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Obesity and biological aging across the life course: A geroscience framework for metabolic health

Paulina Correa-Burrows [a,i,*], Raquel Burrows [b,c], Brian K. Kennedy [d,e], Christian Gonzalez-Billault [b,f,g,h,i,*]

[a] Human Nutrition Unit, Institute of Nutrition and Food Technologies (INTA), Universidad de Chile, Chile
[b] Public Nutrition Unit, Institute of Nutrition and Food Technologies (INTA), Universidad de Chile, Chile
[c] Childhood and Adolescent Obesity Clinic, Institute of Nutrition and Food Technologies (INTA), Universidad de Chile, Chile
[d] Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[e] Departments of Biochemistry and Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[f] Department of Biology, Faculty of Sciences, Universidad de Chile, Chile
[g] Department of Neuroscience, Faculty of Medicine, Universidad de Chile, Chile
[h] The Buck Institute for Research on Aging, USA
[i] Geroscience Center for Brain Health and Metabolism (GERO), Santiago, Chile

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ABSTRACT

In this narrative translational review, we propose that obesity and aging are not merely parallel epidemics, but biologically convergent processes with shared metabolic and molecular substrates. We introduce the Obesity-Accelerated Aging (ObAGE) framework, arguing that excess adiposity functions as a clinically relevant accelerator of biological aging trajectories. Because much of the supporting human evidence is observational, we use acceleration to indicate earlier appearance or increases in aging-related biological signatures and clinical phenotypes, while recognizing that causal strength varies across aging pathways and study designs. By prematurely engaging core aging hallmarks, including dysregulated nutrient sensing, chronic low-grade inflammation, cellular senescence, and epigenetic drift, obesity may intensify aging-related decline without replacing the underlying aging process, progressively eroding physiological resilience before overt cardiometabolic disease becomes clinically manifest. This convergence helps explain why obesity does not simply increase risk for isolated non-communicable diseases but is associated with earlier multimorbidity and functional impairment. Importantly, this biological embedding begins during sensitive life-course windows. Yet, converging evidence from human studies (from lifestyle interventions to incretin-based pharmacotherapy) suggests that several aging-related signatures remain at least partially modifiable through metabolic optimization. Framing obesity within a geroscience paradigm positions metabolic treatment not only as disease management but also as a strategy to preserve physiological capacity and delay aging-related decline.

1. Introduction

Extended life expectancy, one of humanity's greatest medical achievements, has paradoxically increased the number of years lived with chronic disease and disability [1]. Non-communicable diseases (NCDs) now account for the majority of global morbidity and premature mortality [2]. Beneath their heterogeneous clinical manifestations lies aging, the strongest risk factor for most major NCDs, characterized by progressive loss of cellular resilience and systemic homeostasis. Geroscience has increasingly reframed aging from a passive consequence of time to a set of interconnected biological processes that are, at least in part, modifiable [3,4]. Biological age varies among individuals of the same chronological age, predicts clustering of cardiometabolic and other NCDs, and in some contexts appears responsive to targeted metabolic or lifestyle interventions [5]. Critically, early-life exposures can durably imprint these aging trajectories decades later [6,7].

Among population-relevant modifiers of aging biology, obesity warrants particular attention. Beyond excess weight, obesity is a systemic disease characterized by adipose tissue dysfunction, insulin resistance, ectopic fat deposition, chronic low-grade inflammation, and

* Corresponding authors at: Institute of Nutrition and Food Technologies (INTA), Universidad de Chile, Chile.
E-mail address: chrgonza@uchile.cl (C. Gonzalez-Billault).

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altered nutrient-sensing pathways that collectively increase cardiometabolic, oncological, and neurodegenerative risk [8–10]. Now affecting more than one billion individuals worldwide [11], obesity may act as a population-scale accelerator of biological aging trajectories. Mechanistic convergence between obesity and aging biology is increasingly recognized: excess adiposity is associated with engagement or dysregulation of multiple aging hallmarks, including altered insulin/IGF-1 signaling, mitochondrial stress in metabolically active tissues, chronic inflammatory activation resembling senescence-associated secretory phenotypes, and epigenetic alterations observed in human studies [12–14]. This overlap provides a clinically relevant opportunity to better understand how metabolic dysfunction may shift the timing of functional decline, multimorbidity, and frailty across the life course, as well as advancing geromedicine, the clinical application of geroscience [15]. From a geroscience perspective, obesity is more than a risk factor for isolated NCDs; it is increasingly linked to accelerated biological aging signatures associated with earlier loss of intrinsic capacity and reduced physiological resilience. Yet, current epidemiological and clinical frameworks rarely explicitly integrate aging biology into obesity management.

To address this gap, in this narrative translational review, we argue that integrating geroscience with NCD epidemiology provides a unified framework for understanding how obesity shapes aging trajectories across the life course. By aligning population-level epidemiological patterns with mechanistic and clinical evidence, we aim to clarify conceptual blind spots, identify cross-disciplinary research priorities, and illustrate how geroscience-informed perspectives may refine prevention and clinical strategies.

Within this integrative approach, we introduce the Obesity-Accelerated Aging (ObAGE) framework, which conceptualizes obesity not merely as a precursor to disease but as a population-relevant accelerator of biological aging. Here, 'acceleration' refers to the earlier emergence or amplification of aging-associated biological signatures and clinical phenotypes—an inference supported primarily by longitudinal and cross-sectional human studies, with causal strength varying across specific pathways and hallmarks. ObAGE is intended as a conceptual tool rather than a diagnostic construct or formal causal model, integrating biological, clinical, and population evidence to illustrate how excess adiposity may shift the timing and intensity of aging-related changes without displacing established frameworks for obesity or aging.

From an evolutionary perspective, the capacity to store energy in the form of adipose tissue has likely conferred a survival advantage during periods of fluctuating food availability, supporting reproduction, immune function, and resilience to environmental stressors. In contemporary environments characterized by chronic caloric abundance and reduced energetic demands, however, this adaptive trait may become maladaptive [121,122]. This evolutionary mismatch may help explain why sustained excess adiposity leads to persistent metabolic stress and low-grade inflammation, creating conditions that favor the premature engagement of biological aging pathways. Within this framework, obesity can be viewed not only as a risk factor for disease but also as a context in which evolutionarily conserved metabolic programs, when chronically activated, contribute to the acceleration of biological aging processes across the life course.

To support the conceptual framework, we conducted a structured, non-systematic literature search of PubMed, Scopus, Web of Science, OpenAlex, and Semantic Scholar for English publications (Jan 1, 2000–Sept 30, 2025). Search terms covered obesity across the life course, epidemiological endpoints and aging markers. We prioritized meta-analyses, large cohorts, and human interventional studies. Animal or in vitro studies were excluded. Final selection focused on rigor, relevance to life-course obesity, and informing obesity-geroscience links. Details are in Supplementary Appendix 1.

2. Obesity and lifespan: Beyond the BMI curve

Few conditions have reshaped survival trajectories as profoundly as obesity. Decades of epidemiological data show a consistent association between excess adiposity and premature mortality, although this relationship is often reduced to simplified BMI-based curves. Large prospective cohorts, including studies with more than 100,000 participants and extended follow-up, report 1.26–3.14-fold higher all-cause mortality among individuals with obesity compared with normal-weight counterparts. In pooled global analyses, hazard ratios increase progressively from 1.41 to 1.48 in moderate obesity to 2.60–2.92 in severe obesity [16]. Life expectancy is reduced by 2–5 y in obesity [17,18] and by 8–13 y in severe obesity [19,20], with greater reductions often observed in men [9,19–23].

However, these summary estimates obscure substantial biological heterogeneity. Survival differences are strongly influenced by adipose tissue distribution, ectopic fat deposition, insulin resistance, and the chronic inflammatory milieu that characterizes metabolically unhealthy phenotypes. BMI, while convenient for population surveillance, does not distinguish between subcutaneous and visceral adiposity nor capture hepatic steatosis, skeletal muscle lipid infiltration, or cardiometabolic dysfunction [24]. These metabolically active fat depots are closely linked to mitochondrial stress, impaired nutrient sensing, vascular injury, and systemic inflammation, processes also implicated in biological aging.

