Biopsychosocial Science and Medicine Publish Ahead of Print
DOI:10.1097/PSY.0000000000001500

Perceived Social Cohesion Moderates the Association Between Neighborhood Socioeconomic Deprivation and Epigenetic Aging

Koichi Sakakibara, MHS[1], Stephanie Hernandez, PhD[1], Jourdyn A. Lawrence, PhD[1], Anthony Zannas, PhD[2], Adolfo Cuevas, PhD[3], Ichiro Kawachi, PhD[4], Christopher L. Coe, PhD[5], and Agus Surachman, PhD[1]

[1]Department of Epidemiology and Biostatistics, Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania
[2] Department of Psychiatry, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
[3]Department of Social and Behavioral Sciences, School of Global Public Health, New York University, New York, New York
[4]Department of Social and Behavioral Sciences, T. H. Chan School of Public Health, Harvard University, Boston, Massachusetts
[5]Department of Psychology, University of Wisconsin-Madison, Madison, Wisconsin

Article Editor: Suzanne C. Segerstrom
Total Number of Tables: 4; Total Figures: 0; Total Supplemental Digital files: 1

Corresponding author:
Koichi Sakakibara, MHS
Email: ks4298@drexel.edu
Address: Nesbitt Hall, 3215 Market St, Philadelphia, PA 19104

Funding acknowledgement:

This work was partly supported by U54CA267735. Since 1995, the MIDUS study has been funded by the following: John D. and Catherine T. MacArthur Foundation Research Network, National Institute on Aging (P01-AG020166), and National Institute on Aging (U19-AG051426). Biomarker data collection was further supported by the NIH National Center for Advancing Translational Sciences (NCATS) Clinical and Translational Science Award (CTSA) program as follows: UL1TR001409 (Georgetown), UL1TR001881 (UCLA), and 1UL1RR025011 (UW). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Transparency and Openness Statement: This study was not preregistered, nor was the data analysis plan. The data used in this study are publicly available. All analyses are described in the Methods and Supplementary Materials, http://links.lww.com/PSYMED/B193. This study did not employ a reporting guideline.

Abstract

Objective. We investigated the association between socioeconomic contexts and biological aging among U.S. older adults, and whether social cohesion buffers the impact of socioeconomic deprivation on epigenetic aging.
Methods. A pooled cross-sectional analysis was conducted using data from the Midlife in the United States (MIDUS) wave 2 and Refresher projects (n = 1,111). DNA methylation-based epigenetic aging was measured using epigenetic clocks (Hannum, Horvath, Horvath Skin & Blood, PhenoAge, and GrimAge2) and the pace of aging (DunedinPACE). The 2015 Area Deprivation Index was used to assess socioeconomic deprivation. Neighborhood perceived social cohesion was determined from three components of social capital: social trust, norms of mutual assistance, and a sense of belonging. Post hoc moderation analyses were conducted to assess the buffering effects of social cohesion on the adverse impact of socioeconomic deprivation on accelerated aging. Analyses were adjusted for socioeconomic, demographic, and behavioral characteristics.
Results. Higher deprivation was associated with faster GrimAge2 epigenetic age acceleration (EAA; B = 0.03, SE = 0.01, Beta = 0.16, 95%CI: [0.02, 0.05]) and DunedinPACE pace of aging (B = 0.001, SE = 0.00, Beta = 0.21, 95%CI: [0.00, 0.001]. Perceived social cohesion appeared to buffer the adverse impact of socioeconomic deprivation on EAA GrimAge2 (B = -0.02, SE = 0.01, Beta = -0.09, 95%CI: [-0.03, -0.01]) and DunedinPACE (B = -0.00, SE = 0.00, Beta = -0.06, 95%CI: [-0.00, -0.00]).
Conclusions. Both deprivation and cohesion were associated with epigenetic aging. Buffering effects of cohesion on the association between deprivation and epigenetic aging were evident.

Key Words: Epigenetic age acceleration, Epigenetic clock, Neighborhood, Social Capital

List of abbreviations
ADI: the Area Deprivation Index
EAA: epigenetic age acceleration
MIDUS: the Midlife in the United States
BMI: body mass index

INTRODUCTION

A core view in the field of geroscience is that aging is an inevitable, progressive process associated with declining health and mortality. However, there is also evidence that some interventions can slow aging, delay the progression to pathophysiology, prolong the healthspan phase, and extend longevity[1]. Epigenetic aging has emerged as one of the key bioindicators reflecting the chromosomal and cellular changes implicated in the onset of age-related chronic disease and the temporal pace of aging[2–4]. Moreover, individual-level factors, including socioeconomic disadvantage, demographic and psychological factors, and exposure to stressful life events, including discrimination, are believed to be associated with an acceleration of epigenetic aging[5–10]. Epigenetic aging also appears to be a sensitive reflection of physiological wear and tear at the molecular level. Accelerations in the pace at which it occurs have been associated with exposure to psychosocial stressors during both early childhood and later in the adult life course[7,11]. In addition, some studies have documented transgenerational transmission from grandparents who experienced social disadvantages to their grandchildren[9,12]. These findings convey the complexity of the interactions among social, environmental, and biological factors associated with the aging process.

