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Perspective

InflammAging and Human Diversity: Expanding Horizons in Age-Related Chronic Disease

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ABSTRACT: InflammAging (IA) is a sterile, low-grade systemic inflammation characterizing human aging. This chronic inflammatory state, combining "inflammation" and "aging", drives the aging trajectory and associated pathology even in the absence of acute clinical signs. IA is a key etiological factor for numerous age-associated diseases, including neurodegeneration (e.g., Alzheimer's disease), cardiovascular disorders, diabetes, sarcopenia, cancer, frailty, and multimorbidity, by exacerbating tissue/organ damage and impairing endogenous repair. Historically viewed as a universal hallmark of aging, this concept is now being refined. Current research highlights how human diversity—encompassing genetic, ethnic, gender, sex, environmental, socioeconomic, and lifestyle variations—could modulate the expression and severity of IA. This interplay, as emerging hypotheses, represents a new horizon in gerontology and chronic diseases, necessitating a potential paradigm shift from a one-size-fits-all model to personalized, population-specific approaches. This evolving nuanced understanding might be crucial for the successful implementation of precision medicine and for advancing global health strategies targeting age-related chronic diseases.

Keywords: Aging, inflammation, age-related chronic diseases, human diversity, personalized medicine.

INTRODUCTION

The term InflammAging (IA) refers to the gradual inflammatory event that develops with advancing age. Coined in 2000 by Claudio Franceschi and colleagues, it describes "a state where pro-inflammatory markers—such as cytokines like interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP)—accumulate over time without overt infection or injury" [1]. Unlike acute, protective inflammation, IA is a prolonged inflammatory process that significantly increases the risk of chronic disease and injury. This phenomenon is deeply integrated with the established "Hallmarks of Aging" [2, 3], including primary hallmarks (e.g., telomere attrition and genome instability), antagonistic hallmarks (e.g., deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence), and integrative hallmarks (e.g., stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis) (Fig. 1). IA is driven by a complex network of cooperative molecular mechanisms including the activation of key immune and inflammatory pathways (e.g., toll-like receptors (TLRs), nuclear factor kappa B (NF-κB), and nod-like receptor family pyrin domain-containing 3 (NLRP3)-dependent inflammasome), cell death processes, imbalances in ions (e.g., reactive oxygen species (ROS)) and metabolites (e.g., NADH (reduced nicotinamide adenine dinucleotide) / NAD^+ (nicotinamide adenine dinucleotide)), anomalous gene/epigenetic expression flux (e.g., pro-inflammatory pre-microRNAs (miRNAs)/miRNAs, DNA methylation, histone modifications, noncoding RNA species, and transposable elements), and the accumulation of intrinsic damage-associated molecular patterns (DAMPs) and extrinsic pathogen-associated molecular patterns (PAMPs) resulting from mitochondrial leakage/breakage (Fig. 1).

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Furthermore, IA is modulated by a diversity of exogenous (e.g., diet, lifestyle, environmental stress, infections, and socioeconomic status) and endogenous (e.g., genetics, cellular detoxification, and cellular senescence) factors, creating a complex scenario of internal and external interactions that ultimately regulate IA-linked phenotypic progression and influence the likelihood of enjoying a long and healthy life (Fig. 1) [3–8].

