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Neighborhood opportunity and cellular senescence in a national sample of U.S. adults

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ABSTRACT

While prior research has documented associations between neighborhood conditions and physiological markers of aging, the relationship between neighborhood conditions and cellular aging remains underexplored. We quantified the association between neighborhood opportunity and expression of cellular senescence markers among 1,215 biomarker participants in the Midlife in the United States study. Neighborhood opportunity was assessed using the Childhood Opportunity Index 3.0 (Overall, Education, Health and Environment, Social and Economic Resources). Four transcriptomic markers of cellular senescence were examined from peripheral blood mononuclear cells: *CDKN2A* RNA abundance, DNA Damage Response (DDR30) composite score, and two Senescence-Associated Secretory Phenotype (SASP10, SASP57) composite scores. After covariate adjustment, individuals living in low-opportunity neighborhoods had significantly elevated *CDKN2A* RNA abundance ($\beta = 0.32$, 95% CI: 0.04, 0.59, $p = 0.024$) compared to those in high-opportunity neighborhoods. Secondary analysis suggested that this association was potentially driven by low Social and Economic Resources ($\beta = 0.35$, 95% CI: 0.07, 0.63, $p = 0.013$), rather than by Education or Health and Environment domains. No statistically significant relationships were observed for neighborhood opportunity with DDR30, SASP10, and SASP57. These findings provide molecular evidence that low neighborhood opportunity may be biologically embedded at the cellular level. The specificity of associations to social and economic resources and to upstream senescence regulation suggests that neighborhood associations with aging may operate through distinct biological pathways. Future longitudinal studies are needed to establish temporality and explore potential mechanisms linking neighborhood conditions to senescence.

1. Introduction

Persistent health inequities across the United States underscore the influence of structural conditions on the pace of biological aging (Krieger et al., 2024; Lawrence et al., 2020). Individuals living in socioeconomically disadvantaged neighborhoods face elevated risks of chronic disease, functional decline, and premature mortality, even after accounting for individual-level health behaviors and access to medical care (Diez Roux and Mair, 2010; Williams et al., 2019). These population-level patterns may reflect processes of embodiment, whereby sustained exposure to social adversity becomes physiologically inscribed, altering molecular and cellular function and shaping divergent aging trajectories across the life course (Cuevas et al., 2024; Krieger, 2005; Lawrence et al., 2020). Understanding the mechanisms through which neighborhood environments may accelerate biological aging is therefore critical for uncovering the pathways that perpetuate health inequities.

Neighborhood environments constitute a critical meso-level context in which structural opportunity and deprivation are both defined and experienced in daily life (Diez Roux and Mair, 2010). These conditions are multidimensional, organizing access to resources and exposures that accumulate across the life course (Clarke et al., 2014). Opportunity can be understood as the presence of institutional supports, environmental assets, and forms of social capital that together promote health and mobility; manifesting in quality schools, stable housing, clean air, green space, and employment pathways (Acevedo-Garcia et al., 2020).

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Conceptually, these patterns can be understood through the lens of structural violence, in which social arrangements systematically constrain individuals' ability to meet their basic needs, and achieve health and longevity (Farmer et al., 2016). Such neighborhood contexts can extend beyond individual socioeconomic position to shape everyday experiences of opportunity and deprivation (Diez Roux and Mair, 2010).

The weathering hypothesis provides one conceptual framework for understanding the biological embedding of structural inequality (Forde et al., 2019; Geronimus, 1992). It posits that the prolonged and inescapable exposure to social and economic adversity exacts a profound physiological toll, which in turn accelerates multisystemic biological decline (Geronimus et al., 2006; McEwen, 2006). Within this framework, aging is understood not simply as the passage of chronological time but as a socially patterned biological process, unfolding along trajectories shaped by systemic inequities (Forde et al., 2019). Mechanistically, this process centers on the chronic activation of stress response systems, including the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (McEwen, 2006). This persistent state of arousal elevates what is known as "allostatic load," the cumulative burden of adapting to adversity (McEwen, 2013). Over the life course, this physiological "wear and tear" can manifest as multisystem physiological dysregulation (Rentscher et al., 2020). Consistent with the weathering hypothesis, multiple studies have documented that residents of low-opportunity neighborhoods exhibit elevated allostatic load, highlighting how structural inequities can become biologically embodied (Chen et al., 2024; Crump et al., 2025; Tan et al., 2017).

Recent advances in geroscience provide complementary insights into the cellular mechanisms through which this physiological "wear and tear" unfolds (Kennedy et al., 2014; López-Otín et al., 2023). Geroscience, an interdisciplinary field, posits that aging results from the progressive accumulation of molecular and cellular damage across evolutionarily conserved pathways, including genomic instability, cellular senescence, mitochondrial dysfunction, and chronic inflammation, and that interventions targeting these fundamental mechanisms can delay multiple age-related diseases simultaneously (Kennedy et al., 2014; López-Otín et al., 2023). Within this framework, the chronic neuroendocrine activation central to weathering (HPA axis and sympathetic nervous system activity) can directly dysregulate these cellular maintenance systems, accelerating biological aging at the molecular level (Entringer and Epel, 2019; Lyons et al., 2023). Indeed, chronic stress exposure may generate sustained inflammatory signaling and oxidative damage that overwhelm cellular repair capacity, possibly triggering permanent cellular dysfunction that accumulates across tissues and systems (Kivimäki et al., 2023).

While measures such as allostatic load capture the cumulative toll of adversity, emerging research in social genomics reveals that these processes extend even deeper, into the molecular signatures embedded in immune cell function and epigenetic aging (Cole, 2019; Harris et al., 2024; Krieger et al., 2024). For example, Bather and colleagues (2025) demonstrated that adults residing in low-opportunity neighborhoods displayed substantially elevated CD14 expression, a marker of pro-inflammatory monocyte activity. This work highlights how structural disadvantage may become biologically embedded through immune transcriptional reprogramming, offering a mechanistic link between neighborhood opportunity and a pro-inflammatory state (Bather et al., 2025). Building on this work, a complete understanding of how this inflammatory state accelerates biological aging requires moving beyond the activity of immune cells to consider the accumulation of permanently dysfunctional cells. Cellular senescence represents such a mechanism. It provides a critical, complementary lens by capturing a fundamental shift in cellular fate, from transient stress response to irreversible, pro-inflammatory arrest, that may underlie the accelerated aging observed in low-opportunity contexts (Wang et al., 2024).