Neighborhoods and Biological Aging

Neighborhood contexts are hypothesized to influence aging beyond individual-level characteristics. Neighborhood contexts, especially in the United States, are shaped by a history of structural racism and discrimination, contemporary policies, practices, and norms that disadvantage racially minoritized groups and those from lower socioeconomic backgrounds [13,14]. Residential segregation based on race and socioeconomic factors contributes to the unequal distribution of resources across different neighborhoods. Diez Roux and Mair (2010) suggested that residential segregation and inequality in neighborhood resources are fundamental causes of health disparities[15]. Specifically, two domains of neighborhood inequity shape disparities in health and aging: inequity in the neighborhood's physical environment (i.e., quality of the built environment) and inequity in the neighborhood's social environment (i.e., social cohesion and safety/violence).

Neighborhood contexts shape residents' exposure to psychosocial stressors, behavioral patterns, and overall health[15]. More recent literature has emphasized the role of historical and contemporary systemic factors that shape neighborhood contexts that lead to disparities in health [16]. Further, the transdisciplinary model of stress[17] emphasizes the role of contextual factors, including physical and social features of neighborhoods, in shaping stress experience. Residing in neighborhoods with higher levels of deprivation and lower social resources can lead to greater exposure to and greater severity of psychosocial stressors, as well as heightening psychological and physiological reactivity to stress[17]. Combined with unhealthy behaviors (i.e., smoking, lack of physical activity), dysregulation of the perception of stressors contributes to long-term physiological wear-and-tear (i.e., allostatic load), accelerates biological aging, and underlies a higher risk for age-related chronic disease and mortality. Drawing from these interdisciplinary frameworks on neighborhood, stress, and biological aging, we developed a model through which inequities in neighborhood socioeconomic contexts, particularly differences in socioeconomic deprivation and neighborhood social cohesion, influence biological aging through stress and health behaviors (Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/B193), adapted from previous frameworks [15–17].

Neighborhood Socioeconomic Deprivation

Previous research has shown that neighborhood socioeconomic deprivation is associated with age-related morbidity, including atherosclerotic cardiovascular disease and stroke [15,18], and mortality [19–21]. Building on these insights, a growing number of studies have examined the biological correlates of neighborhood physical and social environments. For example, Barber, Hickson et al. (2016) reported that residence in disadvantaged neighborhoods increased the cumulative biological risk among African-American adults [22]. Similarly, Nazmi et al. (2010) linked neighborhood deprivation and cohesion to inflammatory markers, suggesting that chronic inflammation may be a key biological process underlying the associations between neighborhood contexts and health risk [23].

Less is known about whether neighborhood socioeconomic deprivation is associated with molecular and cellular indicators of aging. Evidence suggests that epigenetic aging is associated with environmental and socioeconomic characteristics of neighborhoods. For example, individuals living in neighborhoods with fewer environmental and socioeconomic opportunities, as measured by the Childhood Opportunity Index, evince accelerated epigenetic aging [24]. The association between neighborhood socioeconomic factors and epigenetic aging acceleration has also been repeatedly reported among different populations, such as women with breast cancer and their sisters [25,26], children and young adults [27–29], as well as middle-aged and older adults [24,30,31].

Neighborhood socioeconomic deprivation can be measured using an aggregate of residents' socioeconomic indicators. Recent neighborhood research increasingly employs composite index scores to capture the cumulative effects of multiple socioeconomic factors on health outcomes. The Area Deprivation Index (ADI) provides a composite measure of census-block-level socioeconomic deprivation based on comprehensive indicators of education, employment, income, and housing quality [32].

Social Cohesion

Socioeconomic deprivation represents only one dimension of neighborhood environments. Social cohesion, or the degree of connectedness and solidarity among individuals in neighborhoods, includes three core domains: (1) trust among neighbors, (2) norms of mutual assistance in the neighborhood, and (3) sense of community [33–35]. Perceived neighborhood social cohesion has been suggested as a potentially protective factor that can buffer the adverse health effects of socioeconomic deprivation [22,36–41]. However, empirical evidence is limited on whether social cohesion buffers the association between neighborhood deprivation and accelerated aging [30,42,43].