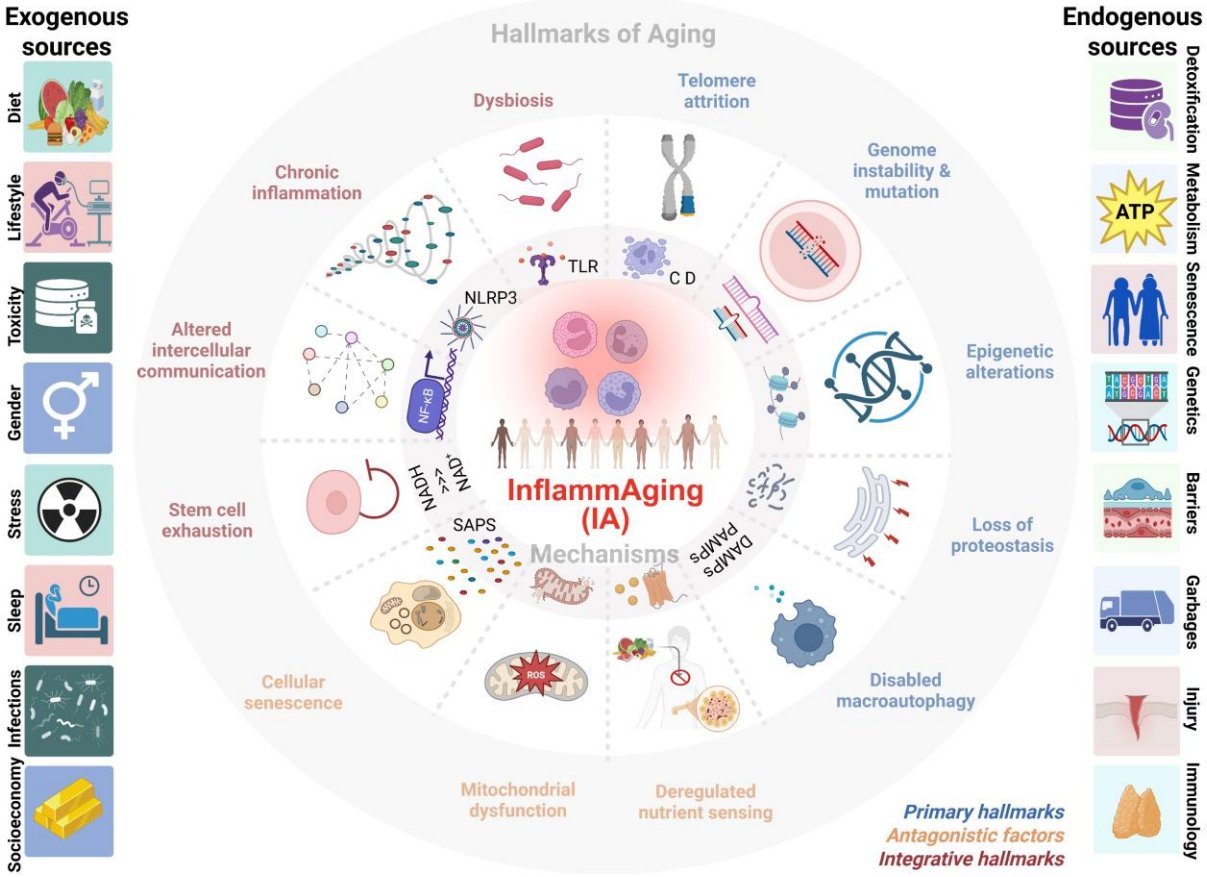

Figure 1. Crosstalk between inflammaging, aging-associated mechanisms and hallmarks. A schematic representation of the main exogenous and endogenous sources that contribute to inflammaging (IA) and their link to the hallmarks of aging (primary hallmarks (in blue), antagonistic factors (in orange), and integrative hallmarks (in red)), and some main mechanisms and signaling pathways that underlie personalized IA. *Abbreviations:* CD, cell death; DAMPs, damage-associated molecular patterns; NADH/NAD$^+$, ratio between reduced and oxidized nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP, nod-like receptor family pyrin domain-containing 3 (NLRP3)-dependent inflammasome; PAMPs, pathogen-associated molecular patterns; SASP, senescence-associated secreted phenotype; TLR, toll-like receptor. *This figure was created with BioRender.com.*

IA is classically correlated with a wide spectrum of age-related chronic diseases (ARCDs) (Fig. 2), including neurodegenerative disorders (e.g., Alzheimer's and Parkinson's diseases), cardiovascular disease (e.g., atherosclerosis and cerebrovascular diseases), neurological disorders, macular degeneration, amyotrophic lateral sclerosis and multiple sclerosis, musculoskeletal disorders (e.g., sarcopenia, myopathies, frailty, osteoporosis, and osteoarthritis), metabolic abnormalities (e.g., type 2 diabetes), and many types of cancer. These conditions, many of which have acute consequences, contribute to high rates of morbidity and mortality (Fig. 2) [9–11]. IA can exacerbate ARCDs by accelerating their progression through elevated levels of pro-inflammatory cytokines and interleukins, which disrupt tissue/organ homeostasis. This disruption is compounded by the promotion of oxidative damage and fibrosis, and the deterioration of endogenous repair capacity, which in turn facilitates the accumulation of genetic errors. Given this profound involvement in pathogenesis, IA is a key risk factor requiring specific/targeted preventive, diagnostic, and therapeutic interventions, which act through complex and multidirectional interactions with the hallmarks of aging and their shared mechanisms [9–11]. This leads to a critically unresolved question: is IA a universal biomarker for both aging hallmarks and ARCDs, or is it a context-specific phenomenon that may be absent or minimal in certain global populations?