Cellular senescence is recognized as a key process in aging biology (Childs et al., 2015; Epel et al., 2004; López-Otín et al., 2023; van Deursen, 2014). Senescent cells permanently stop dividing but remain metabolically active, adopting a pro-inflammatory and tissue-remodeling state known as the senescence-associated secretory phenotype (SASP) (Coppé et al., 2010; He and Sharpless, 2017). The buildup of these cells impairs tissue repair, disrupts metabolic homeostasis, and fuels low-grade chronic inflammation (Childs et al., 2015; Ohtani, 2022). Key molecular markers of senescence include the RNA abundance of *CDKN2A*(p16$^{\mathrm{INK4a}}$), which enforces the halt in cell division; composite indices of the DNA damage response, reflecting genomic instability; and SASP-related transcripts that mark the activation of inflammatory pathways (Huang and Zhou, 2020; Liu et al., 2009; Saul et al., 2022). These markers are linked to declines in physical function, greater frailty, and higher risk for chronic disease (Fielding et al., 2024; Hickson et al., 2019; Millar et al., 2025). Yet, few studies have directly tested how neighborhood opportunity relates to a broad panel of transcriptional senescence markers in adults (Rentscher et al., 2019).

The present study addresses this gap by examining how neighborhood opportunity relates to multiple validated transcriptional indicators of cellular senescence, including *CDKN2A* expression, a composite score capturing the DNA damage response (DDR), and two measures of the SASP, in a national sample of middle-aged and older U.S. adults.

2. Materials and methods

2.1. Study design, setting, and sample

This analysis used data from the Midlife in the United States (MIDUS) study, a national longitudinal investigation of health and well-being in American adults (Brim et al., 2004). The study baseline (MIDUS 1), conducted from 1995 to 1996, enrolled a probability-based sample of 7108 non-institutionalized, English-speaking adults aged 25-74 (Fig. 1). A second wave (MIDUS 2, 2004-2005) successfully followed 4963 participants from the original cohort and added a supplemental sample of 592 African American adults from Milwaukee, Wisconsin, yielding a total of 5555 participants. A third wave (MIDUS 3) began in 2013, with 3683 participants from MIDUS 2. To refresh the initial cohort (MIDUS 1), the MIDUS Refresher study (2011-2014) recruited an additional 4085 adults, including an oversample of 508 African American individuals from Milwaukee.

Subsamples of participants from both the main MIDUS 3 cohort and the Refresher cohort who were healthy enough to travel were invited to participate in biomarker data collection (Dienberg Love et al., 2010). The MIDUS 3 Biomarker Project (2017-2022) and the MIDUS Refresher Biomarker Study (enrollment 2012-2016) followed identical protocols, involving a two-day clinic visit at one of three clinical research sites. Biomarker data were collected at three clinical research sites: UCLA (Los Angeles, California), University of Wisconsin-Madison (Madison, Wisconsin), and Georgetown University (Washington, DC). Participants received compensation of $200, reimbursement for travel and childcare expenses, and the option for older adults to bring companions to the two-day assessment (Dienberg Love et al., 2010). A total of 1610 participants completed these biomarker visits. We restricted the final analytic sample to the 1215 adults with available gene expression data. All participants provided written informed consent in the MIDUS study. Additional details on the study protocols for all MIDUS studies can be found elsewhere (Brim et al., 2004; Dienberg Love et al., 2010; Radler, 2014). The study procedures were approved by the Institutional Review Board at the University of Wisconsin. The secondary data analysis presented herein was deemed exempt by the Institutional Review Board at New York University.

2.2. Ascertainment of cellular aging transcriptomic outcomes

Blood samples for gene expression profiling were collected during participants' two-day clinic visits between 2017 and 2018 for samples from the MIDUS Refresher Biomarker Study and between 2018 and 2022 for samples from the MIDUS 3 Biomarker Project (Dienberg Love et al.,

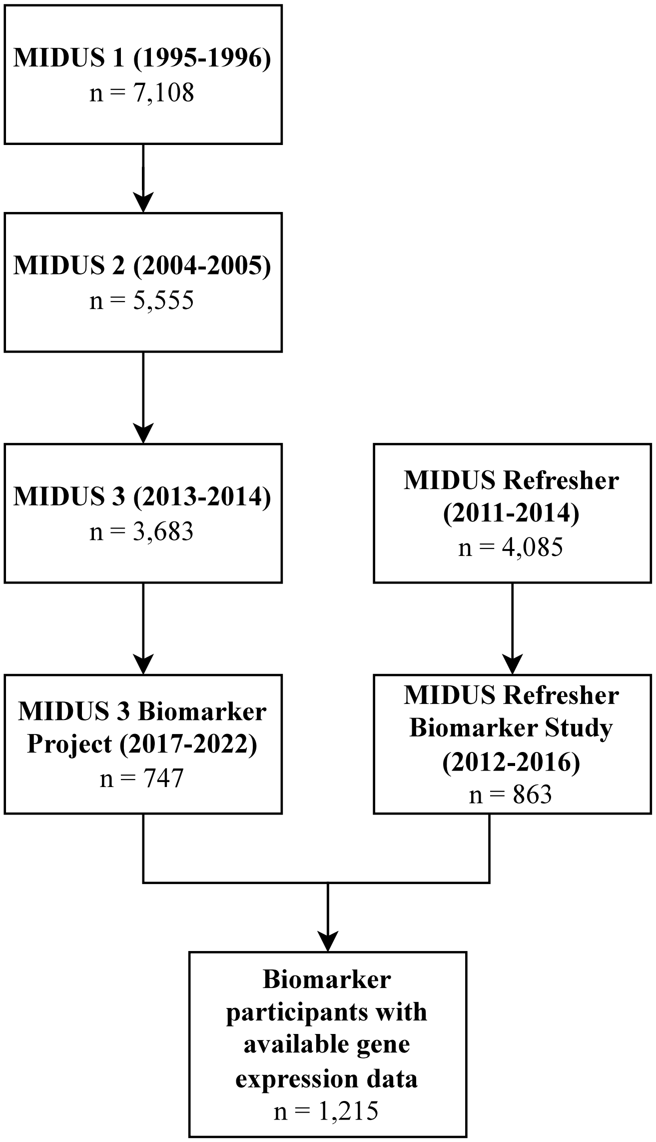

Fig. 1. Analytic sample derivation.

