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Health and aging trajectories: shared and competing risks and resiliencies for chronic diseases associated with aging. A NIH-wide workshop

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Introduction

Many cultures throughout history have pursued the quest to improve longevity (1). Scientific advances, implementation in public health, and the use of vaccines and antibiotics have enhanced life expectancy over the last century (2). These interventions have reduced mortality but may have led to a concomitant rise in age-related multimorbidities (MM). Therefore, intervention initiatives need to incorporate the expanded goals of preventing age-related decline and extending healthspan—the period of life spent in good health and free from chronic diseases and disabilities (3). At its most essential, aging can be considered to result from impaired regulation of homeostasis, with a diminished ability to repair damage to critical molecular-cellular systems, a gradual decline in physiological functions, and accumulation of dysregulated and senescent cells over time. As people age, their immune systems become less resilient, leading to increased vulnerability to diseases and potentially contributing to the aging process. Resilience—the capacity to resist, adapt, recover, or grow in response to challenges—is believed to decrease with age and the development of age-related conditions (4). This definition of resilience for living systems adopted by the trans-NIH Resilience Working Group is relevant across multiple domains including environmental, community, and individual dimensions including genetic, molecular, cellular, physiological, psychological, and behavioral components. Immune resilience, the ability to maintain or regain optimal

health during and after an infection can be indicative of an individual's overall health and aging trajectory. Those who can maintain or quickly return to this optimal state are likely to have a more favorable aging process (5). Behavioral and social factors can also impede or support the adoption of preventive strategies that increase resilience. An enhanced understanding of aging processes and resilience factors could facilitate strategies focused on improving early detection and intervention with the aim to delay the onset of age-related conditions, mitigating their severity, decreasing morbidity and frailty, and fostering healthier aging trajectories (6, 7).

Aging is linked to increased vulnerability to challenges contributing to aging-associated chronic diseases, such as cancer, cardiovascular diseases (CVD), neurodegenerative disorders, pulmonary conditions, and frailty. Preventing these or delaying their onset would improve the quality of life of our increasingly aging population. Identifying factors that promote healthy aging and preserve functional abilities and well-being has become a priority as the world's population ages. Understanding the commonalities and differences of the biological pathways involved in natural aging and age-related diseases is critical to influencing resilience outcomes, promoting health, and effective disease management or prevention (8).

This manuscript summarizes knowledge gaps and current barriers emerging from an NIH workshop organized on the topic of: "Health and Aging Trajectories: Shared and Competing Risks and Resiliencies for Chronic Diseases Associated with Aging" (9). It also discusses novel research opportunities, ongoing efforts to address these gaps, and strategies for future research (Figure 1). We highlight the need for multi-disciplinary, collaborative efforts to develop interventions that enhance resilience and prevent chronic diseases, extend the healthy lifespan, and improve quality of life.

The intricacies of competing and shared risks in aging trajectories

Unlike chronological aging, evenly measured in all individuals, biological aging varies among and within individuals leading to different aging trajectories. A complex interplay between inherent genetic factors and a range of external and lifestyle factors impact the course of biological aging and the onset of age-related chronic diseases (8). As we age, we encounter shared and competing risks that lead to multiple aging trajectories and influence health outcomes (10–12). These risks include genetics and the exposome—the lifetime exposure to internal factors and external environmental influences such as pollution. Critical psychosocial and lifestyle factors include diet, exercise, sleep patterns, and stress levels. Different groups of individuals have different pathways of age-associated molecular changes. Additionally, many age-related conditions share risk factors that often coexist as MM, requiring simultaneous management in individuals (13). MM prevalence presents differently in the general population (14). The COVID-19 pandemic highlighted the variable risk for cognitive impairments in older adults with MM (15). Furthermore, some groups exhibit a higher incidence of neurodegenerative diseases (16, 17). Despite adverse exposures, some people maintain healthier aging trajectories, providing complexity to the role of lifestyle and genetic factors against cognitive decline and age-related diseases. Other factors include sedentarism, unhealthy diets high in processed foods and saturated fats, smoking, excessive alcohol consumption, and chronic stress, which significantly increase the likelihood of developing age-related diseases. Older adults with limited social networks are more likely to experience poor health outcomes, including accelerated cognitive decline and higher mortality rates. Strategies to promote social connectivity, such as community engagement programs and digital tools, are increasingly recognized as important components of healthy aging. It is essential to ensure representation of older adults in clinical trials to better understand diverse healthspan pathways. These findings highlight the complex interplay of genetic predispositions on early onset of disease in susceptible populations (11). The circumstances mentioned create distinct aging patterns identified as "ageotypes", that can contribute to our ability to measure and monitor variable aging trajectories (18). Understanding mechanisms and trajectories will allow us to identify novel approaches that can help slow or even reverse genetic, molecular and cellular hallmarks of aging and extend healthspan and longevity (7, 10–12, 19).