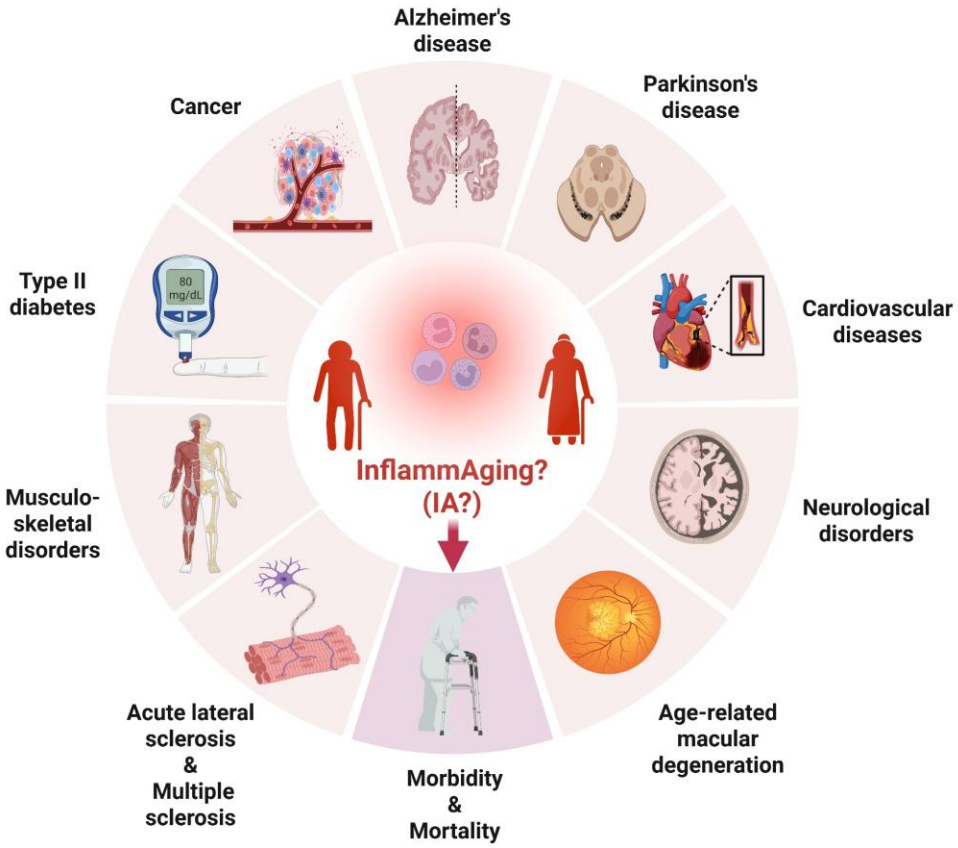

Figure 2. Heads or tails of age-related chronic diseases, inflammaging, and comorbidities. Main age-related chronic diseases (ARCDs) are associated with inflammaging (IA) and comorbidities. Interplay between IA and ARCDs can lead to morbidity and mortality. *This figure was created with BioRender.com.*

Human diversity and its impact on IA

Previous reports have provided evidence that IA does not manifest itself uniformly across all human populations [12, 13]. Human diversity influences IA, revealing it as a dynamic and context-dependent process [8, 14, 15], although this framing should be cautions not to dismiss the core relevance of IA in aging biology universally. This diversity is rooted in endogenous dimensions including genetic polymorphisms (e.g., IL-6 or TNF-α genes) that explain some inter-individual differences, although heritability accounts for only ~20-30% of IA variation. Epigenetic clocks, such as DNA methylation-based measures, show accelerated aging in individuals with high IA, and gene-environment interactions, such as cytomegalovirus infection status, further modulate this expression [16]. Ethnic and racial differences highlight this non-universal pattern [15]. For example, U.S. data from the "Health and Retirement Study" indicate that minoritized racial/ethnic groups (e.g., Black and Hispanic older adults) often exhibit higher levels of specific inflammatory markers (e.g., IL-6 and tumor necrosis factor receptor 1 (TNFR1)) compared with non-Hispanic Whites, reflecting the cumulative impact of socioeconomic stressors, discrimination, and adversity. Importantly, these differences are not uniform across all markers; for instance, CRP levels may be similar while transforming growth factor beta (TGF-β) levels differ, underscoring the need for multimarker assessments.

Population and lifestyle variations significantly enhance this trend. A groundbreaking 2025 study [15] analyzed cytokine profiles across four cohorts: industrialized groups (the Italian InCHIANTI cohort and the "Singapore Longitudinal Aging Study" dataset) *versus* non-industrialized indigenous groups (the Tsimane in the Bolivian Amazon and the Orang Asli in Malaysia). In industrialized cohorts, an IA pathway (e.g., elevated IL-6, and interleukin-1 alpha receptor (IL-1Rα)) strongly correlated with both age and chronic diseases such as kidney disease. Conversely, the indigenous groups showed no age-related increase in this IA pathway; their inflammation was primarily infection-driven (due to parasites and bacteria) and largely unrelated to chronological age or chronic disease. These findings potentially hypothesize that IA might be a Western, Educated, Industrialized, Rich, and Democratic