2010). Peripheral blood mononuclear cells were isolated from fasting blood draws and stored at −60 °C to −80 °C until assayed.

Gene expression profiling was conducted by the UCLA Social Genomics Core Laboratory using whole-transcriptome RNA sequencing. RNA samples were tested for suitable RNA yield and integrity before transcriptome profiling. Transcriptome profiling used a highly efficient mRNA-targeted approach with cDNA library preparation by Lexogen QuantSeq $3'$FWD (MIDUS Refresher) or $5'$FWD (MIDUS 3 Biomarker Project) gene counting assay, followed by sequencing on an Illumina HiSeq 4000 or NovaSeq instrument targeting greater than 10 million single-strand 65-nucleotide reads per sample. cDNA library preparation was carried out in 96-sample batches, with batch controlled in all statistical analyses. Sequence reads were mapped to the consensus human transcriptome and quantified on a per-gene basis using the STAR aligner (Dobin et al., 2013).

Transcript levels were quantified as transcripts per million (TPM) total human transcriptome-mapped reads, normalized to hold constant the average expression of 11 standard reference genes (University of Wisconsin Institute on Aging, & UCLA Social Genomics Core Laboratory, 2024), log2-transformed, and floored at one transcript per million (0 log2 = 1 normalized TPM) to reduce spurious variability. Samples were excluded based on wave-specific quality control criteria ($r < 0.85$ sample-transcriptome profile correlation [MIDUS Refresher] or fewer than 5 million RNA sequencing reads or elevated unmapped reads [MIDUS 3 Biomarker Project]). Gene expression values represent log2-transformed normalized TPM for all samples passing quality control (University of Wisconsin Institute on Aging, & UCLA Social Genomics Core Laboratory, 2024).

For this investigation, we focused on four pre-defined composite scores derived from the transcriptomic data, each representing a dimension of cellular aging and stress. These measures were obtained from the publicly available MIDUS Colectica Portal. The first was *CDKN2A* RNA abundance, a centered log2 measure of transcript abundance for the *CDKN2A* gene (p16$^{\text{INK4a}}$), a key mediator of cellular senescence (Campisi, 2005). The second was the DNA Damage Response (DDR30) composite score, an average of centered log2 expression values for 30 genes involved in responding to DNA damage, including *BRCA1, CDK7, CHEK1, DDB1, DDB2, ERCC1, ERCC2, GADD45A, GADD45B, GADD45GIP1, H2AFX, HUS1, LIG1, MDC1, MLH1, MRE11A, NBN, NTHL1, OGG1, PCNA, RAD50, RAD51, RPA1, SIRT1, TERF2, TERT, TP53, TP53BP1, XPA, XPC* (Hansen et al., 2025). The third and fourth measures were the Senescence-Associated Secretory Phenotype (SASP10) composite score, an average of centered log2 expression values for 10 genes encoding the core inflammatory mediators of the SASP (Campisi, 2005), specifically *IL6, CSF2, CCL8, IL8, CCL13, ICAM1, CXCL1, CXCL2, CXCL3, CXCL8;* and the expanded Senescence-Associated Secretory Phenotype (SASP57) composite score, an average of centered log2 expression values for 57 genes encoding a broader range of SASP factors (Coppé et al., 2010). The SASP57 panel includes the original 10 SASP genes and additional inflammatory cytokines, chemokines, growth factors, and proteases associated with the senescent cell secretome. The complete gene list includes: *ANG, AREG, CCL13, CCL16, CCL2, CCL20, CCL3, CCL6, CCL8, CSF2, CTSB, CXCL1, CXCL12, CXCL2, CXCL8, EGF, EGFR, EREG, FAS, FGF2, FGF7, FN1, HGF, ICAM1, ICAM3, IGFBP2, IGFBP3, IGFBP4, IGFBP6, IGFBP7, IL13, IL15, IL1A, IL1B, IL6, IL6ST, IL7, MIF, MMP1, MMP10, MMP12, MMP13, MMP14, MMP3, NRG1, OPG, PIGF, PLAT, PLAU, PTGS2, SCF, SERPINB2, SERPINE1, TIMP2, TNFRSF1A, TNFRSF1B, VEGFA* (Hansen et al., 2025).

To address heterogeneity in baseline gene expression levels, which can vary by more than 1000-fold across genes, composite scores were computed by first log2-transforming and mean-centering expression values for each gene before averaging across genes within each composite (University of Wisconsin Institute on Aging, & UCLA Social Genomics Core Laboratory, 2024).

2.3. *Neighborhood opportunity*

We linked participants to the Childhood Opportunity Index (COI) 3.0 (Noelke et al., 2024) based on their census tract of residence at MIDUS 2 baseline (2004-2006) for MIDUS 3 participants and at baseline (2011-2014) for MIDUS Refresher participants. The COI is a nationally normed measure of neighborhood context comprising 44 indicators drawn from multiple administrative and survey data sources (Noelke et al., 2024). These 44 indicators are organized into an overall score (Overall Neighborhood Opportunity) spanning three theoretically-driven domains: Education (12 indicators reflecting educational quality, access, and community human capital), Health and Environment (13 indicators capturing environmental quality, toxin exposure, and health infrastructure), and Social and Economic Resources (19 indicators reflecting material resources, employment, income distribution, and social capital; Noelke et al., 2024). The complete list of indicators within each domain is presented in Table 1. These domains capture conceptually distinct but ecologically interrelated dimensions of neighborhood context (Noelke et al., 2024). These indicators are standardized (z-scored), weighted, and aggregated, with COI values nationally normed and derived from 2010 census tract data. Although originally designed to capture neighborhood features relevant to child development, its components are equally relevant for studying

Table 1
Indicators of each subdomain in the Childhood Opportunity Index (Noelke et al., 2024).