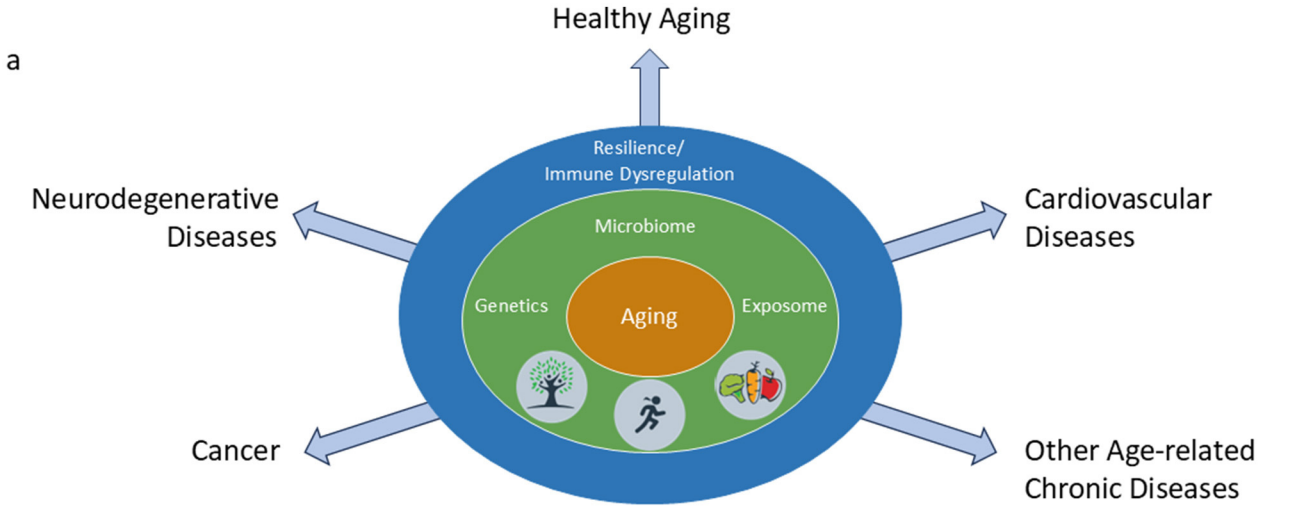
To develop a better understanding of diverse healthspan pathways, it is essential that longitudinal clinical trials strive for population-based recruitment and enrollment. The Baltimore Longitudinal Study of Aging, the longest running study of aging in the United States, has contributed to our knowledge of normal aging processes by looking at multiple phenotypic parameters uncovering a complex, heterogeneous pattern of aging trajectories (20, 21). The Danish Disease Trajectory Browser (22) provides a new perspective on disease progression patterns that can reveal associations between complex multimorbidities and potentially identify preventive strategies for chronic diseases (23). To promote interdisciplinary research on determinants and dynamics of within-person aging-related changes in cognitive and physical capabilities, health, personality, and well-being, the Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA) research network provides access to meta-data from over 100 studies (24, 25).

