on gene expression programs of reduced inflammation and restored fatty acid metabolism. *Geroscience* **46**, 1627–1639 (2023).
142. Justice, J. N. *et al.* A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup. *Geroscience* **40**, 419–436 (2018).
143. Wang, J. *et al.* Effects of metformin treatment on serum levels of C-reactive protein and interleukin-6 in women with polycystic ovary syndrome. *Medicine* **96**, e8183 (2017).
144. Moskalev, A. A. & Shaposhnikov, M. V. Pharmacological Inhibition of Phosphoinositide 3 and TOR Kinases Improves Survival of *Drosophila melanogaster*. *Rejuvenation Res* **13**, 246–247 (2010).
145. Harrison, D. E. *et al.* Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* **460**, 392–395 (2009).
146. Konopka, A. R. *et al.* Blazing a trail for the clinical use of rapamycin as a geroprotecTOR. *Geroscience* **45**, 2769–2783 (2023).
147. Mandrioli, J. *et al.* Randomized, double-blind, placebo-controlled trial of rapamycin in amyotrophic lateral sclerosis. *Nat Commun* **14**, 4970 (2023).
148. Niechcial, A. *et al.* Spermidine Ameliorates Colitis via Induction of Anti-Inflammatory Macrophages and Prevention of Intestinal Dysbiosis. *J Crohns Colitis* **17**, 1489–1503 (2023).
149. Ji, S. *et al.* Cellular rejuvenation: molecular mechanisms and potential therapeutic interventions for diseases. *Signal Transduct Target Ther* **8**, 116 (2023).
150. Ma, S. *et al.* Heterochronic parabiosis induces stem cell revitalization and systemic rejuvenation across aged tissues. *Cell Stem Cell* **29**, 990-1005.e10 (2022).
151. Robbins, P. D. *et al.* Senolytic Drugs: Reducing Senescent Cell Viability to Extend Health Span. *Annu Rev Pharmacol Toxicol* **61**, 779–803 (2021).

152. Krzystyniak, A. *et al.* Combination of dasatinib and quercetin improves cognitive abilities in aged male Wistar rats, alleviates inflammation and changes hippocampal synaptic plasticity and histone H3 methylation profile. *Aging* **14**, 572–595 (2022).
153. Farheen, S. *et al.* Patho-Physiology of Aging and Immune-Senescence: Possible Correlates With Comorbidity and Mortality in Middle-Aged and Old COVID-19 Patients. *Frontiers in Aging* **2**, (2021).
154. Hernández-Silva, D. *et al.* Senescence-Independent Anti-Inflammatory Activity of the Senolytic Drugs Dasatinib, Navitoclax, and Venetoclax in Zebrafish Models of Chronic Inflammation. *Int J Mol Sci* **23**, 10468 (2022).
155. Kirkland, J. L. & Tchkonia, T. Senolytic drugs: from discovery to translation. *J Intern Med* **288**, 518–536 (2020).
156. Hickson, L. J. *et al.* Corrigendum to 'Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease' EBioMedicine 47 (2019) 446–456. *EBioMedicine* **52**, 102595 (2020).
157. Carpenter, V. J., Saleh, T. & Gewirtz, D. A. Senolytics for Cancer Therapy: Is All that Glitters Really Gold? *Cancers (Basel)* **13**, 723 (2021).
158. Batista, M. A. *et al.* Inflammaging in Endemic Areas for Infectious Diseases. *Front Immunol* **11**, (2020).
159. Franck, M. *et al.* Nat. Aging, in press. *Nat Aging* (2025).
160. Nie, C. *et al.* Distinct biological ages of organs and systems identified from a multi-omics study. *Cell Rep* **38**, 110459 (2022).
161. Bracken, O. V., De Maeyer, R. P. H. & Akbar, A. N. Enhancing immunity during ageing by targeting interactions within the tissue environment. *Nat Rev Drug Discov* **24**, 300–315 (2025).
162. Andonian, B. J. *et al.* Inflammation and aging-related disease: A transdisciplinary inflammaging framework. *Geroscience* (2024) doi:10.1007/s11357-024-01364-0.
163. Capri, M. *et al.* Long-term human spaceflight and inflammaging: Does it promote aging? *Ageing Res Rev* **87**, 101909 (2023).
164. Olivieri, F. *et al.* Heart rate variability and autonomic nervous system imbalance: Potential biomarkers and detectable hallmarks of aging and inflammaging. *Ageing Res Rev* **101**, 102521 (2024).
165. Kalyakulina, A. *et al.* Small immunological clocks identified by deep learning and gradient boosting. *Front Immunol* **14**, (2023).
166. Wang, J. *et al.* Effects of metformin treatment on serum levels of C-reactive protein and interleukin-6 in women with polycystic ovary syndrome. *Medicine* **96**, e8183 (2017).
167. Mohammadian, A. *et al.* The effect of acarbose on inflammatory cytokines and adipokines in adults: a systematic review and meta-analysis of randomized clinical trials. *Inflammopharmacology* **32**, 355–376 (2024).
168. Islam, M. T. *et al.* Senolytic drugs, dasatinib and quercetin, attenuate adipose tissue inflammation, and ameliorate metabolic function in old age. *Aging Cell* **22**, (2023).
169. Nauta, M. *et al.* From Anecdotal Evidence to Quantitative Evaluation Methods: A Systematic Review on Evaluating Explainable AI. *ACM Comput Surv* **55**, 1–42 (2023).