phenomenon ("WEIRD"), intrinsically linked to lifestyle factors, such as sedentary behavior, high-fat diets, and low pathogen exposure, rather than aging *per se*. Factors like high physical activity, low-fat diets, and chronic pathogen-burden environments appear to be protective. This emerging perspective emphasizes that IA may be a "norm of reaction"—a phenotype that varies based on the interplay between genotype and environment—and its expression is determined by exogenous factors (i.e., environment, and lifestyle) as much as endogenous factors (i.e., genetics and chronological age), with lifetime exposures defining individual "immunobiography". This term refers to the unique immune biographies, lifetime record of an individual's immune system experiences, representing the sum of all exposures, infections, vaccinations, and environmental interactions an organism has encountered. This concept emphasizes that immunity is not static, but rather a dynamic, evolving, and highly individualized record shaped by age, lifestyle, and geography (Fig. 1) [15].

In this regard, the study by Franck et al. (2025) [15] should be interpreted not as a refutation of the IA concept, but as a key empirical validation that confirms—through harmonized biomarkers and direct population comparisons—a heterogeneity long suggested by evolutionary immunology, biological anthropology, and comparative epidemiology. Therefore, studies on the Tsimane and Orang Asli populations as evidence that AI is not universal require broader meta-analyses or systematic reviews to avoid overgeneralization based on a few case studies.

Expanding horizons in ARCDs: implications for research and interventions

Recognizing that IA is an eco-evolutionarily shaped and context-dependent process, influenced profoundly by human diversity, represents a major paradigm shift in geroscience. Traditional models that assumed that IA was universal are now challenged by recent studies [11, 17–19]. This new emerging approach potentially opens critical avenues for future research and intervention (Fig. 1).

The integration of human diversity into IA research defines new goals for precision gerosciences and personalized medicine/geromedicine [15–20]. I) *Precision personalized medicine.* Treatments can be precisely tailored based on genetic and environmental profiles to reduce disease burden. II) *Global health insights.* Understanding why certain populations age "healthier" (e.g., those in non-industrialized settings with low IA) could inform policies in industrialized nations. III) *Future research.* Focusing on longitudinal studies within underrepresented global groups to map diverse IA trajectories and identify modifiable factors [15, 18, 20–22].

This paradigm shift necessitates new methods and an emphasis on equity. First, rethinking measurement parameters/biomarkers: IA should be addressed using multiomics profiling/measurements and data integration (including genetics, transcripts, proteins, metabolites, cytokines, microbiomes, and clinical lab values) (Fig. 3) rather than relying on single markers like CRP, which fail to capture the heterogeneity and complexity associated with inflammatory profiles and individual microbiomes (Fig. 3). Further, it will be important to establish “Ageotypes” patterns on the basis of the types of molecular pathways that change over time in a given individual reflective of personal lifestyle and medical history [23–25]. This will potentially open composite scores better predict comorbidities and mortality than chronological age. Second, equity in aging research: since most existing data originates from WEIRD populations, expanding research to diverse cohorts *via* global biobanks is crucial. Research must also explicitly account for sex (i.e., biological perspective) and gender (i.e., sociocultural perspective) differences (e.g., higher post-menopausal IA in women due to estrogen loss, socioeconomic disadvantages, and environmental contaminations) (Fig. 3). Importantly, these broad patterns mask considerable heterogeneity within regions, including ongoing epidemiological transitions in many middle- and upper-middle-income settings where lifestyle and risk factor profiles are rapidly evolving. Third, challenges and future directions: interventions must be adapted to address the key challenge of distinguishing "healthy" *versus* "pathological" inflammation. Comparative epidemiological and longitudinal studies in diverse groups and across populations could identify biomarkers for early intervention, potentially extending healthspan. As of 2025, ongoing trials (e.g., Targeting Aging with Metformin (TAME)) [26, 27] emphasize the role of IA, but population-specific adaptations are needed to avoid biases [20, 21]. Fourth, personalized targeted therapies: interventions must also account for human diversity. Senolytics (drugs that clear senescent cells, e.g., dasatinib and quercetin) show promise in reducing the senescence-associated secretory phenotype in preclinical and early human trials for frailty and cardiovascular disease [19, 20]. Anti-inflammatory agents such as metformin or IL-6 inhibitors may benefit industrialized populations where IA is metabolic and lifestyle-driven, but they may be less relevant in infection-heavy settings. Lifestyle interventions (e.g., Mediterranean diet and exercise) can mimic the protective traits observed in indigenous groups by modulating the microbiota and reducing metabolic inflammation (i.e. ‘metaflammation’) (Fig. 3). In summary, the interaction of IA with human diversity

could reveal it as a modifiable horizon in combating ARCDs. By embracing this variability, we might develop inclusive strategies that promote equitable, resilient aging across global populations [18, 20–22].