Methodological considerations further complicate interpretation. Exclusion of smokers and early deaths, reverse causation, and regression dilution may distort effect sizes [25–28]. Many cohorts rely on single BMI assessments, failing to account for cumulative adiposity exposure or life-course metabolic trajectories [29,30]. Long-term follow-up from childhood into adulthood suggests that early-life obesity is associated with elevated midlife mortality, consistent with sustained metabolic embedding. Moreover, the predominance of data from European ancestry populations limits understanding of ethnic variation in adipose distribution and metabolic risk.

From the ObAGE perspective, these patterns may reflect more than excess weight. Obesity is a chronic state of dysregulated energy and inflammation that accelerates aging pathways. Instead of replacing aging, obesity may amplify or prematurely trigger mechanisms that reduce reserve, shortening survival. This metabolic-aging view shifts focus from BMI thresholds to the biological effects of adiposity-driven metabolism stress.

3. Obesity and healthspan: Living longer but unhealthier

Over the past century, global life expectancy has markedly increased. However, gains in survival have not been matched by proportional extensions in metabolically healthy years [1]. A substantial proportion of later life is now spent with cardiometabolic and degenerative disorders that reflect progressive loss of systemic resilience. Obesity contributes materially to this mismatch. Across the life course, excess adiposity is associated with patterns consistent with premature metabolic dysregulation, earlier loss of physiological reserve, and earlier clustering of NCDs, as conceptually illustrated in Fig. 1.

3.1. *Obesity, frailty, and multimorbidity*

Frailty and multimorbidity are often viewed as unavoidable consequences of chronological aging, yet evidence increasingly reveals them as expressions of accelerated biological aging. Multimorbidity, defined as the coexistence of $\geq$2 NCDs, frequently reflects cumulative metabolic stress, chronic low-grade inflammation, and progressive impairment of energy regulation across organ systems. Frailty represents loss of physiological reserve and reduced capacity to recover from stressors. Although conceptually distinct, they frequently overlap, with 72% of frail adults also exhibiting multimorbidity [31]. Obesity amplifies both

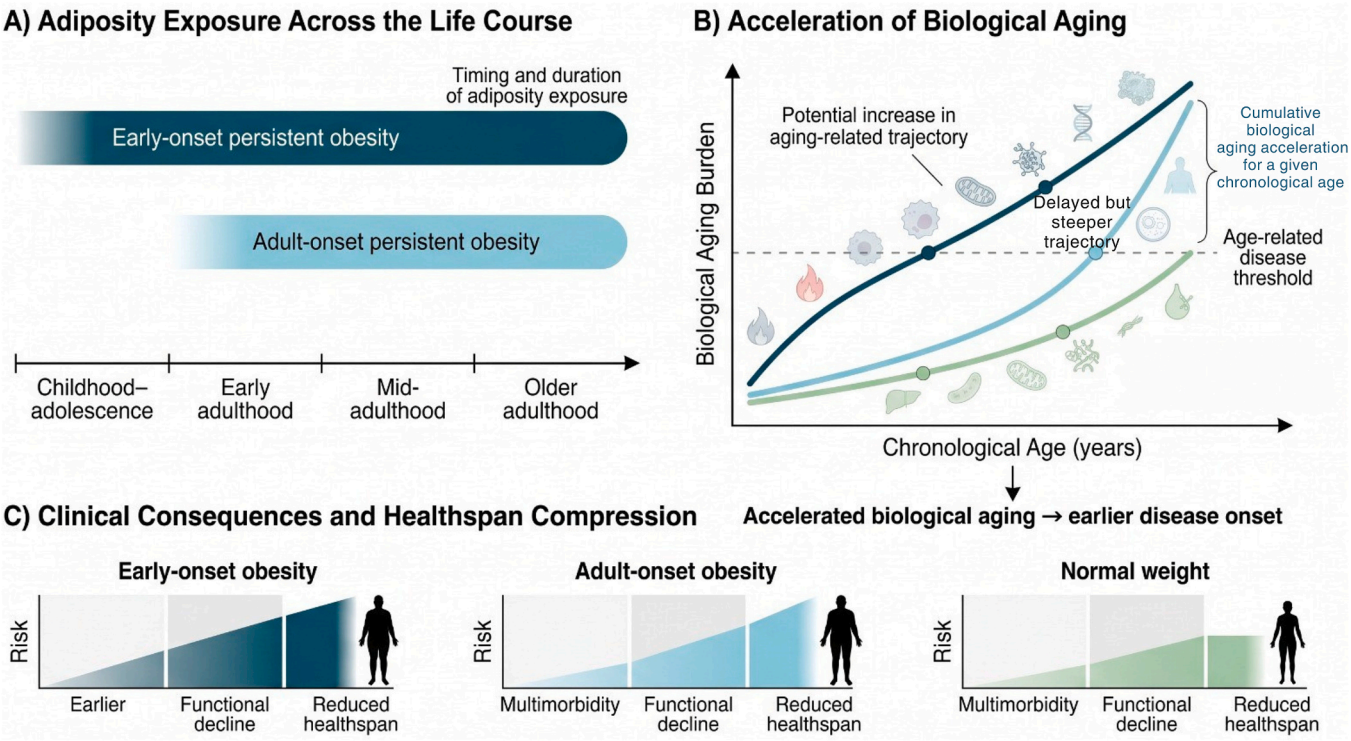

Fig. 1. Life-course obesity is associated with accelerated biological aging trajectories and compression of healthspan. (A) Schematic representation of the timing and duration of adiposity exposure across the life course, distinguishing early-onset persistent obesity from adult-onset obesity. (B) Conceptual trajectories illustrating how obesity exposure may be associated with earlier emergence and/or amplification of biological aging–related processes compared with a reference trajectory. These patterns are consistent with an "acceleration" of biological aging, understood here as a shift in the timing or intensity of aging-related biological changes rather than a strictly causal or unidirectional process. Importantly, these relationships may be bidirectional, as early alterations in metabolic and aging-related pathways can also contribute to the development or persistence of obesity. (C) Potential clinical implications across the life course, where differing obesity trajectories are associated with earlier onset of multimorbidity, functional decline, and reduced healthspan. These patterns reflect cumulative biological burden over time and may vary substantially depending on individual susceptibility, adiposity distribution, and metabolic context. They are also consistent with the ObAGE framework, in which timing and persistence of adiposity exposure shape the tempo and expression of aging-related biological processes.

processes. Longitudinal studies consistently show that midlife obesity increases the likelihood of multimorbidity up to 5-fold compared with normal weight [32,33]. A pooled analysis of 43 studies found a clear dose–response relationship: each 1 kg/m^2 increase in BMI is associated with a 6% increase in multimorbidity risk [34]. Notably, Finnish and UK cohorts reveal that middle-aged adults with obesity develop multimorbidity profiles typically observed in healthy-weight individuals in their 70s [35]. Frailty follows a similar pattern. Obesity at 47 y predicts nearly a 4-fold increase in frailty by 60 y [36], and obesity between 35–50 y strongly predicts later-life frailty in the French GAZEL cohort [37]. Large surveys such as NHANES and SHARE further confirm that overweight, obesity, and severe obesity are each associated with higher frailty scores cross-sectionally and longitudinally [38]. Together, these findings challenge the notion that frailty and multimorbidity are inevitable corollaries of aging. Instead, obesity seems to accelerate the biological clock, compressing later-life vulnerabilities into midlife and shifting the tempo of age-related physiological decline. These epidemiological observations are consistent with sustained insulin resistance, adipose tissue dysfunction, and inflammatory activation acting as shared biological substrates that lower the threshold for multiple disease states to emerge in parallel.

