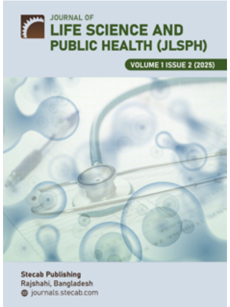

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Review Article

Current Understanding of p53-Dependent Cellular Senescence in Health Disparities: Molecular Insights and Public-Health Strategies

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About Article

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ABSTRACT

Disadvantaged populations age faster and develop chronic disease earlier, but the molecular conduit from social adversity to biology is not fully defined. This review synthesizes molecular, epidemiological, and policy evidence along a single axis: p53-governed cellular senescence. Genomic and metabolic stress stabilize p53, induce p21-mediated cell cycle arrest, and trigger a pro-inflammatory secretory program that compromises tissue function. Conditions concentrated in communities with limited resources, such as, air pollution, ultra-processed diets, chronic stress, and obesity activate these pathways and expand senescent populations in vascular, metabolic, and immune tissues, amplifying atherosclerosis, insulin resistance, and cancer progression. Senolytics (dasatinib plus quercetin, navitoclax, and fisetin) and senomorphics (metformin and rapamycin) show early benefit signals, but translation must be equity-first. The next step is to conduct community-engaged, cluster-randomized pilots that pair senotherapeutics with neighborhood exposure abatement, use co-primary endpoints (multi-omic senescence signatures plus exposure indices), stratify by deprivation, apply adaptive dosing, and track affordability and access, yielding decision rules for scalable, equity-ready implementation.

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1. INTRODUCTION

Cellular senescence is when cells stop dividing permanently due to various stresses, which helps slow down growth and plays a role in aging and preventing tumors (Mijit *et al.*, 2020). The tumor suppressor p53 is a master regulator of this process: upon DNA damage or oncogenic stress, p53 is stabilized (often via ATM/ATR kinases) and transactivates CDKN1A (p21 CIP1), driving cells into senescence or apoptosis to maintain genome integrity (Demidenko *et al.*, 2010; Mijit *et al.*, 2020). Senescent cells also acquire a pro-inflammatory secretory phenotype (SASP) that can alter tissue environments. As such, p53-dependent senescence intersects major age-related pathologies (atherosclerosis, diabetes, neurodegeneration, cancer) (Mijit *et al.*, 2020).

Theory from population health clarifies why these mechanisms matter for disparities. Weathering posits that cumulative social and environmental adversity accelerates physiological wear across the life course (Geronimus, 1992; Geronimus *et al.*, 2006; Forde *et al.*, 2019). John Henryism describes high-effort coping under chronic strain that sustains neuroendocrine and autonomic activation (James *et al.*, 1983; James, 1994; Robinson *et al.*, 2021). Both frameworks predict elevated oxidative and inflammatory load, conditions that produce DNA lesions, stabilize p53, and favor senescence-linked secretory programs.

Concurrently, social determinants profoundly shape population health. Socioeconomic disadvantage, discrimination, and chronic stress in marginalized groups have been linked to “accelerated aging” manifesting as earlier onset of cardiovascular disease, diabetes, and other chronic illnesses (Kivimäki *et al.*, 2025; Noren Hooten *et al.*, 2022). In disadvantaged and minority populations, higher oxidative stress, impaired DNA repair, and chronic inflammation (hallmarks of cellular senescence) are often observed (Noren Hooten *et al.*, 2022). For example, Kivimäki *et al.* recently showed that social disadvantage correlates with age-related proteomic signatures and inflammatory pathways, suggesting that social stratification may accelerate aging via biological mechanisms (Kivimäki *et al.*, 2025; Noren Hooten *et al.*, 2022). These findings highlight that health disparities may reflect, in part, differential biological aging across groups.

Despite this conceptual link, the role of senescence, particularly p53-driven senescence, in mediating health disparities remains underexplored. It is plausible that environmental and lifestyle exposures prevalent in disadvantaged communities (pollution, poor diet, psychosocial stress) trigger DNA damage and oxidative stress, engaging p53 signaling and senescence pathways. Conversely, chronic stress hormones can also dysregulate p53 and promote cell injury (Qin *et al.*, 2024). Such “weathering” at the cellular level may contribute to earlier disease in these populations.

This review synthesizes molecular and population evidence on p53-dependent cellular senescence in the context of health disparities. We first detail p53-senescence pathways and their regulation (RESULTS I). We then examine how environmental, socioeconomic, and lifestyle factors can provoke p53-mediated senescence (RESULTS II). Next, we consider disease contexts where senescence plausibly links to disparity patterns (RESULTS III). We also discuss biomarkers to track senescence (RESULTS IV). In the DISCUSSION, we explore therapeutic and public health strategies and propose future research to bridge molecular geroscience with health equity. Our goal is to illuminate how p53-driven aging intersects with social determinants of health and to identify avenues for interventions that could reduce disparities across the lifespan.

