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Mapping Human Organ Aging: From Cellular Mechanism to Clinical Applications for Precision Medicine in Healthspan to Lifespan

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Abstract

Background: Aging is a complex, multifactorial process that progresses heterogeneously across human organs, resulting in distinct organ-specific lifespans and trajectories of functional decline. Chronological age inadequately captures these nuances, as each organ is governed by intrinsic biological clocks shaped by cellular turnover, regenerative capacity, metabolic activity, and cumulative genetic and environmental stressors.

Objective: To synthesize current knowledge on organ-specific aging, elucidate underlying mechanisms, identify predictive biomarkers, and highlight functional consequences relevant to healthspan and disease vulnerability.

Methods: Review of recent studies employing plasma proteomics, epigenetic profiling, and machine learning approaches to quantify organ-specific biological age across cardiovascular, nervous, musculoskeletal, endocrine, gastrointestinal, respiratory, renal, integumentary, urinary, reproductive, and sensory systems. Mechanistic insights from cellular and systemic aging processes were integrated with functional outcomes.

Results: Organ-specific aging is asynchronous, with age gaps predictive of morbidity, frailty, and mortality. Intrinsic mechanisms (e.g., including mitochondrial dysfunction, stem cell exhaustion, oxidative stress, inflammation) interact with extrinsic influences such as lifestyle, environmental exposures, and comorbidities. Functional consequences are organ-dependent: cardiovascular and renal aging impact systemic homeostasis; neural and musculoskeletal decline impair cognition and mobility; endocrine and reproductive aging modulate metabolism; sensory and integumentary decline affect quality of life.

Conclusions: Understanding organ-specific aging trajectories enables early detection of functional decline, informs precision medicine strategies, and guides targeted interventions to preserve organ viability. This organ-level perspective highlights the mosaic nature of human aging and offers a framework for extending healthspan through organ-targeted approaches.

Keywords

Aging; Organ-specific aging; Systems-level mapping; Biomarkers.

Introduction

Aging is a complex, multifactorial biological process characterized by a progressive decline in physiological integrity, diminished homeostatic capacity, heightened susceptibility to chronic disease, and ultimately, death. Chronological age does not uniformly reflect an individual's functional or biological state [1]; rather is a dynamic process influenced by the interplay of genetic, epigenetic, environmental, and stochastic factors that cumulatively contribute to maintenance (or deterioration) of cellular and tissue function over time [2]. The inter-individual variability in resilience and functional capacity suggests biological age represents a more informative and actionable marker, encapsulating cumulative molecular and cellular damage, systemic inflammation, metabolic dysregulation, and immunosenescence [3]. Biomarkers such as DNA methylation clocks, telomere attrition, proteomic and metabolomic signatures, offer more precise insight into an individual's true physiological condition with stronger correlations to functional outcomes, disease risk, and mortality than chronological age alone [4].

One of the most compelling observations in aging biology is the heterogeneous nature of aging across organ systems. Different tissues and organs age at distinct rates, influenced by their intrinsic regenerative capacity, cellular turnover, metabolic activity, and exposure to systemic and environmental insults5. For instance, high-turnover tissues may show signs of aging earlier due to replicative stress, while low-turnover tissues may accumulate damage over longer periods without evident decline, until thresholds are crossed. This organ-specific rate of aging leads to diverse patterns of functional impairment, disease vulnerability, and clinical manifestations among individuals [6]. The concept of organ-specific lifespan, i.e., the period during which an organ maintains sufficient functional integrity to support systemic homeostasis has emerged as a useful framework for understanding temporal dynamics of decline and identification of subclinical dysfunction at the tissue level, often preceding overt systemic deterioration.