3.2. Obesity and cancer: Accelerating oncogenic aging

Age is the strongest risk factor for cancer, reflecting decades of cumulative genomic damage, impaired immune surveillance, and metabolic decline. Obesity is associated with activation of metabolic and inflammatory pathways that overlap with age-related oncogenic processes. Hyperinsulinemia, altered IGF-1 signaling, adipokine imbalance, and lipid-mediated oxidative stress provide plausible mechanistic bridges between excess adiposity and age-associated tumorigenesis [39,40]. Evidence suggests that carcinogenic risk signatures may begin early in life. Danish health registry studies show that persistent childhood obesity predicts higher adult cancer incidence, including 2.5-fold higher oesophageal, 3.2-fold higher gastric, and 1.3-fold higher pancreatic cancer after age 60 [41,42]. Overweight Israeli adolescents have doubled odds of pancreatic cancer by 40 years of age [43]. Historical data from the UK Carnegie Survey link higher BMI trajectories from 2 to 14 years to a 22% increase in lifetime cancer risk. Sustained obesity in adulthood exacerbates this risk [44]. In the NIH-AARP cohort, individuals with obesity from youth to midlife experienced ~80% higher hepatocellular carcinoma incidence by 62 y [45]. UK Biobank data show that obesity at 40–69 y increases risk for many cancers (e.g., oesophageal, gastric cardia, colon, liver, pancreas, ovary, and brain) by ~40% over 14 y [46]. Collectively, these findings reframe obesity as a powerful contributor and accelerator of oncogenic aging. In an era of precision preventive medicine, interventions that improve metabolic health across childhood, adolescence, and midlife may be as crucial for cancer control as advances in early detection and treatment.

3.3. Obesity and early neurodegenerative risk

Alzheimer's disease and related dementias (ADRD) are leading contributors to global disability. While aging remains the predominant risk factor, midlife obesity is among the strongest modifiable risk factors for ADRD [47]. Emerging evidence indicates that bidirectional metabolic–neuronal signaling is a key mechanism linking obesity to early neurodegeneration. Adipose-derived extracellular vesicles may cross the

blood–brain barrier, disrupting lipid homeostasis and facilitating aggregation of amyloid-β (Aβ) [48]. Central insulin resistance and systemic metabolic inflexibility may further impair neuronal bioenergetics, lowering the threshold for amyloid and tau-related pathology. Circulating $A\beta_{42}$ levels correlate strongly with BMI and fat mass in adults aged 23–64 y [49], and elevated $A\beta_{42}$ is already detectable in adolescents with obesity and insulin resistance [50], implying that amyloidogenic processes may begin decades before clinical symptoms. Longitudinal evidence reinforces the view of midlife as a critical period. In the Whitehall II Study, obesity at age 50 nearly doubled dementia risk [51]. Pooled analyses of the UK Biobank, ARIC, and Framingham Offspring cohorts indicate that individuals with both obesity and metabolic dysfunction have the highest dementia risk (HR = 1.16–1.89) [52]. Abdominal obesity confers greater risk than general obesity [53], and the strongest associations occur when obesity emerges between ages 30–39 (RR = 2.1–5.6) [54]. These findings support the view that obesity relates to sustained metabolic–inflammatory dialogue with the brain, accelerating amyloidogenesis and neuronal vulnerability. Preventing and treating obesity in young and mid-life adults should therefore be a core component of dementia risk-reduction strategies.

3.4. *Obesity and the premature unfolding of cardiometabolic aging*

Cardiometabolic disturbances are core manifestations of biological aging, reflecting convergent changes in inflammation, oxidative stress, mitochondrial dysfunction, vascular remodelling, and pathological fat accumulation. Because aging and metabolism are tightly coupled, obesity—a state of profound metabolic imbalance—does not just precede cardiometabolic disease; it accelerates the tempo of metabolic aging, an early-emerging and clinically detectable dimension of biological aging. Across diverse populations, obesity in infancy, childhood, and adolescence substantially increases risk of hypertension [55,56], T2D [57–59], coronary heart disease [60], and ischemic heart disease [61] in mid-adulthood. In individuals with persistent life-course obesity, dyslipidemia, insulin resistance, and β-cell dysfunction are already detectable in their 20s [6,62–64]. Adipose tissue aging provides a compelling biological explanation. With age, adipose depots undergo mitochondrial damage, hormonal decline, altered adipokine signaling, and increased cellular senescence. Obesity is linked to premature activation of the same pathways [13,14], amplifying susceptibility to metabolic injury [65]. Epidemiological patterns mirror this biology. In the Cardiovascular Disease Lifetime Risk Pooling Project, obesity was associated with higher lifetime CVD risk, earlier onset, and fewer CVD-free years. Hazard ratios for incident CVD rose stepwise across BMI categories, with the highest risks observed in morbid obesity [9]. Women with obesity and rising BMI in early adulthood had a tenfold increased risk of T2D by 40–45 y [66]. Metabolic aging signatures appear in the liver as well: estimated liver age increases by ~2.7 y for every 10-unit rise in BMI [67], and substantial weight gain since adolescence markedly increases NAFLD risk in adulthood [68]. Early-adult obesity also doubles the odds of chronic liver disease later in life [69]. Collectively, these findings support a unifying concept: obesity is associated with earlier and more intense activation of biological aging pathways across metabolic, vascular, cardiac, and hepatic systems, shifting disease onset earlier in the life course and compressing the duration of healthy cardiometabolic function.

4. Obesity and primary aging hallmarks

Aging is increasingly conceptualized as a progressive decline in molecular and metabolic resilience across interconnected cellular and tissue systems, a paradigm captured by the hallmarks of aging [12]. Among the primary hallmarks, those that initiate downstream dysfunction, human evidence indicates that obesity is associated with earlier and more intense engagement of epigenetic drift, telomere attrition, and impaired protein quality control, directly linking excess adiposity to molecular aging processes within the ObAGE framework.

Epigenetic drift, the progressive loss of DNA methylation fidelity affecting gene regulation and metabolic programming, is a fundamental feature of biological aging [70]. Validated epigenetic clocks such as Horvath's, GrimAge, PhenoAge, and Hannum consistently show that obesity is associated with epigenetic age acceleration across diverse populations [67,71–78]. Across population-based cohorts, higher BMI correlates with measurable epigenetic age acceleration, with Finnish twin studies suggesting approximately one month per BMI unit, and US young-adult cohorts showing stronger associations in males [72,75]. Life-course data add resolution: a Chilean birth cohort demonstrated that obesity originating in childhood or adolescence was associated with a 2–5-year increase in biological age by 29 years [6]. This effect appears amplified in metabolically active tissues. In human liver samples, epigenetic age increases by 2.7 years per 10-unit BMI rise [67], and visceral adipose tissue from adults with severe obesity shows pronounced BMI-related age acceleration [76]. Because DNA methylation patterns regulate pathways central to insulin signaling, lipid metabolism, and inflammatory tone, these observations may reflect sustained metabolic stress reshaping gene regulatory networks. Importantly, epigenetic trajectories show partial plasticity. Weight reduction exceeding 5%, achieved through very-low-calorie ketogenic diets, multicomponent lifestyle interventions, or metabolic surgery, has been associated with reductions in epigenetic age ranging from 1 to 9 years, with concurrent improvements in physical function and hepatic steatosis [77–79]. These findings suggest that metabolic optimization may coincide with partial normalization of epigenetic aging signatures, although durability of functional gains requires further longitudinal confirmation.

Telomere attrition constrains cellular replicative capacity and increases susceptibility to NCDs [80,81]. Higher adiposity consistently correlates with shorter leukocyte telomere length across multiple cohorts; in women, obesity-related shortening approximates nearly a decade of biological aging [82]. Mendelian randomization analyses support a directional relationship consistent with adiposity contributing to telomere shortening [83]. Chronic oxidative stress, lipotoxicity, and sustained hyperinsulinemia likely increase replicative stress in proliferative tissues, accelerating telomere erosion. In severe obesity, telomeres may be up to 30% shorter than in lean counterparts, often accompanied by impaired mitochondrial function [84,85]. Interventional data indicate potential reversibility: following gastric bypass, telomere length nearly doubled within six months, alongside marked reductions in telomere oxidation [86]. Mediterranean diet interventions and intragastric balloon treatments show similar favorable shifts in telomere dynamics [87,88].

Emerging human evidence also links obesity to impaired protein quality control. **Proteostasis and macroautophagy**, essential for maintaining cellular integrity, decline with age and are tightly regulated by nutrient-sensing pathways including mTOR and AMPK. Obesity-associated nutrient excess may chronically suppress autophagic flux and proteasomal activity, contributing to proteotoxic stress in metabolically active tissues. Altered autophagic markers have been documented in visceral adipose tissue and adipose-derived stromal cells from individuals with obesity [119,120]. Although mechanistic evidence in humans remains less extensive than for epigenetic and telomeric hallmarks, available data suggest that obesity is associated with convergent disruption of multiple primary aging processes.