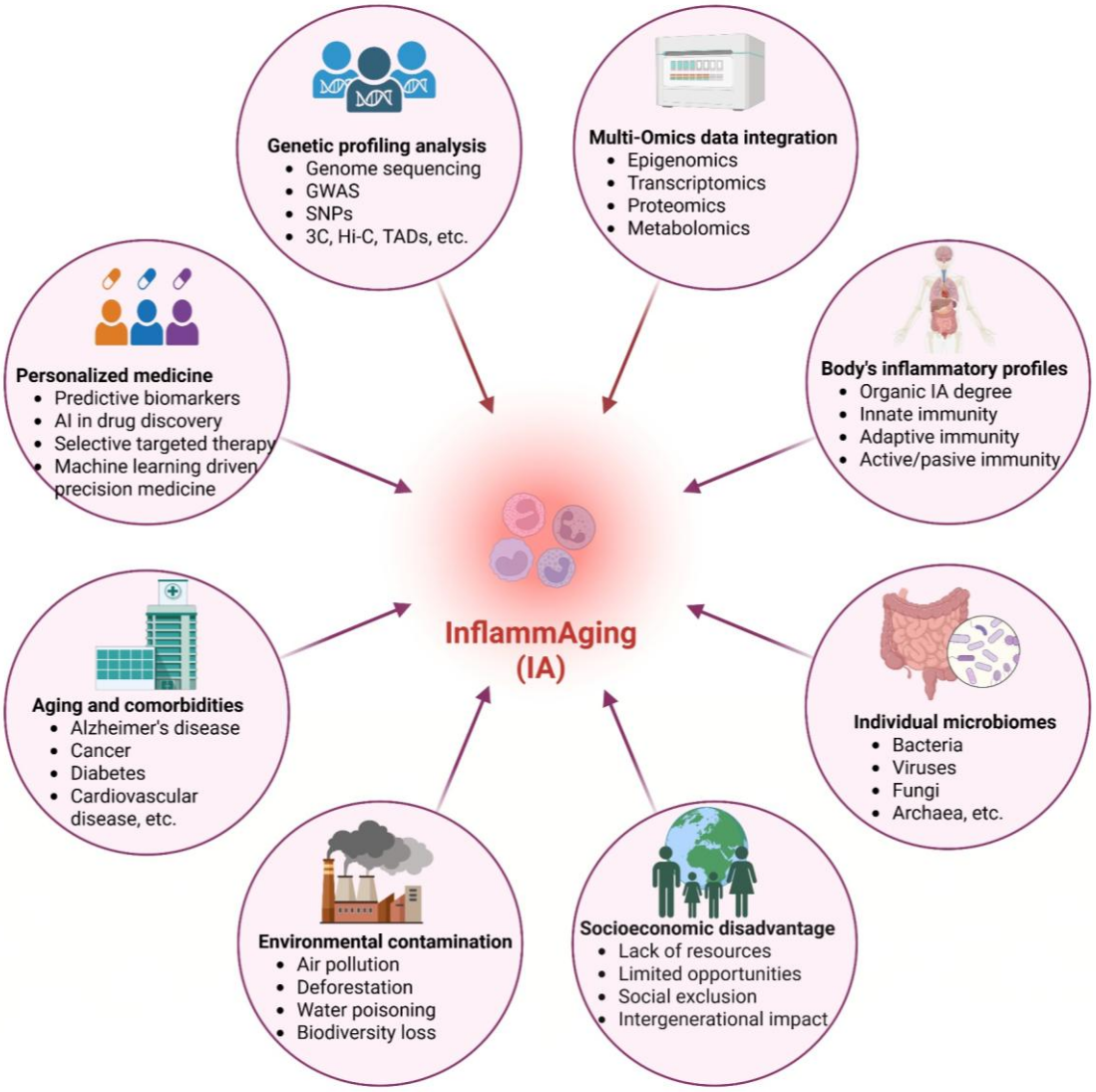

Figure 3. Inflammaging variability across human diversity and implications for personalized geromedicine. Advances in multiomics technologies enable large-scale, longitudinal studies of inflammaging (IA) integrating genetic, epigenetic, transcriptomic, proteomic, metabolomic, immune, and microbiome data across the lifespan. Integration of these datasets allows the development of personalized IA clocks, which, when combined with socioeconomic, cultural, environmental factors, and age-related comorbidities, can yield precise predictive biomarkers. Supported by artificial intelligence and machine-learning approaches, these biomarkers may guide highly targeted interventions, advancing precision geromedicine and improving health promotion across all ages. *Abbreviations:* 3C, chromosome conformation capture (3C)-based genome-wide sequencing technology; GWAS, genome-wide association studies; Hi-C, high-throughput 3D genome mapping; SNPs, single nucleotide polymorphisms; TADs, topologically associating domains. *This figure was created with BioRender.com.*

Epidemiological trends of ARCDs linked to IA across global human populations

The Global Burden of Disease (GBD) studies [28] (including updates through GBD 2021 and 2023, with data extending into recent years (www.healthdata.org/research-analysis/gbd)) supports that IA—and associated age-related chronic conditions—exhibits a higher prevalence in Western (e.g., high-income, and high-socio-demographic index (SDI)) populations compared to many African and Asian (often low- to middle-SDI) populations, though rapid transitions are narrowing these gaps.