Recent advances highlight the potential of organ-specific biological clocks, derived from multi-omics and AI-driven analytics, to quantify and compare the pace of aging across organ systems. Proteomic and transcriptomic signatures can delineate organ trajectories [7], while epigenetic clocks now capture differential rates of methylation change across tissues [8,9]. For example, a blood-based proteomic “brain clock” recently demonstrated strong predictive power for both all-cause mortality and Alzheimer’s disease risk, underscoring the clinical value of system-specific assessments [7,10]. Similarly, steroidomic and metabolomic profiles have been used to model endocrine contributions to differential aging across organ systems [11]. The study of organ-specific aging carries profound implications for clinical practice, precision medicine, and public health. At the individual level, it enables nuanced risk stratification, early detection of degenerative conditions, and development of targeted interventions designed to preserve the functionality of the most vulnerable systems. At the population level, characterizing variability in organ aging can inform prevention strategies, healthcare resource allocation, and policy planning in anticipation of the societal challenges posed by demographic aging. Collectively, shifting from a generalized to a system-specific and biologically grounded perspective is essential to advance the science of aging and optimize strategies to extend healthspan [12].

Literature Review and Theoretical Framework

Definition and overview

Human organ lifespan refers to the duration over which an organ remains functionally viable, defined by its ability to maintain physiological processes essential for systemic homeostasis and survival [13]. This concept encompasses the full timeline of an organ's operational capacity, from embryonic development and postnatal maturation through decades of maintenance and adaptive function, culminating in progressive senescence and eventual decline. Unlike chronological aging at the organismal level, organ lifespan is heterogeneous, reflecting differences in regenerative potential, cellular turnover, metabolic demand, and cumulative exposure to systemic and environmental stressors. Even as organs age and efficiency diminish, the meaningful contribution to systemic function persists, albeit under suboptimal conditions [2].

At the biological level, organ lifespan is governed by intrinsic mechanisms such as cellular senescence, telomere attrition, DNA damage accumulation, and oxidative stress. These hallmarks progressively impair tissue structural and functional integrity. As unrepaired molecular damage accumulates, organ systems become less capable of maintaining homeostasis and responding to physiological stressors, ultimately manifesting as reduced reserve capacity, slower recovery, and increased vulnerability to disease and dysfunction [14].

Understanding organ lifespan is essential for evaluating age-related vulnerability, designing preventive strategies, and optimizing therapeutic interventions. Medical research continues to elucidate the cellular and molecular pathways influencing tissue longevity to identify biomarkers and modulators of organ-specific aging [2,14]. Integrative approaches combining molecular biology, longitudinal monitoring, and systems-level analytics enable researchers to characterize when and how organs deteriorate. Emerging AI-driven models further extend this capability by integrating clinical, imaging, and biomarker data into predictive frameworks. This knowledge supports interventions aimed not merely at delaying aging, but at maintaining organ functionality deep into late life, advancing the goals of geroscience and personalized health management.

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Factors affecting organ lifespan and healthspan

Every organ fulfills specialized physiological functions, yet organs do not age uniformly. Their functionality and longevity reflect a dynamic interplay of intrinsic biological mechanisms and extrinsic lifestyle and environmental factors. Intrinsic influences include genetic and epigenetic architecture, stem cell exhaustion, mitochondrial dysfunction, proteostasis decline, and dysregulation of metabolic and inflammatory pathways, core hallmarks of aging [2,14]. Extrinsic contributors include diet, physical activity, psychosocial stress, exposure to toxins or pollutants, and comorbid conditions, which can accelerate or attenuate organ-specific aging trajectories [6].

A comprehensive understanding of these multidimensional interactions is critical for defining organ-specific lifespan and healthspan. By examining how biological and environmental influences integrate over time, researchers can chart temporal dynamics of organ deterioration, refine risk stratification, and design targeted interventions to preserve organ viability. This systems-level perspective informs precision medicine strategies aligned with the unique vulnerabilities of each organ system.