2. LITERATURE REVIEW

Senotherapeutics has progressed from concept to early human testing; however, evidence remains limited and skewed toward homogeneous cohorts. (Calabrò *et al.*, 2024; Lelarge *et al.*, 2024) The first-in-human pilot study of dasatinib plus quercetin (D+Q) in diabetic kidney disease reduced circulating senescent cells and SASP factors, consistent with preclinical work showing that D+Q lowers the adipose senescent burden and improves metabolic indices in mice (Hickson *et al.*, 2019; Lelarge *et al.*, 2024). Navitoclax (ABT-263), a BCL-2/BCL-XL inhibitor, cleared senescent hematopoietic and muscle stem cells in aged mice and shrank therapy-induced senescent tumor populations, but thrombocytopenia limits dosing (Chang *et al.*, 2016; Gulej *et al.*, 2023). Senomorphic strategies, metformin (AMPK activation, SASP dampening), and mTOR inhibition blunt deleterious secretomes without killing cells, offering a potentially safer, scalable route (Abdelgawad *et al.*, 2023; Cheng *et al.*, 2022; Moiseeva *et al.*, 2013).

Parallel “natural” senostatics underscore that behavior and environment modulate senescent load (Luís *et al.*, 2022). Exercise reduces senescent cell accumulation and activates immune clearance mechanisms in animal and human studies; short training blocks can downregulate senescence-related transcripts in metabolic tissues (Zhang *et al.*, 2022). Diet quality and antioxidant availability likewise influence oxidative DNA damage that feeds p53–p21 signaling (Luís *et al.*, 2022). Yet disadvantaged communities face structural barriers to these interventions, unsafe neighborhoods, food deserts, and shift work, raising the risk that biological aging accelerates where resources are scarcest (Kivimäki *et al.*, 2025).

Recent multi-cohort proteomic work confirms that social disadvantage is biologically legible: individuals with lifelong socioeconomic adversity exhibit accelerated immune-aging signatures and age-associated proteins, supporting the hypothesis that inequity “writes itself” into molecular aging pathways (Kivimäki *et al.*, 2025). Chronic stressors may also imprint stable epigenetic modifications, altered DNA methylation, histone marks, and chromatin accessibility that recalibrate p53 transcriptional output, SASP programming, and immune surveillance across the life course. Integrating senescence biomarkers (p16/p21 expression, γ-H2AX foci, SASP panels) into population surveillance is feasible but demands cost-effective assays and digital tools that do not exacerbate the digital divide (Liu *et al.*, 2009; Park & Shin, 2022). Collectively, the literature argues for a dual-action model, targeting senescent cells pharmacologically while dismantling upstream exposures, to narrow the senescence gap that mirrors health disparities (Calabrò *et al.*, 2024; Park & Shin, 2022).

3. METHODOLOGY

A structured search was conducted to identify peer-reviewed evidence on p53-dependent cellular senescence and health disparities.

Databases: PubMed/MEDLINE, Web of Science Core Collection, and Scopus. Search concepts combined: p53/TP53; cellular senescence/SASP; social determinants/health disparities/structural racism; oxidative stress; DNA damage; ATM/ATR; CDKN1A/p21; and disease contexts (cardiometabolic, neurodegenerative, and cancer).

Filters applied: English language, peer-reviewed journals, and human studies where applicable, with a recency-first policy and targeted reach-back to foundational work. Eligible records included primary studies and reviews measuring senescence markers (e.g., p16INK4a, p21CIP1, SA-β-gal, SASP cytokines) or interrogating p53 signaling in relation to population exposures or outcomes; conference abstracts, editorials, and letters were excluded. Screening proceeded in two stages (title/abstract, then full text) using predefined criteria. The data extracted included design, setting, cohort characteristics, exposures, senescence readouts, outcomes, and an analytic approach. Study quality was appraised pragmatically, prioritizing larger or longitudinal cohorts, validated assays, transparent confounder control, and reproducibility indicators; mechanistic animal or in vitro work was retained when it clarified human biology. Reference lists of key papers were hand-searched and forward citations were inspected via Google Scholar. Evidence was synthesized narratively; no meta-analysis was performed.

4. RESULTS AND DISCUSSION

4.1. Molecular Mechanisms of p53-Dependent Senescence

p53 governs senescence through multiple, context-dependent pathways. The canonical route involves DNA damage or telomere attrition activating kinases (ATM/ATR), which phosphorylate and stabilize p53 (Mijit *et al.*, 2020). Active p53 triggers the production of the p21^CIP1 protein, which stops the cell cycle at the G1/S phase to give the cell time to fix itself (Mijit *et al.*, 2020). Persisting damage or replicative limits then drive cells irreversibly into senescence. Besides p21, p53 upregulates myriad targets (e.g. GADD45, miR-34a) that reinforce arrest or promote autophagy.