Education	Health and environment	Social and economic resources
• private pre-K enrollment • public pre-K enrollment • reading and math test scores • reading and math test score growth • poverty-adjusted reading and math test scores • Advanced Placement course enrollment • college enrollment in nearby institutions • high school graduation rate • adult educational attainment • child enrichment-related non-profits • teacher experience • school poverty	• airborne microparticles • ozone concentration • industrial pollutants in air • water or soil • hazardous waste dump sites • healthy food retailer density • extreme heat exposure • NatureScore • walkability • community safety-related non-profits • vacant housing • health-related non-profits • health insurance coverage	• employment rate • high-skill employment rate • full-time year-round earnings • median household income • poverty rate • public assistance rate • adults with advanced degrees • very high-income households • adults without high school degrees • very low-income households • broadband access • crowded housing • mobility-enhancing friendship networks • single-parent families • non-profit organizations • homeownership rate • aggregate home values • aggregate capital income • aggregate real estate taxes

adult populations (Bather et al., 2025; Gianaros et al., 2023; Slopen et al., 2023). For this analysis, we consolidated the five original COI categories (very low, low, moderate, high, very high) into three levels due to sample size: low ($\leq$40th percentile), moderate ($>$40th to $\leq$60th percentile), and high ($>$60th percentile). Additional details on the construction and validation of the COI can be found elsewhere (Noelke et al., 2024).

2.4. Covariates

All covariates were extracted from self-reported surveys. Sociodemographic covariates included age (measured continuously), sex (male vs. female), educational attainment (high school or less, some college/associate's degree, college degree or higher), annual household income (<\$50,000, \$50,000 to \$100,000, and \$100,000+), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Other [including Asian, Native American/Alaska Native, Native Hawaiian/Pacific Islander]), and marital status (married, divorced/separated/widowed, never married). Number of chronic health conditions in the past 12 months was derived as the sum of the following self-reported indicators: (1) asthma, bronchitis, or emphysema, (2) tuberculosis, (3) other lung problems, (4) arthritis, rheumatism, or other bone or joint diseases, (5) sciatica, lumbago, or recurring backache, (6) persistent skin trouble (e.g., eczema), (7) thyroid disease, (8) hay fever, (9) recurring stomach trouble, indigestion, or diarrhea, (10) urinary or bladder problems, (11) being constipated all or most of the time, (12) gall bladder trouble, (13) persistent foot trouble (e.g., bunions, ingrown toenails), (14) trouble with varicose veins requiring medical treatment, (15) AIDS or HIV infection, (16) lupus or other autoimmune disease, (17) persistent trouble with your gums or mouth, (18) persistent trouble with your teeth, (19) high blood pressure or hypertension, (20) anxiety, depression, or some other emotional disorder, (21) alcohol or drug problems, (22) migraine headaches, (23) chronic sleeping problems, (24) diabetes or high blood sugar, (25) multiple sclerosis, epilepsy, or other neurological disorders, (26) stroke, (27) ulcer, (28) hernia, (29) piles or hemorrhoids, and (30) swallowing problems. We grouped the number of chronic health conditions as 0, 1, or 2 +. We controlled for chronic health conditions because while cellular senescence contributes to age-related diseases (López-Otín et al., 2023), chronic diseases may also independently promote cellular senescence through inflammatory and metabolic pathways (Childs et al., 2016; Cupit-Link et al., 2017; Palmer et al., 2015). Self-reported lifestyle factors included smoking status (never, past, current), past month alcohol consumption (never, $<$1 day a week, 1-2 days a week, 3 or more days a week), and body mass index (BMI; measured continuously).

2.5. Statistical analysis

We employed multivariable linear regression to quantify the relationships between neighborhood opportunity and cellular aging transcriptomic outcomes. Our primary analysis assessed the association between Overall Neighborhood Opportunity and centered log2-*CDKN2A* RNA abundance. We then conducted secondary and exploratory analyses. The secondary analyses examined the associations between each neighborhood opportunity subdomain (Education, Health and Environment, and Social and Economic Resources) and centered log2-*CDKN2A* RNA abundance. The exploratory analyses examined the associations between Overall Neighborhood Opportunity and the three other cellular aging outcomes (the DDR30 composite score, the SASP10 composite score, and the SASP57 composite score).

For each analysis, we fit three sequential models with increasing covariate adjustment. Model 1 controlled for sociodemographic characteristics (age, sex, race/ethnicity, educational attainment, annual household income, and marital status). Model 2 added the number of chronic health conditions. Model 3 further incorporated lifestyle factors (smoking status, alcohol consumption, and BMI). We addressed missing covariate data using multivariate imputation by chained equations with the mice R package (van Buuren and Groothuis-Oudshoorn, 2011). We used ordinal logistic regression for ordered categorical variables (educational attainment, annual household income, number of chronic health conditions), multinomial logistic regression for nominal measures (race/ethnicity and marital status), and predictive mean matching for BMI. We pooled all regression coefficients and standard errors across ten imputed datasets using Rubin's rules (Rubin, 1987). Analyses used R version 4.5.1 (R Core Team, 2023) with statistical significance set at a two-sided $p < 0.05$.