- **Genetic and Molecular Damage:** Genomic instability represents a central hallmark of aging, characterized by the progressive accumulation of DNA damage, point mutations, chromosomal rearrangements, and telomeric attrition that collectively undermine genomic fidelity and cellular homeostasis. Mechanistically, endogenous sources such as replication errors, reactive oxygen species (ROS), and spontaneous deamination, along with exogenous exposures including ionizing radiation and toxins, contribute to a rising burden of single- and double-strand breaks, base modifications, and aneuploidy across the lifespan. Failure of DNA repair pathways—including nucleotide excision repair, homologous recombination, and non-homologous end joining—exacerbates this burden, accelerating mutational drift and epigenetic dysregulation. The consequences of such instability are profound: increased oncogenic potential, impaired stem cell function, neurodegenerative vulnerability, and phenotypic features of premature aging syndromes such as Werner's and Hutchinson-Gilford progeria [2,15,16]. Quantification of DNA damage can be achieved through immunofluorescent γH2AX foci assays, which capture double-strand break frequency, or single-cell gel electrophoresis (comet assays), which assess global DNA strand integrity. High-throughput sequencing enables detection of mutation burden and structural variants across tissues, permitting correlation of genomic instability with both chronological age and organ-specific biological age estimates. Single-cell sequencing approaches further resolve heterogeneity in mutational load within stem cell compartments, highlighting stochastic versus programmed elements of aging.

Telomere attrition represents a fundamental hallmark of aging, characterized by the progressive erosion of terminal DNA repeats (TTAGGG)_n during successive cell divisions due to the end-replication problem. Critical shortening elicits a DNA damage response that triggers replicative senescence or apoptosis, thereby constraining cellular proliferative capacity. This process is tightly linked to age-related pathologies, including cardiovascular disease, pulmonary fibrosis, and oncogenesis [2,17]. Quantitative assessments of telomere length are typically performed by qPCR, Southern blot, or single telomere length analysis (STELA), with longitudinal profiling enabling the evaluation of attrition dynamics across the

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lifespan.

Epigenetic remodeling emerges as another key hallmark of aging, encompassing genome-wide DNA methylation drift, histone modification shifts, and chromatin remodeling. These alterations contribute to aberrant transcriptional regulation, impaired cellular plasticity, and heightened risk for metabolic disorders, cognitive decline, and cancer [2,18]. High-resolution methylation profiling has enabled the development of "epigenetic clocks" (e.g., Horvath, Hannum, and PhenoAge clocks) [19], which serve as quantitative estimators of biological age and predictors of healthspan. Analytical pipelines incorporate differential methylation analysis across tissues, coupled with integrative multi-omic correlation.

- **Loss of Cellular Maintenance and Mitochondrial Dysfunction:** The collapse of protein quality-control systems with aging disrupts proteome integrity, resulting in protein misfolding, impaired chaperone function, diminished autophagy, and proteasome inefficiency. These events drive protein aggregation, a central feature of neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's disease [2,20,21]. Experimental evaluation involves Western blotting, immunofluorescence, or mass spectrometry for detection of misfolded or aggregated species, and enzymatic assays to quantify proteasomal and autophagic activity. Visualization strategies include comparative bar graphs of proteostasis markers across cohorts, alongside correlation plots linking proteostasis collapse to clinical or functional outcomes such as cognition and muscle strength.

Mitochondria serve as both powerhouses and signaling hubs, and their dysfunction constitutes a central hallmark of aging. With age, oxidative phosphorylation declines, ATP production wanes, and reactive oxygen species (ROS) accumulate, leading to macromolecular damage and mtDNA mutations [2,22]. This dysfunction manifests in sarcopenia, neurodegeneration, and metabolic syndrome. Analytical pipelines include Seahorse extracellular flux assays to assess respiratory capacity, fluorometric quantification of ROS, and sequencing for mtDNA mutations. Data visualization includes line plots of ATP production over age and scatterplots correlating ROS burden with functional decline in muscle or neuronal tissues.