A parallel axis involves the INK4a/ARF locus. Oncogenic signals often activate p14^ARF, which binds and inhibits MDM2, the E3 ligase that otherwise degrades p53. This interaction between ARF, MDM2, and p53 acts like a brake on uncontrolled growth: when oncogenes activate ARF, it helps keep p53 stable and promotes senescence, which prevents tumors from forming. Meanwhile, the p16 INK4a–Rb pathway collaborates to maintain arrest. Intriguingly, p53-triggered senescence typically initiates first and is then consolidated by p16 INK4a. Mijit *et al.* (2020) note that the p53–p21 module is crucial for early senescence signaling, whereas p16 INK4a locks in the long-term state. A multi-step model emerges: DNA damage leads to p53/p21 activation, which causes a cell-cycle pause; if the damage persists, p16/Rb maintains an irreversible arrest.

Senescence is also modulated by p53's isoforms and feedback. Humans express multiple p53 variants (Δ40p53, Δ133p53α, p53β, etc.) that alter the outcome of p53 activation (Fujita, 2019). N-terminally truncated isoforms temper full-length p53 activity and defer stable senescence, whereas the C-terminal variant p53β tends to intensify the program (Fujita, 2019). Perturbation of isoform balance has been linked to age-related disease (Fujita, 2019). Beyond enforcing growth arrest, p53 modulates the senescence-associated secretory phenotype through crosstalk with NF-κB and influences immune surveillance of aged cells.

Context can also yield suppression of senescence by p53. In p21-arrested cells, increased p53 activity redirected the phenotype from senescence to quiescence via inhibition of mTOR signaling (Demidenko *et al.*, 2010). Therefore, p53 halts proliferation and, under specific conditions, limits the SASP and metabolic remodeling that contribute to the establishment of senescence. The eventual state, durable senescence versus reversible arrest, depends on cellular context and on interactions with pathways such as mTOR (Demidenko *et al.*, 2010).

The p53 network interacts with key processes of senescence, including the DNA-damage response, telomere shortening, oxidative stress, oncogenic signaling, and chromatin remodeling. Connections include controlling TERT, linking to AMPK when the body is under metabolic stress, and working with apoptotic effectors. Senescent cells demonstrate persistent p53 and p21^CIP1 activity, increased p16^INK4a levels, DNA-damage foci, senescence-associated β-galactosidase, and a pro-inflammatory senescence-associated secretory phenotype (SASP) (Kudlova *et al.*, 2022). Figure 1 outlines these relationships. Persistent senescent cells disrupt tissue architecture and drive pathology; distinguishing the initiating triggers of p53-dependent senescence is difficult because different stressors and lineages produce overlapping yet distinct molecular signatures (Kudlova *et al.*, 2022).

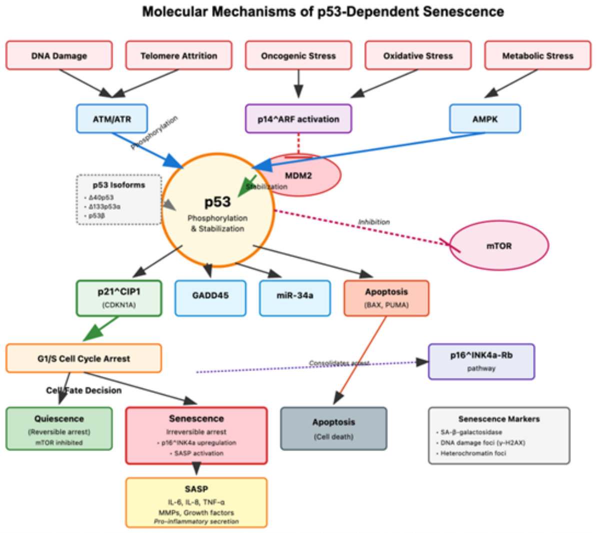

Figure 1. Molecular Mechanisms of p53-Dependent Senescence.

In summary, p53-dependent senescence emerges from a tightly controlled balance of tumor-suppressive signaling. It prevents damaged cell proliferation, but in chronic or widespread form (e.g., in aging tissues), it contributes to dysfunction via inflammation. This duality, which extends life by suppressing cancer and potentially shortens it by promoting age-related decline, paves the way for an examination of how external factors could alter this balance differently in different populations.

4.2. Environmental, Socio-Economic & Lifestyle Determinants

External environments and behaviors profoundly influence p53-mediated senescence. Disadvantaged populations often face higher exposures to pollutants, toxins, and psychosocial stressors that injure DNA or create oxidative stress, prime inducers of p53. For example, urban air pollution (particulate matter, ozone, polycyclic hydrocarbons) generates reactive oxygen species in respiratory and skin cells. Ines Martic *et al.* reviewed how ambient pollutants interact with UV light to inflict oxidative DNA damage in skin, accelerating senescence and premature skin aging (Martic *et al.*, 2022). Heavy metals and tobacco smoke similarly induce genotoxic stress in exposed tissues. Equally, chronic cigarette smoke turns on DNA-damage responses: Nyunoya *et al.* showed that lung fibroblasts exposed to cigarette extract increase ATM/p53/p21 activity, eventually upregulating p16^INK4a and SA-β-gal to enter irreversible senescence. These cellular injuries underlie smoke-related diseases (COPD, lung cancer) (Nyunoya *et al.*, 2006).