The current analysis

In this study, we investigate the links between socioeconomic deprivation, neighborhood social cohesion, and multiple measures of epigenetic aging among middle-aged and older adults in the United States. We hypothesized that lower neighborhood socioeconomic deprivation and higher perceived neighborhood social cohesion would be associated with a slower epigenetic aging. Further, we hypothesized that higher perceived neighborhood social cohesion would buffer the adverse impact of neighborhood socioeconomic deprivation on the acceleration of epigenetic aging. We expected to observe the strongest associations between neighborhood factors and epigenetic aging indices that were trained originally with algorithms that focused on morbidity and mortality (e.g., GrimAge2 and DunedinPace) [44].

METHODS

Data and Participants

The Midlife in the United States (MIDUS) is a longitudinal cohort study of middle-aged and older American adults [45,46]. The initial cohort was recruited between 1995 and 1996 through random-digit dialing, comprised of individuals aged 25 to 75 years in the contiguous United States, with approximately 90% identifying as non-Hispanic white adults. Follow-up assessments occurred roughly every decade (MIDUS 2: 2004–2006; MIDUS 3: 2013–2015). To increase racial diversity among participants, the MIDUS study oversampled participants from Milwaukee, WI, who were primarily Black (labeled MIDUS 2 Milwaukee; *N* = 592; ages 34–85; 94% Black). Further, a new protocol was introduced during 2004-2009 to collect physiological measures of health (MIDUS 2 Biomarker subproject). Participants in the biomarker protocol came from both the MIDUS 2 national sample and the MIDUS 2 Milwaukee (*N* = 1255).

Additionally, to further expand the original MIDUS cohort and replenish the number of younger adult participants in the MIDUS study, another national sample was recruited that was demographically similar to the initial MIDUS participants (ages 25–74; approximately 90% white) (MIDUS R; 2011–2014). Additional Black adults from Milwaukee were recruited for the MIDUS Refresher Milwaukee (*N* = 508; ages 25–64; 57% female; 91% Black). A subset of the participants from both the national sample and Milwaukee oversampling participated in the biomarker protocol (MIDUS R Biomarker [2012-2015]; *N* = 863). This resulted in a total of 2119 potential participants from both the MIDUS 2 and MIDUS R Biomarker recruitments.

Analytic Sample

This pooled cross-sectional analysis uses data from all participants with available epigenetic aging data who had consented to genetic analyses. Out of 2118 potential participants from both cohorts, 2009 consented, which included DNA methylation profiling (Figure S2, Supplemental Digitial Content, http://links.lww.com/PSYMED/B193). Complete DNA methylation-based epigenetic aging information was available from 1310 participants. We restricted our sample further to those who self-identified as non-Hispanic Black and non-Hispanic white, resulting in a final analytic sample of 1111 participants (non-Hispanic Black = 304; non-Hispanic white = 807).

Biomarker Data Collection

Biomarker data were collected during overnight visits at one of three clinical research units (CRUs) located at either Georgetown University (Washington, DC), the University of Wisconsin-Madison (Madison, WI), or UCLA (Los Angeles, CA). The selection of the CRU site was determined based on proximity to each participant's residence. On the first morning of their stay, fasted whole blood samples were drawn and frozen to obtain DNA for the methylation analyses. To maintain consistency, all samples were collected using the same type of EDTA-coated vacutainer (Becton Dickinson) and stored similarly in ultracold freezers, following standardized protocols. All samples were processed at the UCLA Social Genomics Core Laboratory for the DNA methylation assays.

Previous analysis by the MIDUS study team assessed the difference between survey participants and participants with biomarker data collection and determined that there were no significant differences observed on the majority of demographic (age, sex, self-reported race, marital status), socioeconomic (education, income, health insurance coverage), and health variables (BMI, subjective physical health, drinking behaviors), suggesting those participants are sufficiently representative of the recruitment pool [47].

Measures

Area Deprivation Index (ADI)

Area Deprivation Index (ADI) is a publicly available, validated measure of multidimensional neighborhood socioeconomic deprivation [32,48]. ADI Ranking is based on a cumulative assessment of 17 indicators related to education, employment, income, and housing quality (e.g., unemployment rate, percentage of families below the poverty line, median gross rent, household crowding, access to plumbing) at the census block group level. In our analysis, the 2015 ADI was used as a measure of neighborhood disadvantage. National rankings of the 2015 ADI were generated from five-year estimates (2011-2015) from the American Community Survey (ranging from 1 = least disadvantaged to 100 = most disadvantaged). ADI rankings were retrieved from the Neighborhood Atlas (https://www.neighborhoodatlas.medicine.wisc.edu/) and matched participant data for the current study by the MIDUS Administrative Core to maintain confidentiality. MIDUS participants reported their address during the initial survey of MIDUS 2 and Refresher.