The GBD data consistently show higher age-standardized prevalence**,** incidence**,** and disability-adjusted life years (DALYs) for many chronic inflammatory and ARCDs in high-SDI regions (e.g., Western Europe, North America, Australasia, and high-income North America). Some examples include: I) Autoimmune and immune-mediated inflammatory diseases (e.g., rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease (IBD), and diabetes): high-SDI areas report the highest burdens, particularly among older adults (≥60 years). For RA in the elderly, high-SDI regions dominate global prevalence and DALYs, with trends increasing from 1990–2021 and projections continuing upward. II) IBD: follows an epidemiologic stages model—early-industrialized Western regions are in high-prevalence equilibrium, while Asia, Africa, and Latin America show rising incidence but historically lower overall burden. III) Chronic pain and related musculoskeletal conditions: higher age-standardized prevalence in high- and high-middle-SDI regions, linked to degeneration and chronic inflammation, disproportionately affecting older populations. IV) Broader non-communicable diseases (NCDs) with inflammatory components (e.g., cardiovascular diseases, and diabetes-related issues): high-SDI regions often show elevated burdens, though absolute numbers rise globally due to aging populations.

In contrast, low- to middle-SDI regions (e.g., sub-Saharan Africa, South Asia, Southeast Asia, and parts of East Asia) generally report lower age-standardized rates for many of these conditions historically: I) Lower burdens for certain autoimmune diseases, musculoskeletal issues, and some inflammatory markers. II) Sub-saharan Africa often faces a "double burden" (communicable plus emerging NCDs), with lower overall NCD metrics in some analyses but increasing pressures. III) However, rapid increases occur in Asia (e.g., sharp incidence rises due to industrialization, urbanization, "Westernized" diets, and lifestyle shifts), accelerating the epidemiologic transition.

These patterns align with the epidemiologic transition: Western/high-SDI populations have largely completed the shift from communicable to NCD dominance, accumulating higher prevalence of IA-driven conditions. Many African and Asian populations are in earlier stages but experience accelerating incidence from modifiable risks (e.g., high body mass index (BMI), blood pressure, poor diet, and air pollution) and demographic factors (e.g., population aging/growth).

But, while these epidemiological patterns are consistent with a potential role for heightened IA in high-SDI settings (e.g., driven by lifestyle, metabolic, and environmental factors common in affluent societies), such correlations do not directly demonstrate mechanistic differences in IA intensity between regions and should not be interpreted as establishing causality.

However, the INTERHEART study insights on cardiovascular risks (www.phri.ca/research/interheart): this major case-control study (spanning low-, middle-, and high-income countries) found higher overall INTERHEART risk scores in high-income (Western) settings, but paradoxically higher event rates and case fatality in low- and middle-income countries despite lower risk-factor burdens in some cases. It underscores that while Western populations often have higher prevalence of risk factors (e.g., obesity and dyslipidemia) driving chronic inflammation and CVD, outcomes in non-Western regions can be worse due to limited access to care.

Consequently, broader epidemiological trends reveal that ARCD burdens are driven by: I) Population aging and growth (major contributors globally). II) Modifiable risks (e.g., high BMI, blood pressure, dietary factors, and air pollution) explaining much of the attributable burden. III) Transitions: Western regions have largely completed the epidemiologic transition (i.e., shift from communicable to non-communicable dominance), leading to higher accumulated prevalence of chronic inflammatory conditions. In contrast, many African and Asian populations are in earlier stages, with rising incidence as lifestyles "Westernize" (e.g., urbanization, processed diets, reduced activity, etc.). These patterns support explicit discussion of environmental, lifestyle, genetic, and socioeconomic factors contributing to higher chronic inflammation in Western contexts (e.g., processed diets, obesity, microbiome changes, environmental exposures, and reduced early-life infectious challenges) *versus* protective elements in some non-Western populations (e.g., traditional diets, lower obesity historically and different microbial exposures).