Socioeconomic stressors also map onto biological stress pathways. Prolonged psychosocial stress triggers the hypothalamic–pituitary–adrenal axis, raising cortisol and catecholamines. Qin *et al.* (2024) note that chronic stress disrupts mitochondria and sparks oxidative injury to nuclear DNA, thereby activating p53 and promoting accelerated senescence (Qin *et al.*, 2024). In essence, "fight-or-flight" hormones have long-term somatic costs: they push cells into damage responses akin to physical insults. Disadvantaged individuals tend to experience more chronic stress, compounding the biological wear. Inflammation is another conduit: poor diet (high fat/sugar) and obesity provoke systemic inflammation and lipotoxicity. Adipocytes under metabolic duress secrete inflammatory cytokines that create bystander DNA damage, a feedback loop that can involve p53 signaling. Obesity is recognized to induce premature senescence in adipose and liver tissue (Narasimhan *et al.*, 2022). These senescent fat cells produce more SASP factors, perpetuating insulin resistance and vascular inflammation.

Lifestyle choices further modulate this axis. Smoking rates are often higher in lower SES groups, increasing body-wide senescent load via repeated tissue insults. Unhealthy diets (processed foods) and sedentary behavior amplify metabolic stress. By contrast, physical activity is protective: exercise combats senescence by reducing oxidative damage and clearing senescent cells via enhanced immune surveillance (Zhang *et al.*, 2022). Zhang *et al.* propose that regular exercise induces antioxidants and autophagy, preventing cells from reaching the damage threshold that triggers p53-driven senescence (Zhang *et al.*, 2022). Unfortunately, access to safe exercise environments and healthy foods is unequal; many disadvantaged communities live in "food deserts" and environments not conducive to physical activity, reinforcing biological aging disadvantage.

Environmental toxins like tobacco smoke and pollutants disproportionately affect marginalized communities (e.g. areas near highways or industrial sites). The cumulative burden of such exposures, often termed the exposome, raises intracellular oxidative load (Emeny *et al.*, 2021). Emeny *et al.* explain that the "SDOH-exposome" increases stress on cells and long-term inflammation by activating pathways like NF-κB and NLRP3 inflammasomes (Emeny *et al.*, 2021). These, in turn, interact with the p53 network; for instance, NF-κB can suppress p53-mediated apoptosis, potentially favoring senescent phenotypes. Importantly, such exposures are not evenly distributed: lower socioeconomic status correlates with greater pollutant exposure, poor housing (mold, crowding), and limited healthcare access.

Socioeconomic and lifestyle factors modulate cellular aging via p53. We see a cascade: adverse social conditions → increased DNA/oxidative stress → p53 activation → higher senescent cell burden. Over time, this chain reaction raises basal levels of senescence in disadvantaged groups, hastening age-related decline. It is worth noting that some studies (e.g., [83], [124]) use the term "accelerated aging phenotype" to describe these molecular patterns. Although direct measurements (like epigenetic clocks) are still emerging, the congruence of toxic exposures and stress pathways suggests a plausible mechanistic link bridging social inequality to p53-driven cellular senescence (Emeny *et al.*, 2021; Noren Hooten *et al.*, 2022).

4.3. Disease-Specific Manifestations & Disparities

p53-dependent senescence manifests differently across diseases, many of which show marked disparities. In cardiovascular disease (CVD), for example, endothelial and vascular smooth muscle cell senescence are key drivers of atherosclerosis. Ramirez *et al.* (2022) note that senescent endothelial cells secrete inflammatory and matrix-degrading factors, fostering plaque formation. The prevalence of hypertension and early-onset coronary disease is higher in socioeconomically disadvantaged and minority groups. Factors like chronic stress, poor diet, and pollution not only exacerbate CVD risk but may also accelerate vascular senescence via DNA damage and p53 signaling. Epidemiologically, African Americans develop heart disease about a decade earlier on average than whites, potentially a cellular reflection of earlier p53-senescence activation due to life-course stress. These differences reflect patterned exposure to structural and environmental risks rather than intrinsic biological variation associated with racial categories.

Adipocytes, hepatocytes, and pancreatic β-cells all experience cellular senescence as a result of obesity (Narasimhan *et al.*, 2022). Insulin resistance is exacerbated by IL-6, TNF-α, and other SASP mediators released by senescent adipocytes. Excess nutrients and oxidative stress limit the renewal of adipose progenitors by activating p53 in metabolic tissues, upregulating p21, and imposing growth arrest. In line with the dysregulation observed in metabolic syndrome, obesity-linked senescence affects adipogenesis and changes endocrine output (Narasimhan *et al.*, 2022). Senescent cell burdens in metabolic organs are higher in communities with high obesity prevalence and limited access to healthful foods, which raises the incidence of fatty liver disease and type 2 diabetes. Higher inflammatory profiles and faster epigenetic aging are observed in populations with higher diabetes incidence, such as Native Americans and Hispanics, which is consistent with the involvement of p53-regulated pathways. It is critical to emphasize that these disparities are not driven by innate biological differences. Race here operates as a social construct and a proxy for structural disadvantage, food insecurity, environmental exposures, and chronic stress, which elevate oxidative injury and engage the p53-senescence pathway