Collectively, these findings indicate that obesity is associated with earlier disruption of core molecular systems that maintain genomic stability, replicative capacity, and protein quality control, as illustrated in Fig. 2. Improvements in metabolic health appear to coincide with partial normalization of these hallmarks, suggesting that metabolic interventions may influence upstream biological aging pathways, although long-term functional durability remains to be established.

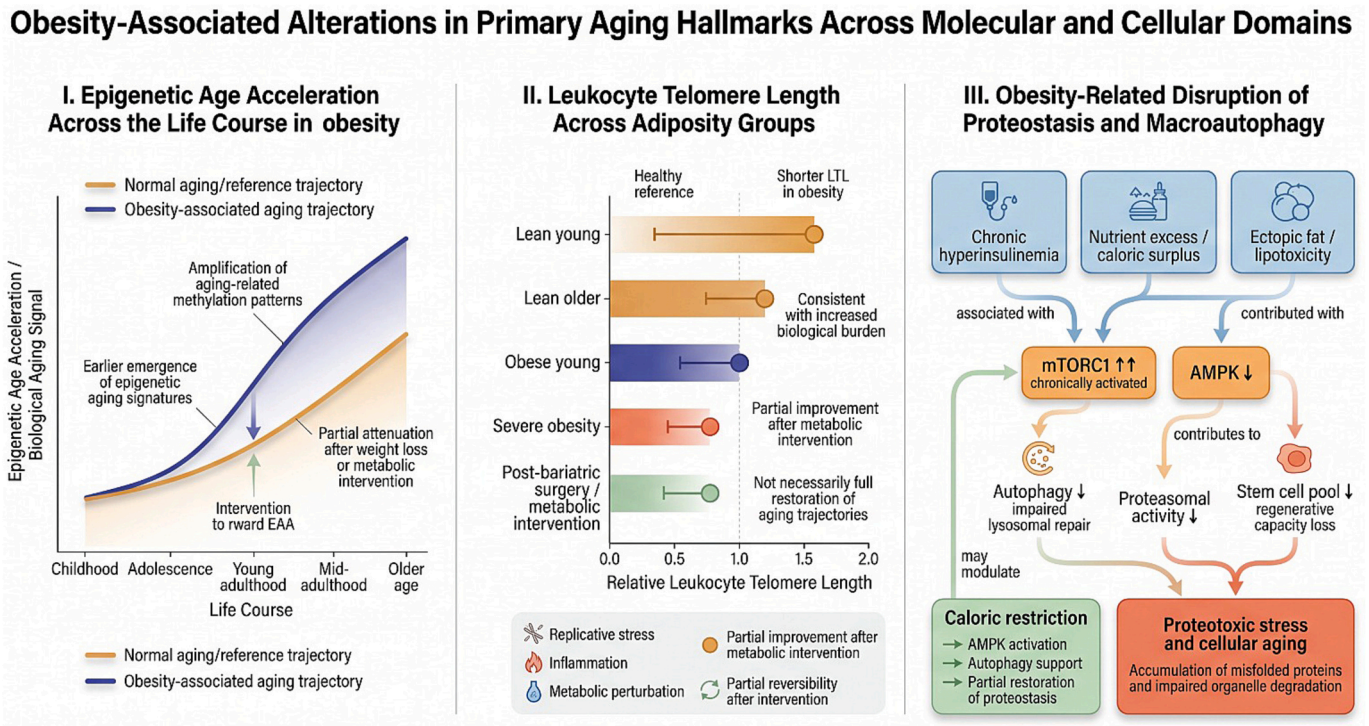

Fig. 2. Obesity-associated alterations in primary aging hallmarks across molecular and cellular domains. (I) Epigenetic age acceleration (EAA) trajectories across the life course, comparing a reference aging trajectory with patterns associated with obesity. Differences are interpreted as earlier emergence or amplification of aging-related epigenetic signatures, rather than strictly causal or unidirectional effects. Interventions such as weight loss are associated with partial attenuation of these signatures, although the magnitude and durability of these changes may vary across contexts. (II) Leukocyte telomere length (LTL) across adiposity groups and following metabolic intervention. Shorter telomere length observed in individuals with obesity is consistent with increased biological burden and replicative stress, although telomere dynamics are influenced by multiple factors beyond aging per se, including inflammation and metabolic perturbation. Improvements following bariatric surgery suggest partial reversibility, but do not necessarily indicate restoration of underlying aging trajectories. (III) Conceptual model linking obesity-related metabolic perturbations to disruption of proteostasis and macroautophagy. Chronic nutrient excess, hyperinsulinemia, and lipotoxicity are associated with sustained activation of mTORC1 and relative suppression of AMPK signaling, contributing to impaired autophagy, reduced proteasomal activity, and accumulation of proteotoxic stress. These processes overlap with established hallmarks of aging, but may also reflect broader responses to metabolic stress. Interventions such as caloric restriction and exercise may modulate these pathways, highlighting their potential, but still incompletely defined, role in shaping aging-related biology.

5. Obesity and antagonistic aging hallmarks

The antagonistic hallmarks (cellular senescence, dysregulated nutrient sensing, and mitochondrial dysfunction) represent adaptive programs that become maladaptive when chronically activated [12]. Human evidence indicates that obesity is associated with sustained activation of these pathways, potentially shifting them from protective responses to contributors to metabolic and systemic decline.

Obesity is consistently associated with markers of **increased cellular senescence** across multiple tissues. In adipose-derived stromal cells, BMI correlates positively with key senescence regulators ($p16^{INK4a}$, $p21^{Cip1}$, p53) and with increased expression of senescence-associated genes (including p16, p21 and p53), together with pro-inflammatory SASP factors such as IL-6 [89]. A systemic 'senescent profile', characterized by elevated circulating activin A, PAI-1, TNFR1, and VEGF alongside reduced RAGE, has been observed in older adults with higher BMI, suggesting overlap with biological aging signatures [90]. These phenotypes extend beyond adipose tissue. Middle-aged adults with obesity demonstrate upregulation of senescence-associated transcripts in skeletal muscle and bone marrow stem cells, accompanied by insulin resistance and increased DNA damage [91]. Importantly, interventional data suggest partial reversibility: calorie restriction has been associated with reductions in circulating SASP factors proportional to weight loss, and exercise interventions may improve skeletal muscle senescence signatures [92,93]. Collectively, these findings are consistent with obesity contributing to a pro-senescent, pro-inflammatory milieu resembling aspects of inflammaging, consistent with the idea that sustained obesity-associated inflammatory and senescent signaling may contribute to the development of aging-like systemic inflammation.

Human studies indicate that **mitochondrial function** and bioenergetic flexibility may also be impaired in obesity-associated tissue environments. Adipose-derived stem cells exposed to an obese extracellular matrix exhibit reduced respiratory capacity and diminished membrane potential [93]. In cardiac tissue, young individuals with obesity show suppressed expression of mitochondrial biogenesis regulators (TFAM, NRF-1), patterns resembling those observed in advanced age [94]. Weight reduction through calorie restriction has been associated with improvements in mitochondrial quality control and reductions in oxidative stress markers [95]. These observations suggest that obesity may interact with age-related mitochondrial vulnerability, particularly in metabolically active tissues.

Obesity is further associated with **dysregulation of nutrient-sensing pathways**, especially within the insulin–IGF axis. Chronic hyperinsulinemia is associated with sustained mTOR pathway activation, potentially impairing autophagy, protein homeostasis, and maintenance of adult stem cell pools. In adults with obesity, acute endurance exercise fails to elicit the expected increase in circulating IGF-1 and IGFBP-3, indicating altered IGF-axis responsiveness [96]. Young adults with persistent life-course obesity display dysregulation of IGF-1 and IGF-2 alongside elevated insulin levels, correlating with epigenetic age acceleration and telomere shortening [6]. In large-scale cohorts such as the UK Biobank, patterns consistent with impaired nutrient signaling are

associated with increased risk of multimorbidity, including fatty liver and hypertension [97], conditions frequently clustering with obesity and reflecting broader metabolic dysregulation.