Although, regional differences in ARCD burden may also be influenced by methodological and demographic factors beyond biological mechanisms. These include survival bias (where longer life expectancy in high-SDI regions allows more individuals to reach ages of elevated ARCD risk), variations in diagnostic practices and access to healthcare (leading to higher detection rates in resource-rich settings), and competing mortality (e.g., from cardiovascular disease, infections, or other causes in lower-SDI regions that may reduce the number of individuals surviving to manifest ARCD). While age-standardized metrics help mitigate some of these effects, they do not fully eliminate them, and future studies integrating harmonized diagnostics and longitudinal data will be essential to disentangle these contributions.

Future perspectives

The future research questions outlined below aim to fill current knowledge gaps and maximize the potential impact of this emerging field. By advancing understanding and serving as the basis for targeted interventions, these studies will integrate multilateralism to ensure equitable consideration of diverse human populations:

First, how do population-specific genetic and epigenetic variations shape IA trajectories? This requires identifying the specific genetic polymorphisms or epigenetic modifications that drive diverse IA profiles across ancestral groups (e.g., African, Asian, Indigenous, and European ancestries). For instance, variations in cytokine genes (e.g., IL-6, TNF-α, and others) influence inflammatory responses, but their allele prevalence varies by population. These genetic factors are further modulated by epigenetic changes induced by lifestyle and environment. Elucidating these interactions could explain why some populations, like the Tsimane, exhibit resilience to age-related inflammation despite high baseline levels. Inclusive study of underrepresented populations will ensure unbiased genetic and Omics databases and equitable precision medicine (Fig. 3).

Second, can population-specific biomarkers for IA-associated diseases be developed? We need to identify unique biomarkers of IA that predict ARCD risk (e.g., cardiovascular, kidney and Alzheimer's diseases) with differential accuracy across populations. Current biomarkers (e.g., IL-6 or CRP) may not universally predict disease risk due to population-specific inflammatory baselines and/or even polymorphisms; for instance, high CRP in non-industrialized groups often does not correlate with cardiovascular risk as it does in Western cohorts [28–30]. Therefore, biomarker discovery must involve diverse cohorts to mitigate Eurocentric bias and ensure diagnostic tools are effective globally (Fig. 3) [31–32].

Third, what is the role of microbiome in population-specific IA? We need to determine how gut microbiome differences, shaped by diet and environment, contribute to IA variability across populations. The microbiome regulates inflammation through the production of short-chain fatty acids and immune modulation. For example, diverse dietary patterns (e.g., high-fiber in non-industrialized groups *versus* processed foods in urban settings) create distinct microbiome profiles, as well as contextual factors (i.e. microbiome diversity, diet, and infectious burden) differentially modulate key inflammatory pathways (i.e. NF-kB, TLR, NLRP3 inflammasome, IL-1β, IL-6, etc.) across populations [33, 34], potentially explaining IA disparities. Studying the microbiomes of diverse and underrepresented populations could uncover novel therapeutic targets, such as probiotics tailored to specific groups (Fig. 3).

Fourth, which environmental and lifestyle factors are the strongest modulators of IA in diverse settings? We need to understand how the interaction of diet, physical activity, urbanization, and pathogen exposure influences IA across industrialized *versus* non-industrialized populations. Environmental mismatches (e.g., modern sedentary lifestyles *versus* ancestral high-activity patterns) are known to amplify IA in urbanized societies. Conversely, non-industrialized groups, such as the Orang Asli, show resilience to ARCDs despite high infectious loads. Identifying the dominant factors will guide lifestyle interventions. Research must incorporate diverse socioeconomic and geographic contexts to develop globally applicable and culturally sensitive interventions (Fig. 3) [35].

Fifth, how does the interplay of sex and gender differences influence IA across cultures? We must investigate how sex-specific biological factors (e.g., hormonal changes) and gender-related social determinants (e.g., access to healthcare) affect IA and ARCDs in diverse cultural contexts. Biological differences—such as the anti-inflammatory effects of estrogen—create distinct inflammatory profiles between women and men. Simultaneously, socioeconomic factors like stress or nutritional access vary culturally, impacting IA. Gender-inclusive research across cultures is necessary to ensure that interventions effectively address both the biological and societal drivers of these health disparities (Fig. 3).

Sixth, how does socioeconomic disparity influence outcomes in IA and ARCD? We must quantify how socioeconomic factors (e.g., access to healthcare, education, and stress) exacerbate IA and ARCDs in marginalized populations. Chronic stress and poor nutrition, often tied to socioeconomic disparities, amplify IA by increasing cortisol and oxidative stress [15]. These factors disproportionately affect marginalized groups, leading to worse health outcomes. Addressing IA requires inclusive policies that target the social determinants of health, ensuring equitable access to preventive care and resources (Fig. 3).