Exposure patterns shape disease risk in the lung. Tobacco use follows socioeconomic gradients and is associated with lung cancer and COPD. Cigarette smoke extract triggers ATM/p53/p21 signaling in lung fibroblasts, which is followed by the induction of p16^INK4a and SA-β-gal and the eventual transition to irreversible senescence (Nyunoya *et al.*, 2006). The airway epithelium exposed to occupational dust and indoor smoke exhibits similar p53-dependent signaling (Nyunoya *et al.*, 2006). In communities with chronic exposure and limited access to cessation support, senescent cells contribute to an earlier onset and greater severity of COPD by impeding tissue repair and intensifying inflammatory tone. Observed racial disparities in COPD incidence and severity should not be interpreted as biologically innate; race functions as a social construct indexing unequal exposure to smoking environments, workplace hazards, housing conditions, and limited cessation support.

Cancer is a complex case. While p53 is most famous for preventing malignancy, paradoxically, senescence in premalignant cells can become a tumor-suppressive barrier. However, disparities exist: certain cancers (e.g., triple-negative breast cancer, prostate cancer in African Americans) are more aggressive and have different p53 mutation profiles. Chronic inflammation and senescent stroma in these tissues could create a pro-tumorigenic niche. For instance, a senescent fibroblast in a breast tumor microenvironment secretes factors that feed tumor growth. Meanwhile, disadvantaged patients often have later-stage diagnoses and less access to care, compounding outcomes. Thus, even if p53 mutations drive cancer, the environment of senescent cells around a tumor may modulate its behavior and treatment response.

Neurodegenerative diseases (e.g., Alzheimer's) show disparity trends too (some racial/ethnic groups have a higher risk). Senescent glia and neurons are increasingly implicated in neurodegeneration. If chronic stress or metabolic disease accelerates CNS aging, p53-dependent neuronal senescence could contribute to earlier dementia onset in some groups. Although data is still emerging, the connection between systemic factors such as diabetes and hypertension and brain senescence indicates a continuum that extends from social stress to cellular aging and ultimately to disease burden.

Finally, infectious diseases and immunity reflect senescence. Disadvantaged groups often face a higher infection risk (e.g., COVID-19 impact). Immune cells undergo replicative senescence with age and stress, partly mediated by p53/p21. The nature med proteomic study found that social disadvantage correlates with signatures of immune aging (Kivimäki *et al.*, 2025), likely reflecting accumulated senescent immune cells. Such immunosenescence may blunt vaccine responses and infection control.

Across these disease contexts, patterns emerge: populations under chronic stress accrue senescent cells in organs, and those cells secrete factors that amplify pathology. Crucially, what drives disparities is not a new disease but an acceleration of normal aging processes. Whether by DNA damage (from pollutants, UV, etc.) or by chronic inflammation (from obesity, stress), the p53-senescence axis appears to be a common conduit by which social and lifestyle differences become biological differences. Nevertheless, causal evidence is still scant: most mechanistic insights come from cell or animal models, and linking these to human disparity patterns requires careful epidemiological work. The rest of this review highlights potential markers and interventions.

4.4. Biomarkers & Surveillance

Measuring cellular senescence in living humans is challenging, but several biomarkers have been proposed. At the tissue level, senescence is often identified by increased p53 and p21 expression, loss of proliferation markers, and senescence-associated β-galactosidase (SA-β-gal) (Kudlova *et al.*, 2022). Since routine biopsies of internal organs are not feasible for population studies, surrogate biomarkers are sought. One approach is to quantify circulating SASP factors (e.g., IL-6, IL-8, MMPs). Elevated plasma IL-6 or TNF-α, for instance, can reflect an inflammatory milieu often driven by senescent cells.

Another marker is the p16^INK4a expression in peripheral blood T-cells, which increases with age and stress. Several groups have shown that leukocyte p16 correlates with chronological age and smoking history, suggesting it reflects a cumulative senescent burden. Similarly, DNA damage markers like γ-H2AX foci in lymphocytes could serve as proxies of systemic senescence. Emerging "aging clocks" also have relevance: epigenetic clocks (DNA methylation patterns) and proteomic clocks capture biological rather than chronological age. Kivimäki *et al.* used a plasma-protein age clock and linked it to social disadvantage (Kivimäki *et al.*, 2025), indirectly showing that disadvantaged groups have molecular signatures of accelerated aging.

Given the centrality of p53, indirect assays of p53 pathway activation may be informative. For example, measuring telomere shortening in blood cells (which activates p53 when uncapped) can indicate replicative senescence pressure. Newer omics methods (transcriptomic "senescence-associated gene signatures") are being tested. Single-cell RNA sequencing can reveal senescent cell transcripts (p21, SASP genes) in tissues, though this is mostly for research use.

For population surveillance, a multi-marker panel might be ideal. Kudlova *et al.* emphasize that no single biomarker is definitive (Kudlova *et al.*, 2022). Instead, combining cell-cycle inhibitors (p16, p21), damage indicators, and secreted factors yields better sensitivity. Wearable devices or minimally invasive tests, e.g., cell-free DNA (with senescence-associated methylation), are speculative future tools.