- **Stem Cell Exhaustion and Intercellular Breakdown:** Aging diminishes stem cell number and function, impairing regeneration in tissues such as skeletal muscle, intestinal epithelium, and skin [2,23]. Intercellular breakdown disrupts communication between cells and their microenvironment, impairing repair, immune responses, and tissue homeostasis. Chronic low-grade inflammation ("inflammaging") propagates a vicious cycle of tissue degradation and miscommunication, reducing repair capacity and increasing susceptibility to chronic disease [24]. Environmental toxins such as pesticides and heavy metals exacerbate stem cell and immune dysfunction [25]. Preserving stem cell reserves, controlling inflammation, and maintaining tissue architecture are essential strategies to extend organ healthspan and lifespan.

Senescence represents a stable state of proliferative arrest induced by DNA damage, telomere attrition, or oxidative stress, wherein cells remain metabolically active but lose regenerative capacity [2,26]. Accumulation of senescent cells contributes to tissue dysfunction, chronic inflammation, and tumorigenesis. Standard assays include senescence-associated β-galactosidase (SA-β-gal) staining and

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flow cytometry or immunostaining for p16^INK4a and p21^CIP1. Representative micrographs provide qualitative visualization, while frequency plots quantify senescent burden across tissues and age cohorts. Senescent cells exert systemic effects through SASP, characterized by secretion of pro-inflammatory cytokines, chemokines, proteases, and growth factors. This paracrine activity fosters chronic low-grade inflammation, tissue remodeling, and tumor progression, while accelerating age-related diseases such as osteoarthritis [26,27]. Multiplex cytokine assays and proteomic profiling define SASP composition, while correlations with systemic inflammatory markers (e.g., CRP, IL-6) provide translational relevance. Data can be represented as heatmaps of SASP factors and network diagrams linking secreted mediators to tissue-specific dysfunction and systemic aging trajectories.

- **Metabolic Disruption and Impaired Nutrient Sensing:** Aging disrupts regulators such as AMPK, mTOR, and IGF-1, leading to insulin resistance, impaired protein turnover, and lipid accumulation [29,29]. Endocrine disruptors like phthalates, BPA, and heavy metals exacerbate this imbalance, promoting systemic inflammation and accelerating organ aging [30]. Interventions enhancing nutrient-sensing efficiency, promoting metabolic flexibility, and reducing chronic inflammation support energy homeostasis and organ longevity.
- **Gut Microbiota Imbalance:** Gut microbiota diversity declines with age, stress, and environmental insults, leading to dysbiosis, systemic inflammation, and impaired organ function [31,32]. Pro-inflammatory microbial shifts damage distant organs, including the liver, brain, and cardiovascular system [33]. Maintaining microbial balance supports immune homeostasis, nutrient bioavailability, and multi-organ resilience, contributing significantly to longevity.
- **Physical Activity and Organ Resilience:** Exercise stimulates pathways that improve mitochondrial function, enhance AMPK and PGC-1α activity, reduce inflammation, support neuroplasticity, preserve stem cell viability, and maintain telomere length [23,28]. Conversely, inactivity reduces regenerative signaling and accelerates decline in multiple organ systems [5,34]. Sustained physical activity preserves organ resilience and extends healthspan.
- **Environmental Pollutants and Multi-Organ Decline:** Cumulative exposure to pollutants (e.g., pesticides, plastics, heavy metals) induces oxidative stress, inflammation, and multi-organ dysfunction [35]. Pollutants compromise respiratory, cardiovascular, nervous, reproductive, and immune systems, accelerating aging and disease susceptibility [36,37]. Minimizing exposure and strengthening physiological defenses are essential to protect organ function and promote healthy aging.

Methodology

- **Conceptual Framework:** Aging is organ-specific, with each organ exhibiting distinct biological clocks influenced by cellular turnover, regenerative capacity, metabolic load, and cumulative environmental and/or genetic stressors [38]. We adopt a multilevel, integrative approach, combining molecular, functional, and structural markers to quantify organ-specific aging trajectories and lifespan. This framework allows comparison across organ systems, linking subclinical decline to clinical outcomes [39]. Chronological age alone cannot capture heterogeneity in physiological decline. Biological age metrics and proteomic markers provide quantitative, organ-specific insight, enabling early detection of functional vulnerability and

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potential interventions.