3. Results

3.1. Primary analysis

The analytic sample included 1215 middle-aged adults (M_{age} 51.7 [SD = 11.4], 53.2% female, 74.7% non-Hispanic White, Table 2). The omnibus test indicated a statistically significant overall association between neighborhood opportunity and *CDKN2A* RNA abundance (F = 3.896, df = 2, $p = 0.021$). Specifically, residing in low overall opportunity neighborhoods was significantly associated with elevated *CDKN2A* RNA abundance compared to high overall opportunity neighborhoods (Table 3 and Fig. 2). In Model 1 (adjusted for age, sex, race/ethnicity, educational attainment, annual household income, and marital status), this association corresponded to a 0.36 increase in centered log2(*CDKN2A*) (95% CI: 0.08, 0.63; $p = 0.010$). Upon further adjustment for the number of chronic health conditions in Model 2, the association was virtually unchanged, with a 0.35 increase (95% CI: 0.08, 0.63; $p = 0.011$). In Model 3, which additionally controlled for lifestyle factors (smoking status, alcohol consumption, and BMI), the association attenuated slightly but remained statistically significant (0.32 increase, 95% CI: 0.04, 0.59; $p = 0.024$).

Table 2
Summary statistics of 1215 participants from the Midlife in the United States study.

Characteristic		Overall Neighborhood Opportunity		
	Overall	High	Moderate	Low
	N = 1215	N = 485	N = 241	N = 489
Age, Mean (SD)	51.7 (11.4)	53.2 (11.5)	51.5 (11.6)	50.4 (11.2)
Sex, No. (%)				
Male	569 (46.8)	247 (50.9)	116 (48.1)	206 (42.1)
Female	646 (53.2)	238 (49.1)	125 (51.9)	283 (57.9)
Race/Ethnicity, No. (%)				
non-Hispanic White	907 (74.7)	423 (87.2)	207 (85.9)	277 (56.6)
non-Hispanic Black	208 (17.1)	16 (3.3)	16 (6.6)	176 (36.0)
Hispanic	36 (3.0)	15 (3.1)	5 (2.1)	16 (3.3)
non-Hispanic Other	60 (4.9)	30 (6.2)	12 (5.0)	18 (3.7)
Missing	4 (0.3)	1 (0.2)	1 (0.4)	2 (0.4)
Educational attainment, No. (%)				
High school or less	250 (20.6)	48 (9.9)	57 (23.7)	145 (29.7)
Some college/ Associate's degree	366 (30.1)	123 (25.4)	68 (28.2)	175 (35.8)
College degree or higher	598 (49.2)	314 (64.7)	115 (47.7)	169 (34.6)
Missing	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)
Annual household income, No. (%)				
<$50,000	541 (44.5)	155 (32.0)	91 (37.8)	295 (60.3)
$50,000 to $100,000	344 (28.3)	127 (26.2)	88 (36.5)	129 (26.4)
$100,000+	267 (22.0)	175 (36.1)	46 (19.1)	46 (9.4)
Missing	63 (5.2)	28 (5.8)	16 (6.6)	19 (3.9)
Marital Status, No. (%)				
Married	791 (65.1)	354 (73.0)	179 (74.3)	258 (52.8)
Divorced/Separated/ Widowed	239 (19.7)	84 (17.3)	37 (15.4)	118 (24.1)
Never married	184 (15.1)	46 (9.5)	25 (10.4)	113 (23.1)
Missing	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Number of chronic conditions, No. (%)				
0	283 (23.3)	121 (24.9)	58 (24.1)	104 (21.3)
1	257 (21.2)	110 (22.7)	54 (22.4)	93 (19.0)
2+	653 (53.7)	245 (50.5)	125 (51.9)	283 (57.9)
Missing	22 (1.8)	9 (1.9)	4 (1.7)	9 (1.8)
Smoking status, No. (%)				
Never	718 (59.1)	315 (64.9)	154 (63.9)	249 (50.9)
Past	350 (28.8)	134 (27.6)	70 (29.0)	146 (29.9)
Current	147 (12.1)	36 (7.4)	17 (7.1)	94 (19.2)
Alcohol consumption, No. (%)				
Never	412 (33.9)	130 (26.8)	84 (34.9)	198 (40.5)
<1 day a week	322 (26.5)	123 (25.4)	70 (29.0)	129 (26.4)
1-2 days a week	204 (16.8)	91 (18.8)	39 (16.2)	74 (15.1)
3+ days a week	277 (22.8)	141 (29.1)	48 (19.9)	88 (18.0)
Body mass index, Mean (SD)	28.6 (6.5)	27.1 (5.6)	28.4 (5.8)	30.1 (7.2)
Missing, No. (%)	49 (4.0)	18 (3.7)	12 (5.0)	19 (3.9)
Education opportunity, No. (%)				
High	550 (45.3)	443 (91.3)	88 (36.5)	19 (3.9)
Moderate	206 (17.0)	36 (7.4)	100 (41.5)	70 (14.3)
Low	459 (37.8)	6 (1.2)	53 (22.0)	400 (81.8)
Health and environment opportunity, No. (%)				
High	294 (24.2)	242 (49.9)	33 (13.7)	19 (3.9)
Moderate	311 (25.6)	145 (29.9)	78 (32.4)	88 (18.0)
Low	610 (50.2)	98 (20.2)	130 (53.9)	382 (78.1)
Social and economic resources, No. (%)				
High	487 (40.1)	446 (92.0)	41 (17.0)	0 (0.0)
Moderate	254 (20.9)	39 (8.0)	174 (72.2)	41 (8.4)
Low	474 (39.0)	0 (0.0)	26 (10.8)	448 (91.6)
***CDKN2A* RNA abundance (centered log2 measure), Mean (SD)**	0.0 (1.9)	−0.1 (1.8)	−0.1 (1.8)	0.1 (2.0)
30 DNA Damage Response composite score (average of centered log2 values), Mean (SD)	0.0 (0.9)	0.0 (0.9)	0.0 (1.0)	0.0 (1.0)
10 Senescence Associated Secretory Phenotype composite score (average of centered log2 values), Mean (SD)	0.0 (0.3)	0.0 (0.3)	0.0 (0.3)	0.0 (0.4)
57 Senescence Associated Secretory Phenotype composite score (average of centered log2 values), Mean (SD)	0.0 (0.4)	0.0 (0.4)	0.0 (0.4)	0.0 (0.4)

Table 3
Primary and secondary analyses: adjusted associations between Overall Neighborhood Opportunity and *CDKN2A* RNA abundance (centered log2 measure) in the Midlife in the United States study.