Clinically, some diseases use senescence markers: e.g., oncology sometimes gauges p53/p21 in tumors, and ADA guidelines note telomere length in type 2 diabetes studies. However, the translation of these findings to public health surveillance is still in its early stages. Research cohorts increasingly measure epigenetic age and inflammatory markers; adding targeted senescence biomarkers could improve the prediction of healthspan.

In summary, while experimental hallmarks (SA-β-gal, cell-cycle arrest) are well-characterized in vitro, human studies rely on composite biomarkers. Current candidates include elevated p16^INK4a and p21 in blood cells, altered serum cytokines

(SASP), and age-acceleration clocks (Kudlova *et al.*, 2022). Yet specificity is an issue: many age-related processes upregulate these markers. Longitudinal research is needed to validate which markers truly reflect p53-driven senescence in diverse populations. This will underpin future efforts to monitor accelerated aging in relation to disparities.

4.5. Discussion

4.5.1. Therapeutic & Public-Health Interventions

Mitigating p53-driven senescence within health disparities benefits from paired strategies: biologically targeted therapies and socio-environmental measures. On the therapeutic side, senotherapeutics have moved into early testing. Senolytic agents, designed to eliminate senescent cells selectively, reduced adipose senescent-cell burden, lowered inflammatory cytokines, and improved metabolic function in aged or obese mice when administered as dasatinib plus quercetin (D+Q) (Islam *et al.*, 2023). A small clinical study in diabetic kidney disease used intermittent D+Q and reported decreases in circulating senescence markers alongside improvements in renal indices (Hickson *et al.*, 2019; X. Zhu *et al.*, 2024). Evidence is still preliminary, yet these signals indicate that pharmacologic targeting of senescent cells could modify age-related comorbidities that disproportionately affect underserved populations.

In experimental systems, several agents exhibit senolytic activity in addition to D+Q. Across models, the BCL-2 family inhibitor Navitoclax facilitates the selective removal of senescent cells (Gulej *et al.*, 2023; Y. Zhu *et al.*, 2016). Similar effects have been observed with the flavonoid fisetin, either alone or in combination with apigenin; preclinical studies have reported reductions in the burden of senescent cells (Yousefzadeh *et al.*, 2018). The targets and tolerability profiles of these compounds vary, and there is currently a dearth of comparable human data. Instead of eliminating cells, a complementary approach aims to reduce harmful senescent phenotypes. Rapamycin and metformin can replicate aspects of p53's anti-senescence regulation while also modulating mTOR and inflammatory signaling (Abdelgawad *et al.*, 2023; Wang *et al.*, 2017). According to that process, mTOR inhibition reduced SASP-linked alterations and steered p21-arrested cells away from senescence and toward quiescence (Demidenko *et al.*, 2010). The necessity for context-specific regimens is highlighted by the fact that p53 agonists, like MDM2 inhibitors, which are helpful in oncology, may increase senescent burden if dosing or scheduling is not optimal.

A key component of any senotherapeutic program is equity considerations. Constrained availability and high acquisition costs run the risk of concentrating benefits among wealthy patients. Diverse populations should be enrolled in trial portfolios in order to identify differences in efficacy and safety, and delivery strategies should take into account actual obstacles to initiation, adherence, and follow-up.

Table 1. Therapeutic & Public-Health Interventions

Agent / Strategy	Class	Principal target & mechanism	Key evidence (model → finding)	Equity-relevant considerations
Dasatinib + Quercetin (D+Q)	Senolytic	Inhibits pro-survival BCR-ABL/SRC kinases (Dasatinib) & PI3K pathways (Quercetin) to trigger apoptosis of senescent cells	Mouse diabetic-kidney-disease model: D+Q lowered senescent podocytes and improved renal function; small first-in-human pilot showed reduced circulating SASP factors (Zhu *et al.*, 2024)	Orally available generics keep cost low, but safety monitoring (myelosuppression) must be accessible to underserved patients
Navitoclax (ABT-263)	Senolytic	BCL-2/BCL-XL inhibitor dismantles anti-apoptotic shield in senescent cells	Aged mice: intermittent dosing cleared senescent hematopoietic and muscle stem cells, rejuvenating function (Y. Zhu *et al.*, 2016)	Dose-limiting thrombocytopenia requires frequent CBCs—a logistical barrier in low-resource settings
Fisetin	Senolytic flavonoid	Disrupts PI3K/AKT and scavenges ROS, selectively killing senescent fibroblasts	Human pilot: oral fisetin lowered senescent PBMC burden and systemic IL-6/IL-8 in older adults (Tavenier *et al.*, 2024; Yousefzadeh *et al.*, 2018)	Over-the-counter nutraceutical pricing improves access, but quality control of supplements is uneven across markets
Metformin	Senomorphic	Activates AMPK, blunts NF-κB; suppresses SASP without clearing cells	Human MSC study: 6-week therapeutic dosing dampened SASP gene expression and pro-inflammatory secretome (Abdelgawad *et al.*, 2023; Acar *et al.*, 2021)	Already on the front-line in diabetes care for many minority/low-income groups, it offers scalable "dual use" for senescence control
Rapamycin / mTOR inhibition	Senomorphic/ "gerostat"	Blocks geroconversion by inhibiting mTOR, maintaining quiescence	In vitro: rapamycin kept p21-arrested cells quiescent, preventing full senescence phenotype (Blagosklonny, 2018; Wang *et al.*, 2017)	Immunosuppressive risk mandates monitoring; cost falling as generics enter LMIC markets