- **Organ Selection and Categorization:** Organs are grouped into physiologically and clinically relevant systems (Table 1). This categorization balances granularity with functional relevance, enabling cross-organ comparisons while preserving clinical interpretability.

System	Organs Included	Key Aging Markers / Functional Outcomes
Cardiovascular	Heart, Vasculature	LV wall thickness, arterial stiffness, blood pressure, proteomic age [39]
Nervous	Brain, Central Structures	Cortical thickness, hippocampal volume, white matter integrity, brain age gap, cognitive function [10,20,40,41]
Musculoskeletal	Muscle, Bone, Joints	Sarcopenia, osteopenia/osteoporosis, cartilage degeneration, motor neuron density [42-45]
Endocrine	Adrenal, Pancreas, Thyroid, Pituitary, Gonads, Hypothalamus	Hormone levels (DHEA, insulin, testosterone, estrogen), GH/IGF-1, GnRH/vasopressin signaling, neuronal density, single-cell transcriptomics, metabolic markers [6,46-48]
Gastrointestinal	Esophagus, Stomach, Small & Large Intestine, Appendix	Motility, absorption, microbiome composition, proteomic age [8,12,49,50]
Respiratory	Lungs	FVC, FEV_1, alveolar compliance, macrophage function [28,36,51–53]
Renal/Urinary	Kidneys	GFR, nephron number, fibrosis, tubular atrophy [54,55]. Detrusor function, innervation density, compliance
Integumentary	Skin, Hair, Nails	Collagen/elastin content, epidermal thickness, MMP activity, pigmentation changes [56,57]
Reproductive	Ovaries, Uterus, Testes, Prostate	Hormone levels, follicle count, structural imaging, sperm quality [58–61]
Sensory	Eye, Ear, Olfactory	Visual acuity, hearing thresholds, olfactory bulb volume [62]
Hepatic	Liver/Gall bladder	Sinusoidal fenestrations, enzyme activity, metabolic clearance [63]
Gallbladder	Gallbladder	Contractility, bile composition [64]
Oral/Salivary	Salivary glands, oral mucosa	Saliva flow, acinar cell integrity, mucosal thickness [62,65]

Table 1: Organs groups by physiologically and clinically relevant systems with key aging markers and functional outcomes.

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- **Data Acquisition Strategy:** We integrate molecular, structural, and functional domains to capture organ-specific aging comprehensively. Literature-based functional assessments encompassed a multi-level strategy ensures a comprehensive synthesis of the literature, enabling identification of consistent biomarkers, structural correlates, and performance measures of aging across organs while highlighting gaps for future empirical validation. Building on the analytical framework, we synthesize evidence on molecular, structural, and functional measures in relation to computational models of organ-specific aging. Studies employing machine learning for biological age estimation, trajectory modelling of longitudinal change, and integrative network analyses will be mapped to evaluate how well organ age gaps predict morbidity, mortality, and resilience. Particular attention will be given to how covariates such as sex, lifestyle, comorbidities, and genetic risk are incorporated, and whether patterns of asynchronous or systemic aging emerge across organ systems. This approach will provide a cohesive overview of methodological strategies, highlight strengths and limitations of current modelling practices, and identify areas where harmonization and standardization are most needed to advance translational relevance.