Together, these convergent alterations indicate that obesity is associated with sustained perturbation of senescence, mitochondrial bioenergetics, and nutrient-sensing pathways central to the metabolic dimension of biological aging, as shown in Fig. 3. Such disturbances may shift the timing at which age-related physiological vulnerability becomes clinically manifest, without replacing the underlying aging process itself.

6. Obesity and integrative hallmarks of aging

Integrative hallmarks (chronic inflammation, stem-cell exhaustion, and impaired intercellular communication) represent the systemic consequences of accumulated cellular damage [12]. In the ObAGE framework, these processes converge to create a biological landscape that mirrors and may contribute to earlier or amplified manifestations of functional decline typically observed with advancing age.

Chronic low-grade inflammation, often referred to as meta-flammation, is a defining signature of obesity. In this context, meta-flammation reflects a nutrient-driven, metabolically induced inflammatory state that may remain partially reversible. When sustained over time, however, it may contribute to the development of a more persistent, systemic inflammatory milieu resembling inflammaging, a hallmark of biological aging. Elevated IL-6 and CRP are consistent across the life course, appearing as early as young adulthood, and correlating with telomere attrition and oxidative stress [6,84,98]. Visceral adipose tissue (vWAT) acts as a central amplifier: in obese adults, vWAT accumulates senescent macrophages (~70% CD68+), a profile associated with impaired insulin action and heightened systemic inflammaging [99,100]. Crucially, this inflammatory trajectory is modifiable. Long-term calorie restriction has been shown to reduce CRP by 40% and TNF-alpha by 50% [101], suggesting that lifestyle-based interventions may partially normalize obesity-associated inflammatory profiles linked to aging biology.

Regarding **stem-cell exhaustion**, obesity is associated with features consistent with impaired regenerative capacity by exhausting mesenchymal stromal/stem cell (MSC) niches. Adipose-derived MSCs from individuals with obesity show premature senescence, reduced proliferative capacity, and impaired angiogenic support [89,102,103]. This exhaustion also extends to the bone marrow, where metabolic and oxidative environments commonly observed in obesity are associated with stromal shifts toward adipogenic lineages, contributing to compromised skeletal integrity and bone fragility [92]. Data from the Finnish Twin Cohort, validated against the UK Biobank, also suggest that obesity disrupts normal age-related patterns of stem cell precursors, patterns consistent with an earlier decline in tissue-specific regenerative

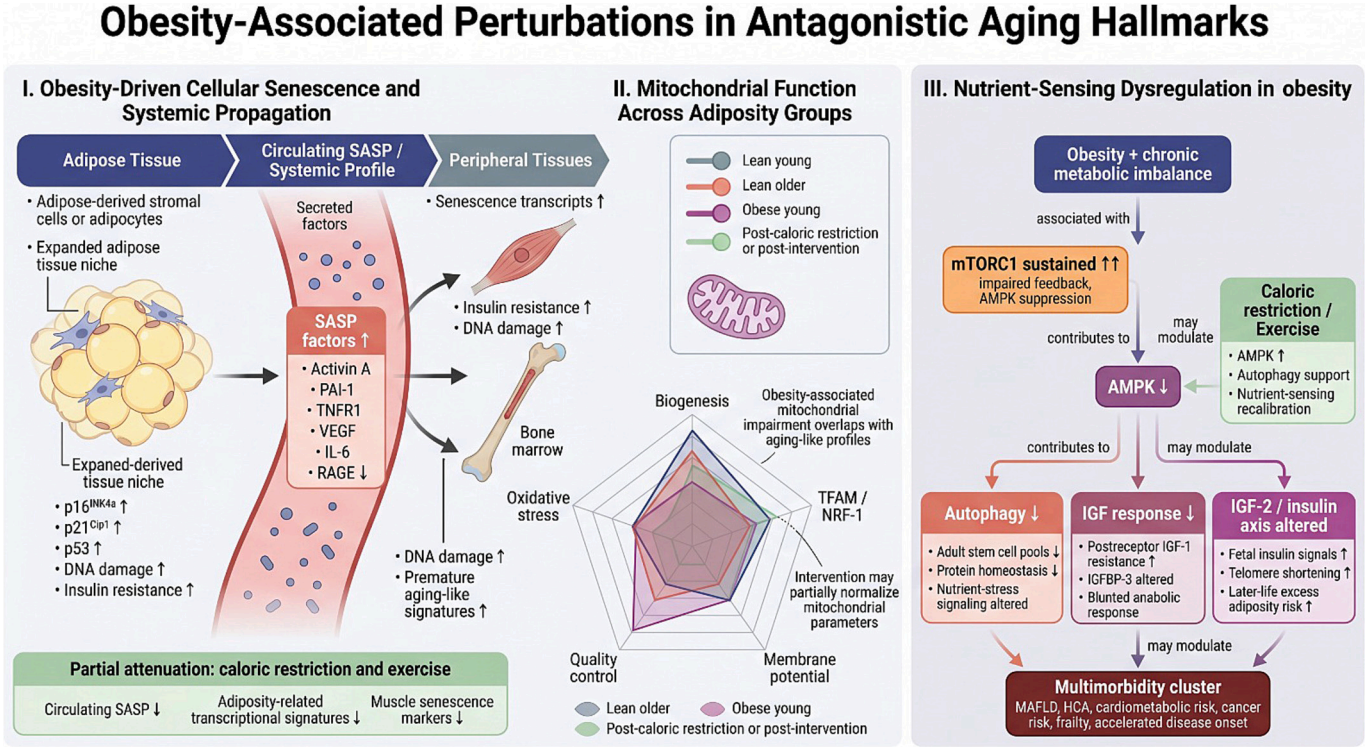

Fig. 3. Obesity-associated perturbations in antagonistic aging hallmarks. (I) Conceptual model of cellular senescence and its systemic propagation in obesity. Adipose-derived stromal cells (ADSCs) from individuals with obesity show increased expression of senescence-associated regulators (e.g., $p16^{INK4a}$, $p21^{Cip1}$, p53), accompanied by insulin resistance and DNA damage. This is associated with a circulating profile enriched in senescence-associated secretory phenotype (SASP) factors, including Activin A, PAI-1, TNFR1, and VEGF, alongside reduced RAGE. Similar transcriptional signatures are observed in skeletal muscle and bone marrow, suggesting a systemic pattern consistent with senescence-related biological changes. Interventions such as caloric restriction and exercise are associated with partial attenuation of these signatures. (II) Radar chart illustrating mitochondrial function across adiposity groups. Individuals with obesity exhibit patterns consistent with reduced mitochondrial biogenesis, impaired membrane potential, diminished quality control, and increased oxidative stress, resembling profiles observed in older individuals. Post-intervention states (e.g., caloric restriction) are associated with partial normalization of these parameters, although the extent to which these changes reflect modification of underlying aging processes remains uncertain. (III) Conceptual cascade of nutrient-sensing dysregulation in obesity. Chronic metabolic imbalance is associated with sustained activation of mTORC1 and relative suppression of AMPK signaling, contributing to impaired autophagy, altered IGF-axis responsiveness, and downstream metabolic and cellular consequences. These alterations overlap with established antagonistic aging hallmarks, but may also reflect adaptive or maladaptive responses to persistent nutrient excess. Together, these pathways are associated with increased multimorbidity risk, although their role in driving versus reflecting biological aging processes may vary across contexts. These associations are predominantly observational and should be interpreted with caution.

potential [104].