* Change with «Loss of…»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Chronological age = 56
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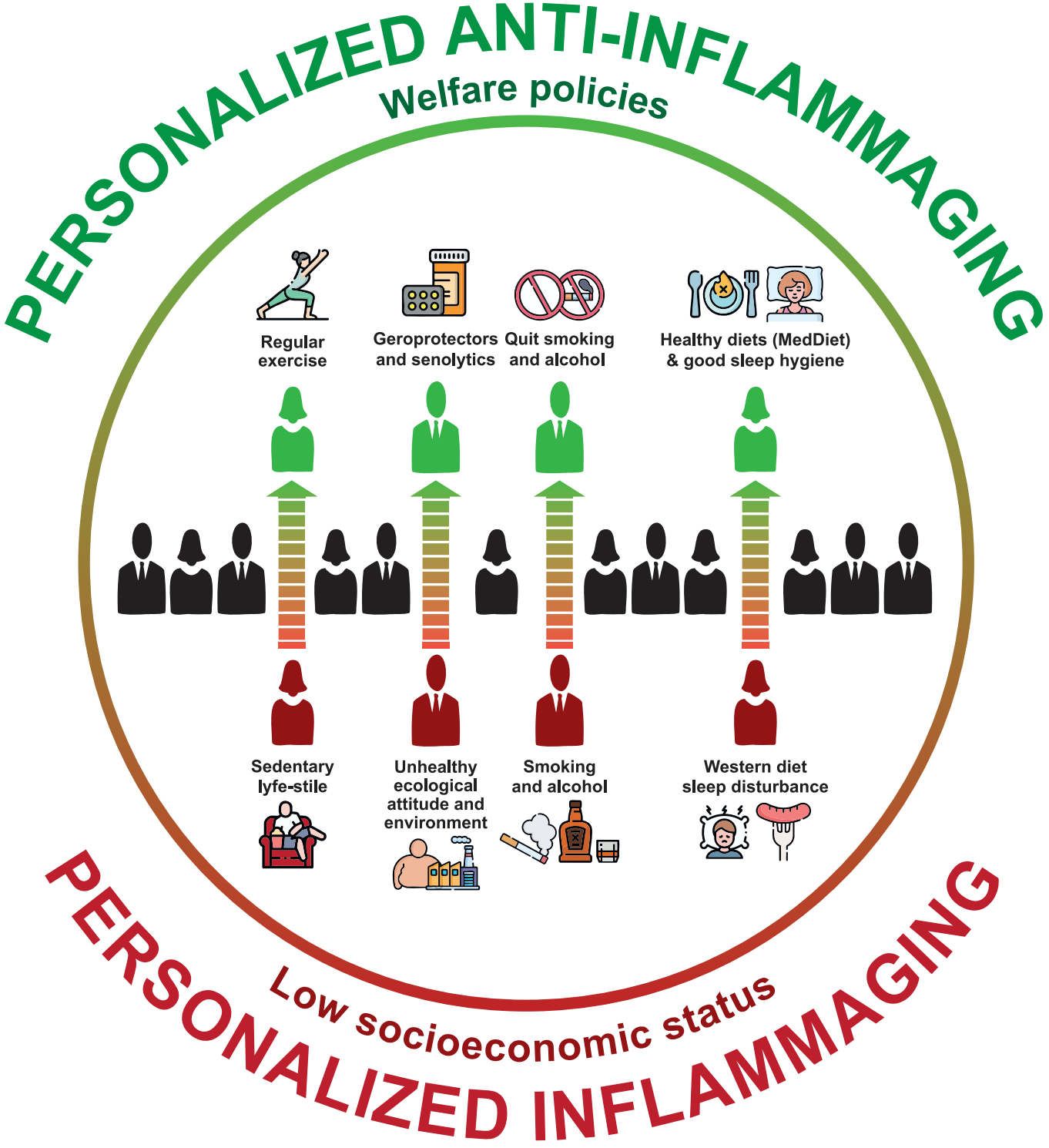
PERSONALIZED ANTI-INFLAMMAGING
Welfare policies
Regular exercise
Geroprotectors and senolytics
Quit smoking and alcohol
Healthy diets (MedDiet) & good sleep hygiene
Sedentary lyfe-stile
Unhealthy ecological attitude and environment
Smoking and alcohol
Western diet sleep disturbance
Low socioeconomic status
PERSONALIZED INFLAMMAGING

PERSONALIZED EXPLAINABLE INFLAMMAGING CLOCKS