Characteristic	Model 1		Model 2		Model 3	
	Beta (95% CI)	**p value**	**Beta (95% CI)**	**p value**	**Beta (95% CI)**	**p value**
Primary analysis						
Overall Neighborhood Opportunity						
High						
Moderate	0.01 (−0.29, 0.31)	0.93	0.01 (−0.29, 0.31)	0.94	−0.01 (−0.31, 0.29)	0.94
Low	**0.36 (0.08, 0.63)**	**0.010**	**0.35 (0.08, 0.63)**	**0.011**	**0.32 (0.04, 0.59)**	**0.024**
Secondary analyses						
Education domain						
High						
Moderate	0.02 (−0.29, 0.33)	0.90	0.02 (−0.29, 0.33)	0.89	0.00 (−0.31, 0.31)	1.00
Low	0.22 (−0.05, 0.49)	0.10	0.22 (−0.05, 0.49)	0.11	0.20 (−0.07, 0.47)	0.15
Health and Environment domain						
High						
Moderate	0.01 (−0.30, 0.32)	0.95	0.02 (−0.29, 0.33)	0.89	0.01 (−0.30, 0.32)	0.97
Low	0.07 (−0.20, 0.35)	0.60	0.08 (−0.20, 0.35)	0.58	0.06 (−0.22, 0.33)	0.69
Social and Economic Resources domain						
High						
Moderate	0.06 (−0.24, 0.35)	0.70	0.06 (−0.24, 0.35)	0.71	0.03 (−0.27, 0.33)	0.85
Low	**0.39 (0.12, 0.67)**	**0.005**	**0.39 (0.11, 0.67)**	**0.006**	**0.35 (0.07, 0.63)**	**0.013**

Results were pooled across ten imputed datasets.
Bold indicates $p < 0.05$.
Model 1 controlled for age, sex, race/ethnicity, educational attainment, annual household income, and marital status.
Model 2: Model 1 + number of chronic health conditions.
Model 3: Model 2 + smoking status, alcohol consumption, and body mass index.

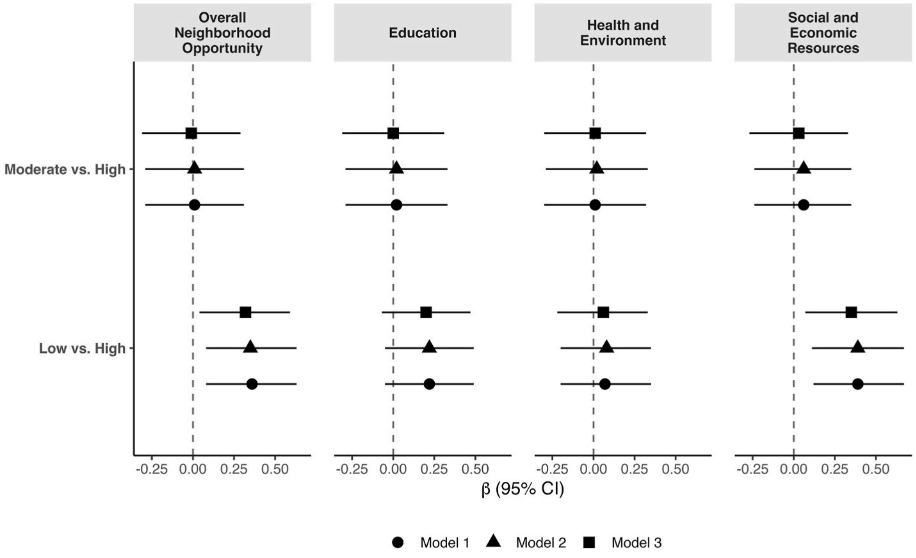

Fig. 2. Adjusted associations between neighborhood opportunity and *CDKN2A* RNA abundance (centered log2 measure) in the Midlife in the United States study.

3.2. Secondary and exploratory analyses

Examination of the specific neighborhood opportunity subdomains revealed that the association between Overall Neighborhood Opportunity and *CDKN2A* was potentially driven by the Social and Economic Resources domain (Table 3). In Model 1, low opportunity in this domain was associated with a 0.39 increase in centered log2(*CDKN2A*) (95% CI: 0.12, 0.67; $p = 0.005$). This association remained stable after adjustment for number of chronic health conditions (Model 2; $\beta = 0.39$, 95% CI: 0.11, 0.67; $p = 0.006$) and was slightly attenuated yet remained significant with the addition of lifestyle factors in Model 3 ($\beta = 0.35$, 95% CI: 0.07, 0.63; $p = 0.013$). Conversely, the Education and Health and Environment domains were not statistically associated with *CDKN2A* abundance across all three models (all $p \geq 0.10$). In exploratory analyses examining the other transcriptomic outcomes, Overall Neighborhood Opportunity was not significantly associated with the DDR30 composite score, the SASP10 composite score, or the SASP57 composite score in any of the adjusted models (all $p \geq 0.14$, Table 4).

Table 4
Exploratory analysis: adjusted associations between Overall Neighborhood Opportunity and other cellular aging transcriptomic outcomes in the Midlife in the United States study.

Characteristic	Model 1		Model 2		Model 3	
	Beta (95% CI)	**p value**	**Beta (95% CI)**	**p value**	**Beta (95% CI)**	**p value**
30 DNA Damage Response composite score (average of centered log2 *values)*						
Overall Neighborhood Opportunity						
High						
Moderate	−0.01 (−0.16, 0.14)	0.93	−0.01 (−0.16, 0.14)	0.93	−0.01 (−0.16, 0.14)	0.85
Low	0.10 (−0.03, 0.24)	0.14	0.10 (−0.03, 0.24)	0.14	0.09 (−0.05, 0.23)	0.20
10 Senescence Associated Secretory Phenotype composite score (average of centered log2 *values)*						
Overall Neighborhood Opportunity						
High						
Moderate	−0.01 (−0.07, 0.04)	0.60	−0.01 (−0.07, 0.04)	0.60	−0.02 (−0.07, 0.04)	0.58
Low	−0.01 (−0.06, 0.04)	0.76	−0.01 (−0.06, 0.04)	0.76	−0.01 (−0.06, 0.04)	0.62
57 Senescence Associated Secretory Phenotype composite score (average of centered log2 *values)*						
Overall Neighborhood Opportunity						
High						
Moderate	0.01 (−0.06, 0.07)	0.86	0.01 (−0.06, 0.07)	0.86	0.00 (−0.06, 0.07)	0.92
Low	0.03 (−0.03, 0.10)	0.26	0.04 (−0.03, 0.10)	0.26	0.03 (−0.03, 0.09)	0.40

Results were pooled across ten imputed datasets.
Model 1 controlled for age, sex, race/ethnicity, educational attainment, annual household income, and marital status.
Model 2: Model 1 + number of chronic health conditions.
Model 3: Model 2 + smoking status, alcohol consumption, and body mass index.