Biological processes promoting divergent aging trajectories

Several biological processes—briefly listed below—have been shown to contribute to aging trajectories and are inextricably linked to the emergence of age-related chronic diseases (7). Some of these processes affect cells and tissues across the whole body; others are specific to particular tissues and physiological functions.

Cellular senescence

Cellular senescence is a fundamental aspect of aging in which a growing number of cells with increasingly anti-apoptotic mutations continue to exist within the tissue ecosystem but cease to divide (26, 27). Senescent cells accumulate within all tissues impairing cellular functions through production of various proinflammatory molecules (termed senescence-associated secretory phenotype). Senescent cells contribute to a range of age-related conditions that



b

Aging Biology and Disease Mechanisms

- Pathological age-related processes versus natural aging
- Microbiome impact on aging
- Key cell types driving age-related diseases
- Immune dysfunction and inflammaging
- Intestinal barrier's role in chronic inflammation and aging

Prevention, Intervention, and Resilience

- Lifestyle interventions and protective pathways or factors to boost resilience and healthspan
- Long-term impact of stress and stress-related biomarkers
- Develop effective senotherapeutics
- Best practices to manage multimorbidities
- Impact of lifestyle changes across different life stages and populations
- Identify optimal times for sustainable interventions

Methodological Improvements

- Lifespan perspective in aging research
- Longitudinal studies across the lifespan
- Interdisciplinary approach to aging research
- Wearables, AI, ML, personalized prevention
- Consensus definitions of age-related terms
- Biomarkers, models for biological aging, resilience, and senescence.
- Link aging biology and cancer research

FIGURE 1
Factors that contribute to aging trajectories and possible research opportunity areas to address age-related diseases. **(a)** The interaction of complex factors such as genetics and lifestyle influences converge to drive an organism toward healthy aging or to the development of age-related diseases. **(b)** Research opportunity areas identified during the workshop. Increased understanding and collaborations across various expertise areas are needed to enhance health span and prevent or moderate the development of age-related disorders.

result from disruptions in normal cell functions across various bodily systems (28). Within the central nervous system, senescent cells contribute to structural brain changes and cognitive decline (29). They can also tilt the scale toward the development of cancer (30–32). Cellular senescence is also associated with reduced resilience and a shortened lifespan, and represents a potential therapeutic target to reduce severity and morbidity in COVID-19 infections (33). Consequently, there is a burgeoning interest in the development of senolytics, a category of drugs aimed at targeting and eliminating senescent cells. This therapeutic strategy holds the potential to mitigate age-related chronic diseases, thereby enhancing resilience and extending healthspan (34–38). The exploration of senolytics has yielded promising results, though it remains premature to draw definitive conclusions (39, 40). Enhancing the specificity of these compounds and optimizing treatment protocols, including dosage, is critical to mitigate adverse effects. Interestingly, senolytics have been identified in natural compounds, indicating future potential approaches for nutraceuticals in managing aging-related diseases (41).

Malignancy

The transformation from normal to malignant cells, as outlined by the somatic evolution theory, establishes a connection between aging and the development of cancer (42). As we age, our DNA repair mechanisms become less efficient, leading to an accumulation of mutations. These mutations, combined with changes in the immune system, can contribute to the onset of cancer, atherosclerosis, and other chronic diseases. Aging and cancer share several key features, including genomic instability, alterations in metabolism, changes in telomeres, and cell senescence, all of which present potential targets for therapeutic intervention (43–45).

Hematopoietic dysregulation and immune system dysfunction

Disruptions of generation and function in both innate and adaptive immune cells, coincides with the manifestation of aging-associated morbidities. At the generation step, hematopoiesis is shifted toward myelopoiesis at the expense of lymphopoiesis in the bone marrow, reducing the output of lymphocytes (46–48). Together with thymic involution and a life-long antigen exposure, naïve B cells and T cells are reduced, and antigen-experienced memory B cells and T cell subsets are increased in the periphery (49–52), thereby limiting responses to infections, tissue impairments, and cancer. Aging-associated B cells (53, 54) inhibit survival of pro-B cells in the bone marrow (55) and