The deterioration of **intercellular communication** across hormonal, metabolic, and immune networks is a defining feature of aging. Obesity is associated with features consistent with impaired intercellular signaling, in part through dysfunctional SASP-mediated crosstalk [89,102]. For example, young adults with obesity display features consistent with B-cell immunosenescence and autoimmune IgG secretion comparable to lean older individuals, a phenotype associated with elevated palmitate exposure [92]. These findings are consistent with obesity-associated immune dysregulation and may reflect altered intercellular communication within metabolic and immune networks. Also, young adults with life-course obesity show impaired muscle-adipose tissue communication with higher apelin, irisin, myostatin, osteocrin, and oncostatin vs healthy controls, consistent with altered myokine patterns that may be metabolically maladaptive [6]. This cell-to-cell communicative breakdown has systemic reach:

- Hematopoietic: Obesity has been linked to clonal hematopoiesis, a marker of myeloid bias and elevated cardiovascular risk [105].
- Musculoskeletal: Fat infiltration into muscle (myosteatosis) and maladaptive myokine signaling (e.g., apelin, myostatin) may exacerbate sarcopenia and reduce physiological resilience [6,106].
- Neurodegenerative: Adipocyte-derived extracellular vesicles enriched with pro-inflammatory and pro-senescent markers can cross the blood–brain barrier, potentially linking early-life obesity to later neurodegenerative risk through amyloidogenic priming [47–49].

Together, these integrative hallmarks support the view that obesity extends beyond isolated disease risk, altering hormonal, immune, and metabolic communication networks that help maintain systemic homeostasis across the lifespan (Fig. 4). While gut microbiome changes are linked to aging biology, evidence linking obesity-related dysbiosis to biological aging metrics is lacking. We focus on integrative hallmarks supported by convergent human data.

7. Discussion: Clinical and translational implications of obesity-associated biological aging

7.1. *Mechanistic convergence and biological aging*

The strength of evidence linking obesity to aging biology varies across levels of investigation. Large epidemiological studies consistently demonstrate associations with premature mortality, multimorbidity,

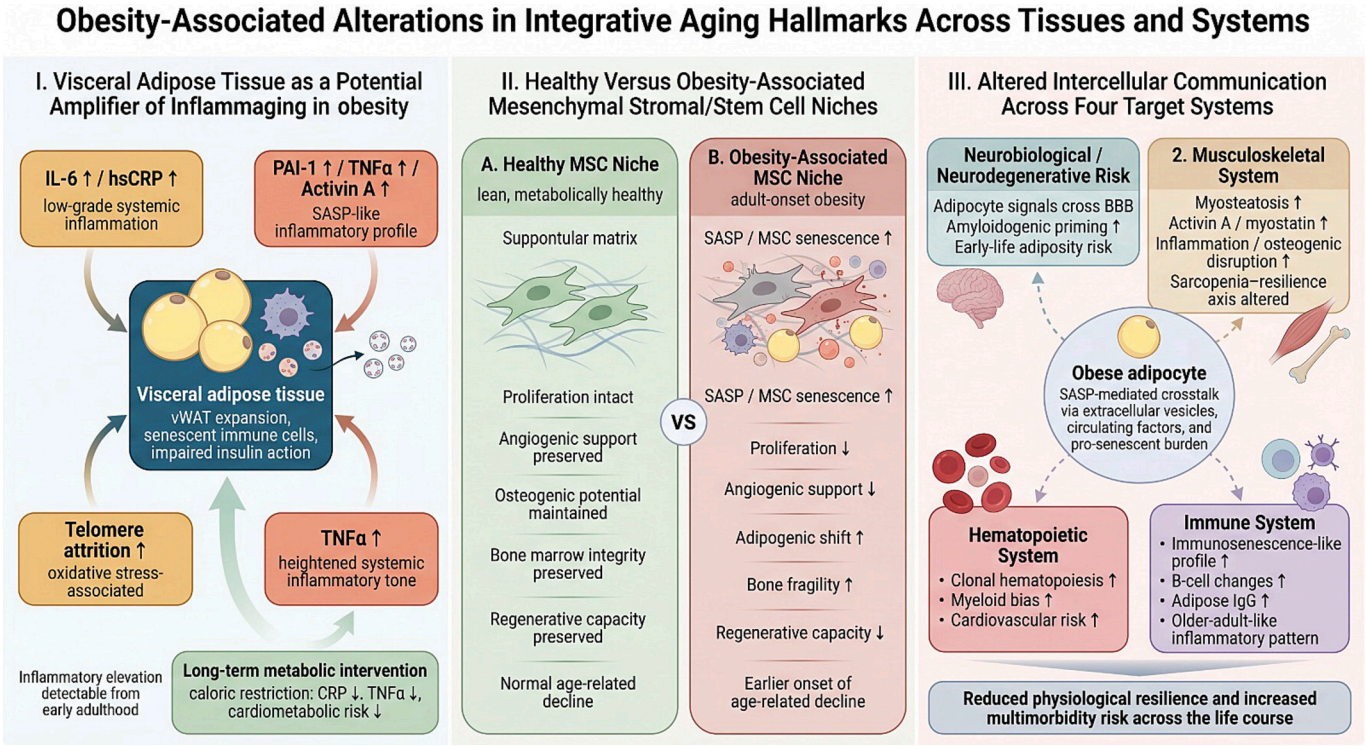

Fig. 4. Obesity-associated alterations in integrative aging hallmarks across tissues and systems. (I) Visceral adipose tissue (vWAT) as a central amplifier of systemic inflammation in obesity. In individuals with obesity, vWAT accumulates senescent immune cells and exhibits increased secretion of pro-inflammatory mediators (e.g., IL-6, TNFα, PAI-1, Activin A), contributing to a chronic, nutrient-associated inflammatory state. This profile overlaps with features of inflammaging, although it may arise from sustained metabolic stress rather than intrinsic aging processes. Markers of inflammation are detectable from early adulthood and are associated with oxidative stress and telomere attrition. Long-term metabolic interventions (e.g., caloric restriction) are associated with partial attenuation of these inflammatory signatures. (II) Comparison of healthy versus obesity-associated mesenchymal stromal/stem cell (MSC) niches. In metabolically healthy conditions, MSCs maintain proliferative capacity, angiogenic support, and regenerative potential. In obesity, these niches exhibit features consistent with premature functional decline, including reduced proliferation, altered differentiation bias, and increased secretion of senescence-associated factors. These changes are consistent with earlier emergence of aging-related phenotypes, although their extent and reversibility may vary across tissues and individuals. (III) Conceptual model of altered intercellular communication across organ systems in obesity. Obese adipose tissue is associated with systemic crosstalk mediated in part by extracellular vesicles and circulating factors, influencing immune, hematopoietic, musculoskeletal, and neurobiological pathways. These alterations are associated with patterns resembling immunosenescence, clonal hematopoiesis, impaired muscle maintenance, and increased neurodegenerative risk. However, these processes likely reflect complex interactions between metabolic stress, tissue-specific vulnerability, and aging-related pathways, rather than a single unifying mechanism. Together, these integrative alterations may contribute to increased multimorbidity risk and reduced physiological resilience across the life course. I. Visceral adipose tissue as potential amplifier of inflammaging in obesity. II. Healthy vs obesity-associated mesenchymal stromal/stem cell niches. III. Breakdown of intercellular communication across four target systems.

and reduced functional reserve. Associations with molecular aging markers, such as epigenetic clocks, telomere dynamics, and nutrient-sensing alterations, are more heterogeneous and often context-dependent. Nevertheless, across hallmarks, a coherent pattern emerges: excess adiposity is associated with engagement of biological pathways that overlap substantially with those implicated in aging, suggesting that obesity may function as a driver of accelerated biological aging, particularly through metabolic pathways. Rather than viewing obesity and aging as parallel processes, the available human evidence supports the concept of convergence between metabolic dysfunction and biological aging processes. Obesity is associated with earlier or amplified expression of aging-related biological signatures across multiple tissues, including adipose, liver, muscle, and vascular compartments. Importantly, much of this evidence remains observational, and causal strength likely differs across pathways. However, the consistency of multi-system involvement provides a biologically plausible explanation for why obesity-related multimorbidity frequently resembles clinical phenotypes typically observed at more advanced chronological ages. Many of these processes converge within adipose tissue itself, where excess adiposity alters nutrient sensing, mitochondrial function, inflammatory signaling, and cellular senescence pathways, positioning dysfunctional adipose depots as central nodes linking metabolic disease with biological aging. From a metabolic perspective, this convergence reframes obesity as a condition characterized not only by excess adiposity but by altered biological aging within metabolically active tissues. This construct may help integrate molecular findings with clinical observations of early cardiometabolic deterioration, reduced physiological reserve, and vulnerability to stressors.