Lifestyle interventions remain critical. Exercise, as discussed, has a senostatic effect (Mayo Clinic Staff, 2021). Thus, public health initiatives to increase physical activity in underserved communities, e.g., safe parks and community fitness programs, could serve as "natural senolytics" and should be a priority. Similarly, dietary improvements (antioxidant-rich foods) may reduce systemic DNA damage and inflammation (Duthie *et al.*, 1996). Encouraging social support and stress reduction (mindfulness, counseling) could blunt neuroendocrine senescence triggers. These interventions should be bundled with efforts to tackle root causes: ensuring all neighborhoods have access to healthy food, clean air, and healthcare.

At the policy level, it is vital to address environmental justice. Regulation of pollutants, such as air-quality standards and emissions controls, can reduce one source of DNA damage. Smoking-cessation programs targeted to high-risk populations could dramatically cut senescence induction (studies show even quitting late reduces damage) (Oba *et al.*, 2019; Priemé *et al.*, 1998). Education campaigns about healthy aging, framed in culturally sensitive ways, might increase community engagement with preventive behaviors.

From a clinical perspective, geroscientific clinics could assess at-risk individuals using senescence biomarkers and prescribe interventions (e.g., supervised exercise, vitamin D supplementation) tailored to reduce cellular aging. Pharmacologically, low-dose senolytics or senostatics might be integrated into the management of chronic diseases. For example, metformin, widely used in diabetes, has been noted to have senomorphic effects, and its use is prevalent in many minority communities for diabetes management (Abdelgawad *et al.*, 2023).

Controversies remain. The causal role of senescence in diseases is debated: is it a by-product or driver? Interventions might help in some contexts but not others. Furthermore, senotherapies carry risks (e.g., cytopenias with navitoclax). Equitable distribution of any future drug (should it be approved) is a challenge. Figure 2 illustrates how biological and social interventions synergise within a 'Gero-Equity' framework to tackle both the seed (p53-driven senescence) and the soil (social determinants) of health disparities

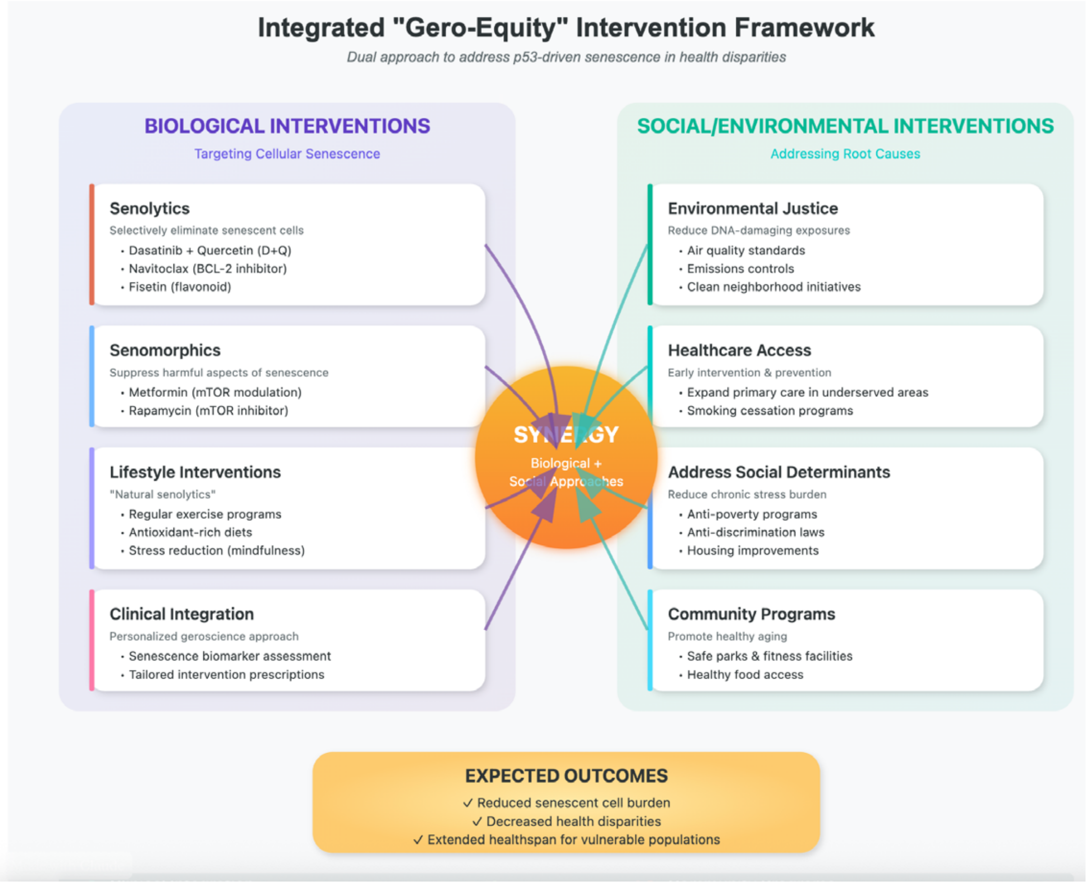

Figure 2. Integrated "Gero-Equity" intervention framework.