Perceived Neighborhood Social Cohesion

Perceived neighborhood cohesion is a summary score based on three core indicators [33,35,49]: (a) social trust, (b) norms of mutual assistance in the neighborhood, and (c) sense of belonging. The social trust domain was based on a single item, in which participants responded to the question, "People in my neighborhood trust each other." The norms of mutual assistance in the neighborhood were based on participants' responses to a single question, "I could call on a neighbor for help if I needed it." Finally, the sense of belonging domain was based on three items: 1) I don't feel I belong to anything I'd call a community, 2) I feel close to other people in my community, and 3) my community is a source of comfort. Participants responded to all items on a 7-point Likert scale, and the mean scores were calculated and rescaled (range = 1-7), with higher scores indicating greater cohesion. This scale demonstrated acceptable reliability (Cronbach's alpha = .76).

DNA Methylation-Based Epigenetic Aging

DNA methylation profiling was performed in 2019. Following quality control assessment for DNA yield and integrity, genome-wide methylation was measured using Illumina Methylation EPIC microarrays. Beta values, representing the percentage of methylation at each CpG site, were normalized, mapped to the Illumina 450K array of CpG sites, and subjected to standard quality control procedures. In 2022, established algorithms were applied to these methylation profiles to calculate epigenetic age using the Hammum[50] and Horvath[51] (first-generation) epigenetic clocks, the PhenoAge[52] and GrimAge2[53,54] (second-generation) epigenetic clocks, and DunedinPACE pace of aging[55]. Additional information about each epigenetic aging measure is detailed in other publications[56]. Epigenetic age acceleration (EAA) was calculated for five epigenetic clocks (Horvath, Horvath (skin and blood), Hannum, PhenoAge, and GrimAge2) using residuals from regressing each clock on chronological age. Thus, EAA values above 0 represent accelerated epigenetic aging (i.e., biological age older than chronological age). Finally, the DunedinPACE measures the pace of aging as a predictor of within-individual change in the overall physiological system, with a value of 1 indicating an equal pace of aging to that of chronological time (in a 12-month unit). Further details about the data collection and the derivation of epigenetic age indices are also available in the public documentation for the MIDUS study (https://midus.colectica.org/). Bivariate correlations among the 5 epigenetic aging clocks are presented in Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/B193).

Covariates

To measure the total effect of neighborhood socioeconomic contexts on epigenetic aging acceleration, sociodemographic factors that are assumed to be the common cause of neighborhood socioeconomic contexts and epigenetic aging were added as covariates, including chronological age (years), sex (male vs. female), educational attainment (less than a bachelor's degree vs. bachelor's degree or higher), and marital status (currently married vs. others). In addition to those confounders, health-related factors (body mass index (BMI; kg/m^2) and smoking history) were included. As illustrated in our model (Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/B193), those factors are considered potential mediators of the association between neighborhood socioeconomic contexts and accelerated epigenetic aging. Indeed, previous studies have reported that neighborhood socioeconomic contexts influence tobacco use and BMI[15], and that accelerated epigenetic aging is associated with tobacco use and BMI[5,8].

Analytic Strategy

Before conducting the moderation analysis, linear regressions were conducted to examine the independent associations between neighborhood contexts (ADI and social cohesion) and each epigenetic aging measure. First, we conducted simple linear regression to determine crude associations between neighborhood contexts and each epigenetic aging measure. We then progressively adjust for covariates: first, chronological age and sex, followed by the addition of sociodemographic factors (i.e., educational attainment, marital status). The model further included potential mediators, BMI and smoking history.

To assess the buffering effect of social cohesion on the association between neighborhood socioeconomic deprivation and epigenetic aging, we added ADI, social cohesion, and an interaction term between ADI and social cohesion (both mean-centered) to the regression model, along with adjustments for chronological age, sex, educational attainment, and marital status. When a significant interaction is observed, we probe the interaction by analyzing epigenetic aging at the mean and at one standard deviation above and below the mean of social cohesion. We further conducted "probing" an interaction using an additional inferential test to determine at which values of the moderator the association between the exposure and outcome was statistically significant. In other words, we examine the levels of perceived social cohesion at which the effect of neighborhood disadvantage on the acceleration of epigenetic aging becomes non-significant. We applied the Johnson–Neyman technique, which identifies the values of the moderator where the conditional effect of the exposure on the outcome transitions between statistical significance and non-significance at a specified alpha level. The Johnson–Neyman technique provides the points along the moderator continuum at which the ratio of the conditional effect to its standard error equals the critical t-value. These points define the Region of Significance (RoS), indicating the range of social cohesion values for which the association between ADI and epigenetic aging acceleration was statistically significant. More details can be found elsewhere . To adjust for multiple comparisons, we applied a Bonferroni correction, setting the statistical significance level at alpha 0.01 (0.05/5), corresponding to 99% confidence intervals.