While the framework presented here emphasizes obesity as a potential accelerator of biological aging, the directionality of these relationships is likely complex and, in many cases, bidirectional. Early or subclinical alterations in aging-related pathways, such as low-grade inflammation, mitochondrial dysfunction, hormonal changes, and declines in physical activity, may themselves contribute to the development or progression of obesity. These reciprocal interactions suggest self-reinforcing feedback loops in which metabolic dysfunction and aging-related biological changes amplify one another over time. As such, in several contexts, obesity may act both as a driver and as a consequence of underlying biological processes associated with aging. While longitudinal and interventional studies provide stronger support for temporal relationships in specific domains, much of the available human evidence remains observational, and causal inference should therefore be interpreted with appropriate caution.

An additional consideration relates to the specificity of commonly used aging biomarkers. Many markers discussed in this context, including epigenetic clocks, inflammatory indices, and metabolic signatures, are not exclusive to aging processes per se but may also reflect broader states of physiological stress or chronic metabolic perturbation. In this sense, their interpretation as indicators of "accelerated aging" should be made with caution. Within the ObAGE framework, the concept of "acceleration" is not intended to imply a singular or strictly causal process, but rather to capture a spectrum of related phenomena, including earlier onset of aging-associated biological changes, amplification of underlying pathways, or increased co-occurrence of processes driven by shared upstream mechanisms. This interpretation is consistent with the predominantly observational nature of the available human evidence and aims to preserve conceptual clarity while avoiding overextension of causal inference.

7.2. Clinical implications: From anthropometry to biological risk stratification

Modern clinical management of obesity has traditionally focused on individual disease risk (e.g., type 2 diabetes, cardiovascular disease, fatty liver disease, and cancer) [107,108], often guided primarily by BMI thresholds. While BMI remains useful at a population level, it provides limited insight into metabolic heterogeneity and does not capture the biological processes underlying differential risk [29]. A metabolic-aging framework suggests that risk stratification may benefit from integrating markers that reflect tissue-specific injury and biological resilience. Measures of fat distribution (e.g., visceral and ectopic fat), insulin resistance, inflammatory burden, and, where feasible, emerging aging-related biomarkers may offer a more nuanced understanding of risk than anthropometry alone. Such an approach does not replace existing metabolic models but extends them by incorporating indicators of biological tempo. Importantly, this perspective shifts the clinical question from whether obesity increases risk to how obesity may modify the timing and intensity of metabolic decline. Identifying individuals in whom obesity is associated with accelerated biological signatures may enable earlier intervention and more precise targeting of therapies aimed at restoring metabolic stability and preserving functional capacity. Moving beyond anthropometric measures toward biologically informed risk assessment may reshape how obesity-related risk is conceptualized in both clinical practice and research settings. Selected clinical and translational considerations emerging from this perspective are summarized in Table 1.

7.3. Early metabolic imprinting and vulnerability windows

A key insight from integrating life-course epidemiology with geroscience is that obesity may influence biological aging trajectories much earlier than traditionally appreciated. Human data indicate that persistent obesity from childhood or adolescence is associated with measurable alterations in epigenetic age acceleration, nutrient-sensing pathways, insulin–IGF signaling, and inflammatory tone in young adulthood [6,7]. These findings suggest that early-life metabolic environments may shape long-term biological tempo. From a clinical perspective, this concept reframes obesity in youth not only as a predictor of future disease, but as a potential modifier of underlying aging-related biology within metabolically active tissues. Early adiposity is associated with persistent insulin resistance, altered adipokine profiles, and chronic low-grade inflammation—conditions that overlap mechanistically with pathways implicated in age-related decline. While causality remains to be definitively established, the convergence of molecular, tissue-specific, and longitudinal cohort data supports the plausibility of early metabolic imprinting. This framework may also help explain why certain clinical phenotypes emerge prematurely. For example, individuals with obesity whose biological age substantially exceeds their chronological age may exhibit cardiometabolic risk profiles typically observed decades later [6,7,75]. In women, such shifts could intersect with hormonal transitions, potentially altering the timing of loss of estrogen-associated cardiometabolic protection. These hypotheses require further validation but align with observed patterns of earlier multimorbidity in individuals with persistent life-course obesity. Importantly, recognizing early metabolic imprinting does not imply irreversibility. Rather, it underscores the importance of identifying critical windows in which interventions may have disproportionate long-term effects on metabolic resilience. Preventive strategies targeting childhood, adolescence, and early adulthood may therefore represent opportunities not only to reduce disease incidence but to modulate the biological trajectories that shape aging-related changes in metabolic function. While the concept of early-life metabolic imprinting and sensitive windows is supported by converging biological and epidemiological observations, the longitudinal evidence directly demonstrating sustained effects on biological aging trajectories remains limited. As such, the current framework relies in part on biological plausibility and indirect inference from cross-sectional and cohort data. Future studies integrating long-term follow-up, repeated biomarker assessments, and interventional designs across the life course will be essential to define the timing, persistence, and reversibility of these effects. Clarifying these dynamics represents a key priority for advancing the integration of life-course epidemiology with geroscience.

Table 1
Clinical and translational implications of obesity-associated accelerated biological aging.

- **Expand risk stratification beyond anthropometric measures.** While traditional indices such as BMI capture body size, they do not reflect the underlying biological processes associated with metabolic injury. Incorporating emerging biomarkers—such as epigenetic clocks, inflammatory signatures, and senescence-associated profiles—may improve risk stratification by capturing inter-individual variability in biological aging trajectories. Although their clinical implementation remains under active investigation, these approaches may help identify individuals at higher risk of early functional decline and inform more targeted prevention and intervention strategies.
- **Prioritize early and midlife intervention windows.** Evidence from life-course studies suggests that obesity-related biological processes may become established early in life. Prevention and metabolic optimization during childhood, adolescence, and midlife may therefore represent key opportunities to support healthier aging trajectories.
- **Consider metabolic optimization as a potential modulator of aging-related pathways.** Interventions such as lifestyle modification, bariatric surgery, and incretin-based therapies (e.g., GLP-1 receptor agonists) may influence molecular processes linked to aging biology, although the extent to which these interventions modify biological aging signatures remains an active area of research.
- **Develop multidomain prevention strategies integrating metabolic and geroscience perspectives.** Future clinical approaches may combine metabolic risk management with interventions targeting chronic inflammation, senescence, or nutrient-sensing pathways to improve long-term healthspan outcomes.
- **Advance translational research linking metabolic interventions to biological aging endpoints.** Clinical studies incorporating biomarkers of biological aging alongside functional outcomes may help clarify whether modifying obesity-related metabolic pathways can meaningfully influence aging trajectories.
- **Address equity considerations as precision metabolic and geroscience approaches evolve.** As biological-age biomarkers and multiomic profiling enter clinical research, efforts to ensure diverse representation and equitable access will be essential to avoid widening existing health disparities.
- **Evaluate the feasibility of integrating biological-aging indicators into clinical and population research frameworks.** Validated biomarkers of aging may eventually complement traditional metabolic indicators in monitoring long-term health trajectories and evaluating intervention efficacy.

7.4. Modifiability and translational implications

One of the most clinically relevant implications of this synthesis is that obesity-associated aging signatures appear, at least partially, modifiable. Human interventional studies show that metabolic improvement, through intensive lifestyle modification, bariatric surgery, or selected pharmacologic therapies, is associated with shifts in epigenetic age metrics, reductions in circulating senescence-associated factors, improvements in inflammatory tone, and restoration of mitochondrial-related markers [77–79,86–88,101]. These observations support the concept that obesity-related perturbations in aging hallmarks are not fixed states but dynamic biological processes responsive to metabolic recalibration. However, interpreting biomarker improvement requires caution. Changes in epigenetic clocks, telomere dynamics, or senescence-associated profiles do not automatically translate into durable gains in intrinsic capacity, resilience, or delayed multimorbidity. Molecular recalibration may precede, accompany, or, in some cases, fail to produce measurable functional benefit. Future trials should integrate aging-related biomarkers with clinically meaningful endpoints, including cardiorespiratory fitness, muscle strength, hepatic function, cognitive performance, and long-term disease incidence.