Clinical implications

Aging is a heterogeneous, multi-dimensional process characterized by distinct organ-specific trajectories and molecular hallmarks that collectively shape healthspan, functional decline, and disease susceptibility [2,14,39]. Chronological age alone is insufficient to guide care, as individuals often exhibit asynchronous aging across organs; instead, biomarkers such as proteomic signatures, epigenetic clocks, telomere length, and mitochondrial function enable personalized biological age assessment and risk stratification for cardiovascular, neurodegenerative, metabolic, and musculoskeletal diseases [17]. Subclinical organ-specific decline, including vascular stiffening, hippocampal atrophy, or pancreatic β-cell dysfunction, can be detected prior to overt disease onset, creating opportunities for preventive interventions such as lifestyle modification, pharmacologic therapy, regenerative medicine, or senolytic approaches to preserve function [66]. Because organ systems age interdependently, integrated monitoring of organ-specific biomarkers alongside cellular hallmarks such as senescence, SASP, and stem cell exhaustion is essential for guiding multidisciplinary care [26,27]. Table 2 displays the differences in aging across organs and organ systems. Therapeutic strategies targeting hallmarks of aging, including genomic stability, telomere preservation, proteostasis, and mitochondrial optimization, offer translational promise to mitigate systemic decline, while senolytics that eliminate SASP-producing senescent cells may reduce chronic inflammation and improve resilience [67]. Ultimately, mapping organ-specific and molecular aging markers to clinical outcomes such as cognition, mobility, and sensory function enables precision geroscience approaches, where interventions like cognitive training, exercise, hearing restoration, and nutritional optimization are prioritized for individuals at highest risk. Table 3 provides estimated lifespan of human organs in systems.

Limitations

Despite rapid advances, significant limitations constrain the clinical translation of organ-specific and molecular aging markers. A central challenge is the heterogeneity of biomarkers: aging trajectories vary markedly across tissues, individuals, and populations, with proteomic, epigenetic, and telomeric signatures influenced by genetic background, environmental exposures, and lifestyle, thereby limiting

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predictive accuracy and the establishment of standardized benchmarks [39]. Most existing studies are cross-sectional, providing static snapshots rather than longitudinal insight into the tempo and sequence of aging, underscoring the need for decades-long prospective studies to validate predictive models and refine risk stratification [2]. Furthermore, organ accessibility remains a major barrier, as direct assessment of critical tissues such as the brain, pancreas, and hypothalamus often requires invasive procedures or costly imaging and omics platforms, while non-invasive surrogates (e.g., blood or saliva biomarkers) may incompletely reflect tissue-specific heterogeneity. Translating molecular hallmarks into interventions is equally complex: approaches such as senolytics, mitochondrial-targeted therapies, and stem cell strategies are largely experimental, with uncertain long-term efficacy and potential safety risks, while the interdependence of organ systems limits the benefit of single-target interventions. Finally, demographic variables (e.g., sex, ethnicity, socioeconomic context) as well as age-related comorbidities such as diabetes, hypertension, and renal dysfunction, significantly influence both biomarker expression and organ-specific vulnerability, necessitating stratified analyses and raising questions about generalizability across populations. Collectively, these constraints highlight the need for standardized, longitudinal, and demographically inclusive approaches to establish aging biomarkers as reliable tools for precision medicine.

Conclusion

Aging is a complex, multi-layered process governed by molecular, cellular, and organ-specific dynamics. Integrating organ-specific functional trajectories with molecular hallmarks provides a framework for understanding the heterogeneity of aging and its clinical consequences. Organs age asynchronously, creating "organ age gaps" that predict disease susceptibility and mortality [39]. Genomic instability, telomere attrition, epigenetic dysregulation, loss of proteostasis, mitochondrial dysfunction, stem cell exhaustion, and cellular senescence collectively drive tissue decline [2,67]. Early detection of accelerated organ and cellular aging can guide preventive strategies, inform personalized interventions, and prioritize systemic resilience in aging populations. Longitudinal, multi-organ studies integrating molecular, cellular, and functional biomarkers are needed to refine predictive models, identify high-risk individuals, and develop safe, effective therapies to extend healthspan.

Ultimately, a biologically informed understanding of aging can shift the paradigm from reactive disease management to proactive preservation of physiological function, supporting longer, healthier, and more resilient lives.