cause polarization of peripheral Th17 and Th1 cells (56), while aging-activated innate B1 B cells promote insulin resistance in older adults (57) and induce potentially autoimmune CD8+ T cells (58). Myeloid cells, such as monocytes and macrophages, show impaired phagocytosis, thus inefficiently clearing apoptotic cells and pathogens in aging (59, 60). The dysregulation as well as decline in immune function (termed immune senescence) increases in advanced age, contributing to the increased incidence of CVD, cancer, and degenerative conditions (61). Additionally, clonal hematopoiesis, which is characterized by the accumulation of somatic mutations in hematopoietic stem cells, has also been implicated in the onset of various age-related diseases (62–65).

Endothelial dysfunction

Endothelial dysfunction, a key aspect of aging-related metabolic shifts, leads to impaired vascular tone, pro-thrombotic and pro-inflammatory states, contributing to widespread vascular and organ decline (66). This dysfunction underpins the progression of CVD, cancer, and degenerative conditions like vascular dementia (67–71). Age-driven vascular changes in the brain, which are more frequently observed in women, can diminish cognitive function and brain volume, potentially marking early signs of brain aging (72).

Dysbiosis

Accumulating evidence demonstrates the gut microbiome's role in age-related changes in metabolism, digestion, immunity, mood, and cognition, influencing individuals' health. Aging can shift the microbiome toward pro-inflammatory bacteria, affecting metabolism, weakening intestinal integrity, and leading to low-grade inflammation (73). This microbiome evolution, linked to brain health via the gut-brain axis, may contribute to neurodegenerative diseases (74). Given its sensitivity to diet, medication, and environment, influencing the microbiome offers a potential strategy for preventing and treating age-related conditions (75–78).

Immune dysregulation

Both innate and adaptive immune cell compartments, impairing their function and increasing chronic low-levels of harmful inflammation is defined as inflammaging (47, 48, 79). As such, directly or by contributing to inflammaging, the dysregulated immune cells in turn further age-related pathologies and diseases. Dysbiosis and activation of myeloid cells inhibit lymphopoiesis in the bone marrow, while accumulation of potentially pathogenic B cells contributes to increased insulin resistance in aging (57) and neurodegeneration (80).

Neuropathology

Alzheimer's Disease and related dementias (ADRD) are characterized by changes in neuronal and perineuronal protein structure and function. The most notable and long-studied neuropathology includes amyloid plaques and hyperphosphorylated tau in neurofibrillary tangles. Implementing interventions earlier in ADRD progression, such as in those with mild cognitive impairment (MCI), could potentially reduce or prevent the progression of cognitive decline and dementia (81, 82). Utilizing biomarkers like plasma amyloid and tau alongside neuroimaging can reveal the neurocognitive impacts of aging, concomitant with the contribution of various risk factors such as hypertension, genetics, and lifestyle on health outcomes (83, 84).

Psychogenic aging

Psychological factors—including responses to stress and resilience—contribute to healthspan and lifespan. For example, childhood experiences can have an impact on chronic diseases and early mortality. Brain-body circuits play a pivotal role in mediating interactions between environment, lifestyle, and aging. The body's cellular responses to stress begin in the nervous system, with the release of neurotransmitters and the stimulation of neuroendocrine pathways (e.g. the hypothalamic-pituitary-adrenal axis) which have the potential to influence various biological aging processes. Stress-related chemokines can trigger the mobilization of immune cells from the bone marrow and can lead to neuroinflammation (85). The identification of biomarkers associated with the psychogenic aging could reveal the profound effects of depression and loneliness on age-related morbidity, enhancing our comprehension of psychosocial resilience and its contribution to longevity and healthspan.