The rapid expansion of incretin-based therapies provides a contemporary example of large-scale metabolic intervention with potential implications beyond glycemic control and weight reduction. GLP-1 receptor agonists and dual incretin agonists improve insulin sensitivity, reduce visceral adiposity, attenuate systemic inflammation, and influence mitochondrial and nutrient-sensing pathways [109–112]. Whether these pharmacologic effects translate into sustained modification of biological aging trajectories remains uncertain, but they offer a clinically tractable model to investigate the interface between metabolic optimization and aging biology in humans. Similarly, interest in senescence-modulating therapies and agents such as metformin reflects growing recognition that metabolic and aging pathways are deeply intertwined [113–116]. Obesity, by engaging multiple hallmarks simultaneously, may represent a clinically accessible context in which to test whether targeting fundamental aging-related mechanisms yields additive benefit beyond conventional metabolic control. Ultimately, the translational challenge is not to redefine aging as a disease, but to determine whether integrating biological aging metrics into obesity management improves risk stratification, therapeutic selection, and long-term outcomes. Addressing this question will require rigorously designed trials, extended follow-up, and careful interpretation of biomarker-function relationships. Although emerging evidence suggests that obesity-associated aging signatures may be at least partially modifiable, major knowledge gaps remain regarding the durability, functional relevance, and optimal timing of interventions. Key research priorities that may help address these gaps are outlined in Table 2.

Table 2
Research priorities linking obesity, metabolism, and biological aging.

Priority area	Guiding principles & recommendations
Longitudinal multi-omics and exposome cohorts	Integrate epigenomics, proteomics, metabolomics, and microbiome profiling with detailed environmental and lifestyle phenotyping (the exposome) in diverse populations to characterize biological aging processes associated with obesity and metabolic dysfunction.
Life-course biological-age mapping	Identify sensitive developmental windows (e.g., gestation, childhood, puberty, midlife) during which adiposity is most strongly associated with shifts in biological aging trajectories, helping define optimal timing for preventive metabolic interventions.
Interventional trials with aging endpoints	Use obesity as a clinically tractable model of accelerated biological aging to test interventions targeting aging-related pathways. Clinical trials should complement conventional metabolic outcomes with validated biological aging metrics as exploratory or secondary endpoints.
Mechanistic links to functional decline	Clarify causal pathways linking cellular hallmarks of aging with clinical manifestations such as frailty, sarcopenia, and loss of intrinsic capacity. Particular attention should be given to adipose–muscle crosstalk and systemic metabolic inflammation.
Integration of biological and social determinants of aging	Investigate how social exposures (e.g., chronic stress, socioeconomic adversity) interact with metabolic and molecular pathways to influence biological aging trajectories in populations affected by obesity.
Translation into guidelines and policy	Evaluate the feasibility of incorporating biological-aging biomarkers into metabolic and obesity research, including their use in risk stratification, patient phenotyping, and monitoring responses to metabolic interventions.
Equity considerations in aging biomarker research	Ensure that emerging biological-age tools are validated across diverse populations and implemented in ways that avoid reinforcing health disparities, including efforts to standardize assays and broaden accessibility in clinical research settings.

7.5. Obesity as a clinical model of accelerated biological aging

A persistent barrier in aging research is the difficulty of studying biological aging trajectories within conventional clinical frameworks [117,118]. Obesity offers a clinically definable, measurable, and mechanistically enriched context in which multiple aging-related pathways are simultaneously engaged. Unlike chronological aging,

excess adiposity is a modifiable exposure, allowing investigators to observe how metabolic recalibration influences molecular and functional aging signatures over relatively short time frames. From a translational standpoint, obesity therefore represents not merely a risk state but a human model of accelerated biological aging, particularly along metabolic pathways. Interventions targeting weight reduction, visceral fat redistribution, insulin signaling, and inflammatory tone offer an opportunity to examine whether modulating metabolic stress can meaningfully alter aging-related biological markers and downstream clinical trajectories. This approach does not require redefining aging as a disease, but rather leverages obesity as a tractable entry point for studying aging biology within established metabolic and endocrine paradigms. By embedding aging endpoints into obesity-focused clinical trials, future research can clarify whether improvements in metabolic homeostasis translate into sustained preservation of physiological reserve and delayed multimorbidity.

In this context, considering clinically distinct phenotypes may further refine the interpretation of obesity within aging biology. Among this, sarcopenic obesity represents a particularly informative clinical phenotype at the intersection of obesity and aging biology [123–125]. Characterized by the coexistence of excess adiposity and reduced muscle mass and/or function, it exemplifies how alterations in body composition, rather than adiposity alone, may critically shape aging trajectories. This phenotype is strongly associated with frailty [126], impaired physical performance [127], insulin resistance, and increased risk of adverse outcomes [128], often exceeding the impact of either obesity or sarcopenia alone. From a geroscience perspective, sarcopenic obesity may reflect a state in which metabolic dysregulation, chronic inflammation, and impaired anabolic signaling contribute to the accelerated decline in physiological resilience [123]. As such, it provides a clinically relevant illustration of how obesity-related processes may interact with core aging mechanisms across tissues, reinforcing the importance of moving beyond anthropometric measures toward a more integrated assessment of body composition and functional capacity. This example further highlights the need to translate the ObAGE framework into clinically actionable approaches.

From a clinical perspective, translating the ObAGE framework into practice requires careful consideration of which biological markers and functional measures are sufficiently robust, accessible, and informative for routine use. At present, widely available clinical indicators, such as measures of adiposity distribution, insulin resistance, lipid profiles, inflammatory markers (e.g., hs-CRP), and physical function, provide clinically actionable, albeit indirect, insight into processes that overlap with biological aging. In contrast, more advanced biomarkers, including epigenetic clocks and senescence-associated signatures, remain primarily research tools, with ongoing efforts to improve their standardization, interpretability, and clinical applicability. Within this context, the proposed framework does not seek to redefine clinical decision-making based on aging biomarkers alone, but rather to complement existing risk stratification approaches by integrating metabolic, functional, and emerging biological dimensions. This perspective may support earlier identification of individuals at risk of accelerated functional decline and inform more targeted prevention strategies, while acknowledging that clinically actionable thresholds and long-term outcome validation remain areas of active investigation.

8. Conclusion

Obesity and aging intersect across molecular, cellular, and systemic levels. Accumulating human evidence indicates that excess adiposity is associated with earlier or amplified engagement of aging-related biological pathways, contributing to the premature emergence of multimorbidity and functional decline. While causal strength varies across hallmarks and study designs, the convergence of epidemiologic, tissue-level, and interventional data supports viewing obesity as a modifier of biological aging trajectories. Reframing obesity in a geroscience-informed metabolic context extends, not replaces, clinical models. Incorporating biological aging metrics with traditional assessments can enhance risk stratification and refine therapies. Recognizing obesity as a dynamic factor in aging highlights opportunities: restoring metabolic balance may affect disease risk and systemic decline. Whether this extends healthspan is an empirical question, addressable within metabolic medicine.

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The funders had no role in the study design or conduct; in the selection, analysis, or interpretation of the literature; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication.

Authors' contribution

PC and CGB conceived the review and developed the ObAGE framework. PC and RB designed the search strategy and selection criteria. PC conducted the literature search, which was independently validated by RB. PC drafted the manuscript and designed the tables and figures. BKK and CGB provided supervision and critical intellectual input. PC, CGB, and RB acquired funding. All authors approved the final version and take responsibility for the decision to submit.

CRediT authorship contribution statement

Paulina Correa: Writing – original draft, Funding acquisition, Formal analysis, Conceptualization. **Raquel Burrows:** Writing – original draft, Funding acquisition. **Brian K. Kennedy:** Writing – original draft. **Christian Gonzalez-Billault:** Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization.

Consent for publication

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Grammarly Pro (v14.1258.5 for Windows) to review grammar and enhance readability. Revised versions of all figures were developed with the assistance of the Artlist AI platform, using the authors' original figure designs as the basis. The authors carefully reviewed all AI-assisted outputs and take full responsibility for the final content of the manuscript.

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Declaration of competing interest

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2026.156634.

Data availability

Not applicable.

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