Organ/System	Onset of Aging (yrs)	Estimated Lifespan	Rationale / Evidence Basis
Central Nervous System			
Brain (cerebral cortex) [68,69]	~40	40	Cortical thinning, synaptic loss, and impaired neurotransmission.
Cerebellum [70,71]	~50	40	Purkinje cell loss and motor coordination decline.

Spinal Cord [72]	~40	40	Neuronal loss, demyelination, and reduced plasticity begin in midlife.
Pineal Gland [73]	~40	40	Decline in melatonin production affects circadian regulation and sleep.
Endocrine System			
Adrenal Glands [74]	~20	20	Early decline in adrenal androgen secretion (DHEA/DHEAS) contributes to immune, metabolic, and musculoskeletal changes.
Hypothalamus [47]	~50	40	Decline in hypothalamic regulation of endocrine and circadian systems.
Pituitary Gland [46]	~40	40	Decline in GH and gonadotropins; contributes to sarcopenia and reproductive senescence.
Parathyroid Glands	~50	50	Altered calcium homeostasis; contributes to osteoporosis and frailty.
Thyroid Gland [75]	~60	60	Reduced hormone output; metabolic decline and susceptibility to hypothyroidism.
Cardiopulmonary System			
Heart [39,72,76]	~30	30	Early changes in diastolic function, arterial stiffening, and reduced cardiovascular reserve.
Arteries [76]	~30	30	Onset of endothelial dysfunction and arterial stiffening, predictive of hypertension/atherosclerosis.
Lung [53]	~35	35	Decline in FEV1 and FVC; reduced elastic recoil and alveolar surface area.
Bronchi [53]	~35	35	Structural airway changes and increased susceptibility to obstruction/infection.
Diaphragm [44]	35	40	Reduced contractile strength and endurance; contributes to decreased ventilatory reserve with aging.

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Trachea [77]	35	40	Loss of cartilage flexibility and mucociliary clearance; predisposes to airway collapse and infection.
Larynx [51]	35	40	Vocal fold atrophy and calcification of laryngeal cartilages; presbyphonia and swallowing difficulties emerge.
Pharynx [78]	35	50	Reduced neuromuscular coordination and sensory function; increased aspiration and dysphagia risk
Diaphragm [44]	35	35	Reduced contractile strength and endurance; contributes to decreased ventilatory reserve with aging.
Nasal Cavity [79]	35	40	Decreased mucosal blood flow and olfactory receptor function; impaired smell and mucociliary clearance.
Nose [52]	35	40	Structural weakening and cartilage changes alter airflow; diminished olfaction and increased dryness.
Musculoskeletal System			
Skeletal Muscle [42,80]	~30	30	Sarcopenia begins with loss of muscle fibers and motor neurons; progressive decline in strength and function.
Muscles (general) [42,80]	~30	30	Reduced oxidative capacity, mitochondrial dysfunction, and impaired regenerative potential.
Bone [43,81,82]	~35	35	Reduced bone mineral density, especially in trabecular bone; accelerated in women post-menopause.
Tendon [45]	~35	40	Collagen cross-linking and reduced vascularity impair repair capacity.

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Ligament [82]	~40	40	Decreased elasticity and impaired repair; predisposes to musculoskeletal injury.
Joints [43,82]	~50	50	Onset of cartilage degeneration, osteoarthritis, and inflammation.
Renal/Urinary			
Kidney	~35	40	Progressive decline in renal blood flow and glomerular filtration rate (GFR); loss of nephron mass and reduced concentrating ability.
Bladder	~40	40	Decreased bladder capacity and compliance; detrusor overactivity and impaired contractility contribute to urgency and incontinence.
Ureters/Urethra	~60	60	Decreased elasticity and sphincter function; higher risk of urinary retention, incontinence, and infection.
Gastrointestinal System			
Pancreas [83]	~40	John et al., 2004	Reduced β-cell function and insulin sensitivity, increasing risk for diabetes.
Reproductive Systems			
Seminal vesicles [61,84]	40	40	Decline in secretory function and reduced seminal volume with age.
Cowper's gland [85]	40	40	Reduced glandular secretion contributes to ejaculatory and fertility decline.
Vas deferens [61,84]	40	40	Structural changes impair sperm transport efficiency.
Epididymides [61,84]	40	40	Loss of motility maturation support for sperm with advancing age.
Prostate [58]	40	40	Hyperplasia and altered androgen responsiveness develop with age.
Penis [61,84]	40	40	Vascular and connective tissue changes contribute to erectile dysfunction.
Testes [61,84]	40	40	Decline in spermatogenesis, testosterone, and increased DNA fragmentation in sperm.
Scrotum [61,84]	40	40	Loss of elasticity and altered thermoregulation affecting testicular function.