Discussion: shared and competing risks to improve aging trajectories

A pressing research priority in the field of aging is the identification, stratification, and management of shared and distinct disease risks. Understanding how these risks interplay and how they can be mitigated is critical to extend healthspan. Regular physical activity, a Mediterranean-style diet rich in fruits, vegetables, whole grains, and omega-3 fatty acids, cognitive engagement, and stress management have shown promise in delaying or preventing cognitive decline, reducing cardiovascular risk, and improving overall health. Pleiotropic interventions—those producing multiple positive effects on health—represent an efficient path to improve health outcomes (86–89). For example, weight loss has shown wide-ranging benefits, improving health outcomes in patients with anxiety, depression, rheumatoid arthritis, diabetes, hypertension, and cancer (90, 91). Importantly, applying weight reduction strategies early in childhood and adolescence can potentially delay the onset of multiple chronic conditions later in life, highlighting the importance of timing for optimal intervention (92, 93). Exercise similarly demonstrates strong evidence for both slowing disease progression and preventing chronic conditions (93).

Mental stimulation and physical activity have also been shown to reduce the risk of MCI (82), while improved sleep duration is linked to reduction in inflammatory cytokines, mental health issues, and other outcomes crucial for healthy aging (94).

Additional factors such as access to health care, social support, adherence to medications, reducing environmental pollution, and practices like mindfulness meditation have proven effective in improving risk factors and long-term health outcomes (95–100). Combining multiple effective interventions, and identifying critical life stages for testing and intervention hold immense promise for advancing preventive strategies and promoting better aging trajectories.

The evaluation of individual health and disease status requires detailed, longitudinal measurements. Technological advancements in artificial intelligence (AI) such as machine learning (ML) and large language models (LLMs) offer transformative opportunities for personalized care, early disease detection, and targeted interventions (101). Wearable devices, which provide continuous health monitoring, enable a deeper understanding of the interplay between genetics, environment, and lifestyle. These tools facilitate the development of personalized preventive and treatment strategies for age-related chronic diseases (102).

Aging has been considered as either a disease or a normal biological process. This classification has driven strategies such as testing drugs intended for age-related diseases as an indirect means of addressing aging. Alternative strategies need to be carefully evaluated to avoid potential health risks. There is an urgent need for a standardized definition of normal aging vs. age-related chronic diseases, along with associated biomarkers, and the creation of innovative models for studying biological aging. These measures are crucial for establishing reliable and effective intervention strategies (1). The field of geroscience seeks to understand how factors impacting common cellular and molecular processes lead to physiological dysfunction and chronic diseases. It aims to identify novel approaches to help slow down or even reverse genetic, molecular, and cellular hallmarks of aging and extend healthspan and longevity (10, 21, 103–105).

A forward-looking research agenda must integrate multidisciplinary approaches, incorporating advanced knowledge of genomics, other omics, and the exposome. Environmental exposures can interfere with gene expression pathways, biochemical traits, and physiological functions. Individual psychological traits, cognitive processes, and emotional responses also influence the ability to cope with challenges and adopt healthy behaviors (21, 104, 105). Closing the gap between lifespan and healthspan requires the creation of innovative strategies to make age-related diseases more predictable, preventable, and manageable. Gaining insights into the essential elements that maintain balance throughout life and the factors that disrupt this balance could lead to the identification of novel diagnostic markers and treatment targets (106, 107). Clinical longitudinal studies will help identify critical periods for effective interventions. Furthermore, compiling comprehensive and diverse datasets through cutting-edge technologies will accelerate discoveries and their clinical applications. Achieving the ambitious research goals set forth in this workshop demands interdisciplinary collaborations to address the complexities of aging and improve early disease detection. It is equally critical to prioritize the perspectives of patients in all phases of research. Finally, translating research findings from the laboratory into clinical practice will be pivotal in delivering tangible benefits to the aging population.

Author contributions

IR: Writing – original draft, Writing – review & editing. AB: Writing – review & editing. LB: Writing – review & editing. ZG: Writing – original draft, Conceptualization. MK: Writing – review & editing. SK: Writing – review & editing. JS: Writing – review & editing. AW: Writing – review & editing. DX: Writing – review & editing. RY: Writing – review & editing. GR: Writing – original draft, Writing – review & editing, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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