4. Discussion

The present study provides novel molecular evidence potentially linking neighborhood opportunity to cellular senescence processes in U. S. adults, suggesting that structural conditions of opportunity may be associated with biological processes implicated in divergent aging trajectories (Graf et al., 2022; Kivimäki et al., 2025). Our findings suggest that adults residing in low-opportunity neighborhoods exhibit significantly elevated expression of *CDKN2A*(p16$^{\text{INK4a}}$), a key mediator of cellular senescence, compared to those from high-opportunity neighborhoods. This association remained robust after adjustment for sociodemographic, health, and lifestyle factors. Subdomain analyses further clarified that the association between residing in low-opportunity neighborhoods and *CDKN2A* expression was potentially driven by deficits in social and economic resources, rather than by educational or health and environmental domains. The absence of association with other senescence-related transcriptomic markers (DDR30, SASP10, SASP57) suggests potential specificity in how neighborhood conditions relate to different dimensions of the senescence pathway.

Our observation that neighborhood disadvantage associates with elevated *CDKN2A* expression extends converging evidence linking neighborhood characteristics to accelerated biological aging across multiple physiological systems. These findings align with prior work demonstrating associations between neighborhood opportunity and systemic physiological dysregulation (Crump et al., 2025), pro-inflammatory immune cell signaling (Bather et al., 2025), and epigenetic aging (Cuevas et al., 2025; Krieger et al., 2024). The specificity to *CDKN2A*, a central mediator of cell-cycle arrest (Wang et al., 2024), suggests that the molecular correlates of neighborhood opportunity may be most pronounced in the upstream initiation of senescence, the commitment to irreversible growth arrest (Wang et al., 2024), rather than in the broader signatures of genomic instability (DDR) or inflammatory secretion (SASP) that characterize the established senescent phenotype (Li et al., 2023). This upstream positioning is critically important, as it suggests that neighborhood adversity may drive the accumulation of senescent cells that subsequently amplify inflammation and dysfunction via the SASP.

The finding that social and economic resources, rather than educational or health and environmental factors, were the primary drivers of the association between neighborhood opportunity and *CDKN2A* expression potentially points to chronic psychosocial stress as a central pathway. Stressors related to income, employment, and housing are not occasional but persistent conditions that shape daily life (Bhat et al., 2022; Crump et al., 2025). These conditions function as recurrent activators of stress-response systems, maintaining prolonged neuroendocrine and inflammatory signaling that, over time, may promote the inflammation, oxidative stress, and genomic instability known to accelerate cellular senescence (Lyons et al., 2023; Merz et al., 2023; Zalewski et al., 2012). In comparison, the influence of educational opportunity may operate through more distal or mediated pathways, such as shaping long-term socioeconomic trajectories, rather than constituting a direct, ongoing psychosocial stressor (Singh-Manoux et al., 2002). Likewise, current health and environmental indicators may not adequately capture the timing or intensity of exposures most relevant to biological aging. This pattern aligns with prior work, such as Crump and colleagues' finding that constraints in social and economic resources were most consistently associated with elevated allostatic load in their study of neighborhood opportunity (Crump et al., 2025).

The absence of significant associations with DDR30 and SASP markers still requires consideration of the distinct biological roles these markers represent within the senescence pathway. The DDR pathway encompasses both damage detection and repair processes (Jackson and Bartek, 2009); consequently, expression levels at a single timepoint may reflect post-repair DDR signaling rather than absence of prior damage, because DDR activation and checkpoint signaling are often transient and time-dependent (Jackson and Bartek, 2009). This cross-sectional design cannot distinguish between active damage responses and resolved damage events, whereas CDKN2A upregulation marks a more stable cellular state (Sharpless and Sherr, 2015); once p16^{INK4a} mediates cell cycle arrest, this growth-arrested phenotype typically persists even if the initiating stressor or damage is later reduced (Sharpless and Sherr, 2015). The absence of SASP elevation may reflect detectability constraints in senescent cell accumulation; the SASP comprises secretions from established senescent cells (Coppé et al., 2010), and detectable systemic elevation may require a sufficient senescent-cell burden or the right tissue sources and timing for circulating signals. In midlife populations, neighborhood-related stress may induce senescence initiation through p16^{INK4a} upregulation without yet generating the senescent cell density necessary for robust SASP signals. Alternatively, the inflammatory mediators comprising the SASP composites may capture general inflammatory activation rather than specifically reflecting senescent cell-derived secretion, introducing measurement heterogeneity that obscures neighborhood associations. This pattern aligns with geroscience frameworks (Kennedy et al., 2014; López-Otín et al., 2023) in which cellular stress can activate growth-arrest mechanisms, while the secretory phenotype is context-dependent and shaped by persistence, cell type, and senescent-cell accumulation (Coppé et al., 2010; Tchkonia et al., 2013). Together, these findings highlight the importance of multi-tissue, multi-marker approaches to fully capture the complexity of senescence biology and its social determinants.