Vagina [59]	30	30	Collagen loss and reduced lubrication begin peri-menopause.
Clitoris [59]	30	30	Decline in vascularity and sensitivity observed relatively early.
Mammary gland	25	30	Earliest onset; involution and stromal remodeling begin in mid-20s.
Ovaries [59]	30	30	Follicular depletion and mitochondrial dysfunction underpin reproductive aging.
Vulva [59]	30	30	Thinning epithelium and reduced elasticity reflect estrogen decline.
Fallopian tubes [59]	30	30	Ciliary loss and fibrosis impair gamete transport by early adulthood.
Cervix [59]	30	30	Early epithelial and stromal remodeling reduce regenerative potential.
Uterus [59]	30	30	Early fibrotic changes and reduced regenerative potential occur in reproductive years.
Sensory System			
Ear [96]	30	30	Presbycusis begins with progressive loss of high-frequency hearing.
Olfactory epithelium [62]	60	40	Decline in olfactory receptor neurons and neurogenesis, often later than other senses.
Eye [10,69]	40	40	Presbyopia, lens stiffening, and age-related retinal decline begin mid-life.

Table 2: Age of Onset Across Organs and Organ Systems with Scientific Rationale.

Contributions

Mohd Iskandar Jumat: Conceptualization, Writing – original draft, Writing – review & editing. Florisa Landa: Writing – review & editing. Nur Shafawati Saili: Writing – review & editing. Siti Azmah Jambo: Writing – review & editing. Fiona Macniesia Thomas: Writing & data collection. Raz Haziqah Hani Razali: Writing & data collection. Max Michael Samson: Writing & data collection. Brenda Son Pei Chui: Writing & data collection. Aziera Farhanah Adihidayah Suardi: Writing & data collection. Mike KS Chan: Supervision, editing & reviewing. Michelle BF Wong: Supervision, editing & reviewing. Krista Casazza:

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Supervision, editing & reviewing. Jonathan RT Lakey: Supervision, editing & reviewing. Thomas Skutella: Supervision, editing & reviewing.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

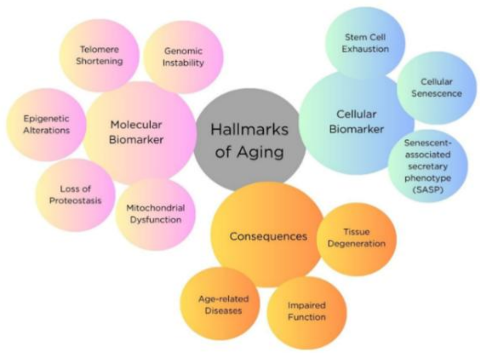

Figure 1: The hallmarks of aging categorized into molecular and cellular biomarkers. Molecular biomarkers include genomic instability, telomere shortening, epigenetic alterations, and mitochondrial dysfunction, which contribute to tissue degeneration. Cellular biomarkers such as stem cell exhaustion, cellular senescence, and the senescence-associated secretory phenotype (SASP) collectively promote age-related diseases. Both molecular and cellular alterations synergistically impair physiological functions, accelerating tissue decline and increasing susceptibility to chronic diseases associated with aging.

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