Thus, parallel public health strategies are essential. MacGuire argues that robust policy frameworks (addressing income inequality, education, and housing) can "reverse the embodiment of disadvantage" and yield healthier aging (MacGuire, 2020). For example, improving early childhood conditions (nutrition, infection prevention) can reduce lifelong inflammatory burden. Expanding access to primary care in poor neighborhoods ensures early management of hypertension and diabetes, which limits organ damage and reduces secondary senescence. Health disparities often originate in social, not biological, determinants, so bridging those gaps (through anti-poverty programs, anti-discrimination laws, and environmental cleanups) is a form of senescence prevention.

In summary, interventions can be grouped into:1) Biological therapies (senolytics, senomorphics, and immune modulators) aimed at cellular aging itself and 2) Social/environmental policies that remove upstream triggers of senescence. The former holds promise for reducing disease severity, but the latter are essential to prevent inequitable exposures. Ultimately, an integrative "gero-equity" approach is needed—one that couples cutting-edge molecular treatments with the societal changes that reduce stress on vulnerable cells.

4.5.2. Future Directions & Research Gaps

This interdisciplinary field faces many unknowns. First, longitudinal epidemiological studies are needed to directly link cellular senescence markers with health outcomes across social strata. Most current data are cross-sectional or animal-based. Prospective cohorts could measure senescence biomarkers (p16, SASP cytokines, epigenetic age) in diverse participants and track disease incidence. This would test whether accelerated senescence mediates the link between disadvantage and morbidity.

Mechanistic research should determine how particular social exposures interact with p53 networks. For example, do certain stressors (e.g., noise pollution, financial strain) preferentially activate p53-p21 vs. other senescence pathways? The heterogeneity of senescence (as highlighted by Mijit and Fujita) means we must map which cell types are most affected by which exposures. Single-cell profiling could clarify this: if peripheral blood mononuclear cells from stressed individuals show a distinct p53-driven senescent subpopulation, that would be compelling.

Another gap is genetic and epigenetic variation in p53 pathways. Different populations might have subtle polymorphisms affecting p53 regulation or miRNA that modulate its activity. Investigating whether these differences contribute to health disparities could provide valuable insights, but caution is necessary to avoid arguments based on genetic determinism.

On the translational front, clinical trials of senolytics or senomorphics should stratify by socioeconomic factors. We need to know if, say, exercise or a senolytic drug has equal efficacy in all groups, or if dosing and safety vary. The Demidenko study suggests context is relevant for p53 outcomes (Demidenko *et al.*, 2010); similarly, stress-hormone levels or metabolic state might alter drug response.

Methodologically, there is a need for better senescence assays. Current biomarkers (p16, SA-β-gal) have limitations. New tools, such as imaging probes for senescent cells or blood tests for senescence-associated microRNAs, could facilitate surveillance. Standardizing these and validating them in human studies is a priority.

Finally, we must bridge geroscience and social epidemiology. As MacGuire and Emeny note, interventions must be multilevel (Emeny *et al.*, 2021; MacGuire, 2020). Researchers should collaborate with public health and policy experts to design community-level experiments (e.g., introducing green spaces, improving housing) and measure biological aging outcomes. This would provide evidence on which social policies confer true cellular resilience.

Future research should cover everything from molecules to society: closely studying p53-senescence biology along with population studies and interventions that focus on equity. Only by working together in this way can we find the best ways to disconnect disadvantage from faster aging. Only through such synergy can we find the best way to sever the link between disadvantage and accelerated aging.

5. CONCLUSIONS

Molecular aging and social inequality converge in p53-dependent cellular senescence. Evidence indicates that adverse environments and constrained choices activate senescence pathways, helping explain patterned disparities in cardiometabolic, oncologic, and pulmonary outcomes. Closing these gaps requires paired action: therapeutics that reduce senescent burden and public-health measures that lower chronic stress and toxic exposures. The argument for a gero-equity agenda is not only based on scientific evidence; it also represents a moral imperative that aligns with population health goals to prevent diseases earlier, extend healthy lifespans, and ensure that benefits reach the communities most in need. Practical steps follow from this stance: design inclusive trials with equity endpoints; integrate senescence biomarkers into risk surveillance without widening the digital divide; and invest in place-based exposure reduction (clean air, safe housing, healthy food, and opportunities for activity). Advancing geroscience alongside structural reforms offers a credible path to healthier aging for populations, not just patients.

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