Our primary results provide preliminary molecular evidence consistent with the weathering hypothesis by extending its empirical foundation beyond physiological markers of allostatic load to encompass fundamental cellular aging processes (Forde et al., 2019), integrating population-level weathering frameworks with molecular geroscience principles (Kennedy et al., 2014; López-Otín et al., 2023). The association between low neighborhood opportunity and elevated *CDKN2A* expression in U.S. adults is consistent with the hypothesis' core premise of accelerated decline due to ongoing adversity (Geronimus et al., 2006). Prior research suggests that chronic activation of stress response systems (e.g., the HPA axis and sympathetic nervous system) may promote cellular senescence through systemic inflammation, oxidative stress, DNA damage, telomere attrition, and mitochondrial dysfunction (Li et al., 2023; McEwen, 2006; Kivimäki et al., 2023), providing a plausible mechanistic pathway linking neighborhood disadvantage to elevated *CDKN2A* expression, though we did not directly assess these intermediate biological processes. The accumulation of senescent cells, contributing to tissue dysfunction via the senescence-associated secretory phenotype (Moiseeva et al., 2023), positions cellular senescence as a plausible intermediate pathway linking social conditions to health inequities. Although behavioral and psychological factors represent plausible mediating mechanisms, with health behaviors, sleep quality, and psychosocial distress each associated with neighborhood opportunity and senescence-related biology (Demaria et al., 2023; Diez Roux, 2016; Carroll et al., 2016; Calubag et al., 2024; Coppé et al., 2010; Lee, 2020; Putnick et al., 2025), the cross-sectional nature of our study precludes formal mediation analysis. As such, future longitudinal investigations with repeated assessments of neighborhood exposures, behavioral and psychological factors, and transcriptomic profiles would be necessary to disentangle these temporal relationships and formally test mediating pathways.

Finally, these findings suggest that cellular senescence biomarkers may provide relevant measures for investigating the relationship between structural conditions and aging-related biological processes. Identifying *CDKN2A* as a transcriptional marker responsive to structural adversity provides a potential endpoint for future research. Moreover, this work advances the growing integration of social epidemiology and molecular geroscience. As senescence-targeting therapies (senolytics and senomorphics) are actively investigated (Zhang et al., 2022), understanding how social conditions shape senescence biology becomes crucial for developing a complete etiological picture of aging. Future longitudinal studies should examine whether neighborhood-induced elevations in cellular senescence mediate associations with later-life health outcomes and investigate the dynamics of these biological signatures over time.

4.1. *Strengths, limitations, and future directions*

The present study has several notable strengths. It draws on a large, national sample, incorporates a comprehensive, multi-domain assessment of neighborhood opportunity, and leverages validated transcriptomic markers of cellular senescence. Together, these features enhance both the robustness and the translational relevance of our findings. However, several limitations should be acknowledged. First, the cross-sectional design and use of current rather than life-course neighborhood measures limit causal inferences about the temporal relationship between neighborhood conditions and cellular aging. Second, gene expression was measured in peripheral blood mononuclear cells, which may not fully capture senescence processes in other tissues (Zhao et al., 2024). Third, although we adjusted for numerous covariates, residual confounding by unmeasured factors cannot be excluded. Fourth, the transcriptomic measures employed here capture only part of the senescence landscape, omitting protein-level markers of senescent cell burden in specific tissues. Fifth, our analysis focused on publicly available composite scores for established senescence pathways rather than individual gene-level expression data or comprehensive transcriptomic analysis. While these composite scores have been validated in prior research (Carroll et al., 2016), access to the full transcriptomic data derived from RNA-sequencing would enable examination of additional senescence markers (e.g., p21, p53) and identification of novel pathways through genome-wide analyses. Sixth, chronic health conditions were modeled as the standard MIDUS count of 30 self-reported conditions. While this preserves comparability (Rodrigues et al., 2025; Willroth et al., 2021) and avoids subjective selection of conditions, it does not distinguish severity or biological relevance across diseases. Finally, MIDUS does not collect residential history data to protect participant confidentiality, precluding assessment of cumulative neighborhood exposure, residential mobility, and length of residence. Thus, we could not distinguish between long-term residents and recent movers or account for prior neighborhood exposures. Future research with residential histories would enable examination of cumulative exposure effects, critical period hypotheses, and residential mobility as a potential stressor.

Future research should build on our work and address these limitations through longitudinal, life-course designs that incorporate repeated biomarker assessments and measures of neighborhood exposure across the life course to characterize the temporal dynamics of neighborhood effects. Studies that can capture both historical and current neighborhood exposures will be valuable for understanding whether observed associations reflect cumulative life-course effects or more proximate neighborhood influences. Integrating multiomic measures, including epigenetic clocks, proteomic SASP panels, and metabolic indicators, will allow for a more comprehensive mapping of the biology of weathering. Studies that include more racially and ethnically diverse populations are also needed to clarify how structural inequities become biologically embedded across the life course.

5. Conclusion

This study provides novel molecular evidence that neighborhood opportunity may be linked to cellular senescence, a fundamental hallmark of biological aging, in U.S. adults, providing support for the weathering hypothesis in the context of aging biology. Elevated *CDKN2A* expression among individuals from low opportunity neighborhoods underscores how structural inequality may be biologically embedded, with implications for health inequities. By identifying cellular senescence as a mechanistically informative process, this work contributes to the integration of social epidemiology and molecular geroscience. Demonstrating that neighborhood conditions are associated with transcriptional markers of senescence-related biology highlights a molecular mechanism through which structural inequality may influence biological processes relevant to aging. Future longitudinal and multi-omic research will be essential to further elucidate these pathways and to clarify how socially patterned adversity becomes embedded in the biology of aging.

Clinical trial number

Not applicable.

Ethics approval/statement EA not required

The study procedures were approved by the Institutional Review Board at the University of Wisconsin. The secondary data analysis presented herein was deemed exempt by the Institutional Review Board at New York University.

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CRediT authorship contribution statement

Mariana Rodrigues: Conceptualization, Formal analysis, Investigation, Methodology, Software, Writing – original draft. **Jemar R. Bather:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Alisha A. Crump:** Writing – review & editing. **Emiko O. Kranz:** Writing – review & editing. **Steven W. Cole:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Validation, Writing – review & editing. **Adolfo G. Cuevas:** Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2026.119196.

Data availability

Data availability statement: The data that support this study's findings are publicly available on the MIDUS Colectica Portal.

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