Seventh, can longitudinal studies across diverse populations redefine IA as a context-specific phenomenon? Recent evidence suggests IA is not inevitable, as non-industrialized populations often exhibit stable inflammatory profiles with age and low rates of ARCDs. Longitudinal data are essential to determine if IA is a byproduct of modern lifestyles rather than a core aging mechanism. Conducting global, inclusive cohort studies is critical to challenge Western-centric aging models and redefine healthy aging paradigms (Fig. 3).

Eighth, how can interventions be optimally tailored to mitigate IA across diverse populations? We need to identify the most effective anti-IA interventions (e.g., geroprotectors, senolytics, dietary changes, exercise, and healthy habits) for different genetic, environmental, and cultural contexts. The efficacy of promising interventions, such as senolytics or lifestyle changes, may vary significantly due to underlying genetic or environmental factors [15, 20]. For example, exercise may be more effective in industrialized settings, while pathogen control may be key in non-industrialized settings. Clinical trials must recruit diverse participants to ensure interventions are equitable and effective for all, moving away from one-size-fits-all approaches (Fig. 3).

These questions highlight critical research avenues at the nexus of IA, human diversity, personalized medicine, healthcare equity, and longevity. IA, defined as chronic low-grade inflammation associated with aging, exhibits significant population variation and is a likely determinant of ARCDs. Future research requires multi- and inter-disciplinary approaches to integrate diverse genetic, environmental, and psycho-socioeconomic contexts. This holistic perspective is essential for promoting equitable healthcare and extending healthy life expectancy. These interventions must align with evidence that IA is conditioned by an individual's biology, social context, and environment. Furthermore, identifying unique pathological signatures (biomarker collection) in individual patients is crucial for achieving precision medicine in chronic inflammation and ARCDs. This necessitates the development of personalized model systems to enhance understanding of ARCD pathogenesis and guide tailored treatment selection. Ultimately, inflammatory disease phenotypes will likely be fragmented into smaller, distinct diseases, each with specific treatments for defined patient groups.

Concluding remarks

To strengthen the mechanistic basis and its linkage to human diversity, future iterations should explicitly anchor inflammatory aging within defined biological circuits—such as cGAS-STING, NLRP3 inflammasome, NF-κB/SASP, mitochondrial DAMP signaling, and trained immunity—and connect them to measurable biomarkers across diverse populations. The incorporation of these new data from multiomic assays, quantifying DNA damage, mitochondrial DNA release, senescence burden, EV-associated nucleic acids, and pathway activation markers (e.g., IL-1β, NF-κB, etc.) would translate descriptive cytokine data into causal and testable mechanisms of aging. Linking these markers to longitudinal, multiancestry cohorts through the integration of genome-wide association studies (GWAS) /epigenome-wide association studies (EWAS)/protein quantitative trait loci (pQTL), and microbiome-metabolome profiling will clarify how genetic, environmental, and lifestyle factors differentially shape IA trajectories [17, 18, 21, 22] (Fig. 1 and 2).

At the same time, the incorporation of equity and diversity as design principles—through biomarker reference ranges calibrated for ethnicity, inclusive recruitment, culturally contextualized intervention and lifestyle studies—will ensure that IA is redefined as a contextual and modifiable process, rather than a universal hallmark. These additions would elevate the concerns introduced in this *Perspective* from conceptual synthesis to a roadmap for precision geroscience and geromedicine, aligning mechanistic insight with global, population-specific strategies to potentially mitigate chronic inflammation and promote resilient aging [15, 19, 20, 22]. Modern advances in hygiene, sanitation, antibiotics, and vaccines have extended life expectancy by curbing infectious disease mortality—even amid recent pandemics—yet this progress highlights an evolutionary mismatch in aging: reduced early mortality may dysregulate immune function in later life, potentially contributing to the rise of ARCDs. Industrialized populations can counter ARCDs tied to modern lifestyles through evidence-based measures like regular physical activity, nutrient-rich diets (e.g., Mediterranean-style), cardiovascular risk management, lifelong cognitive stimulation, and strong social connections, which can delay onset or lessen prevalence despite greater longevity. Extended lifespans profoundly reshape our view of mortality. As of 2025, Japan leads with ~85 years, while Spain stands at ~84 years, exemplifying how higher longevity inevitably elevates ARCD rates and calls for cultural/societal reevaluation of death and aging. These shifts strain advanced societies in economics, science, healthcare, education, and culture, spurring trendy anti-aging efforts and an "arms race" for therapies to overcome evolution's cap on immortality. Ultimately, it is wise to embrace Japanese-inspired wisdom—resonating with "memento mori"—that while we live, we must ready ourselves for death. After all, life itself may be the only truly lethal disease.

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Author information

JMI conceived, designed, and drafted the manuscript.

Competing interests

The author declares no conflicts of interest.

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