Missing Data

Missing data were minimal (see Table 1). A total of 74 participants (6.8%) were missing ADI data. The likelihood of missing ADI data was significantly higher among non-Hispanic

white and married individuals, but did not differ by chronological age or sex. Missing data were handled using listwise deletion in our regression analyses.

RESULTS

Descriptive Information of the Participants

The demographic characteristics of 1111 participants used in the analyses are presented in Table 1. The mean chronological age was 54 years (*SD* = 13), and 55% of participants were female. The mean perceived neighborhood cohesion was 5.4 (SD = 1.00), and the mean ADI National Rank was 48.0 (SD = 27.4). Of 1111 participants, 47.3% had a bachelor's degree or higher, and 58.6% were married. Mean BMI was 30.4 (SD = 7.1), and 508 participants (45.7%) had a smoking history. Bivariate correlations among all variables are presented in the Supplementary Materials (Figure S3, http://links.lww.com/PSYMED/B193).

Neighborhood Socioeconomic Deprivation and Accelerated Epigenetic Age

Table 2 presents the results of regression analyses examining the association between ADI and epigenetic aging acceleration. The unstandardized regression coefficients (*B*s) represent the change in epigenetic aging score per 1.0-point increase in ADI score, while the standardized regression coefficients (Betas) represent the effect size, or the change in epigenetic aging (in standard deviations) for a one-standard-deviation increase in ADI score. In the crude model (Model 1), ADI was significantly inversely associated with PhenoAge EAA (B = 0.017, SE = 0.007, Beta = 0.079, 99%CI: [0.000, 0.034]), GrimAge2 EAA (B = 0.054, SE = 0.006, Beta =0.275, 99%CI: [0.039, 0.069]), and DunedinPACE pace of aging (B = 0.002, SE = 0.000, Beta =0.313, 99%CI: [0.001, 0.002]).

Those significant associations remained even after adjusting for chronological age and sex (Model 2): PhenoAge EAA (B = 0.018, SE = 0.007, Beta = 0.082, 99%CI: [0.001, 0.035]), GrimAge2 EAA (B = 0.057, SE = 0.006, Beta = 0.288, 99%CI: [0.042, 0.071]), and DunedinPACE pace of aging (B = 0.002, SE = 0.000, Beta = 0.34, 99%CI: [0.001, 0.002]). After adjusting for educational attainment and marital status (Model 3), the significant associations were still evident, although the magnitudes were slightly attenuated: EAA PhenoAge (B = 0.014, SE = 0.007, Beta = 0.066, 95%CI: [-0.004, 0.033]), EAA GrimAge2 (B= 0.035, SE = 0.006, Beta = 0.177, 99%CI: [0.019, 0.050]), and DunedinPACE pace of aging (B = 0.001, SE = 0.000, Beta = 0.224, 99%CI: [0.001, 0.002]). Finally, when BMI and smoking history were considered in the model, higher ADI remained significantly associated with faster EAA GrimAge2 (B = 0.026, SE = 0.005, Beta = 0.130, 99%CI: [0.012, 0.039]) and DunedinPACE pace of aging (B = 0.001, SE = 0.000, Beta = 0.174, 99%CI: [0.001, 0.001]), but not EAA PhenoAge (Est. = 0.008, SE = 0.007, Beta = 0.038, 99%CI: [-0.010, 0.027]).

Perceived Neighborhood Social Cohesion and Accelerated Epigenetic Age

The results of the regression analyses on the association between perceived neighborhood social cohesion and epigenetic aging acceleration are presented in Table 3. The unstandardized regression coefficients (*B*s) represent the change in epigenetic aging score per 1.0-point increase in the cohesion scale. The standardized regression coefficients (Betas) represent the effect size, or the change in epigenetic aging (in standard deviations) for a one-standard deviation increase in social cohesion. In the least adjusted model (Model 1), perceived neighborhood social cohesion was significantly inversely associated with epigenetic age acceleration based on EAA GrimAge2

(B = -1.071, SE = 0.159, Beta = -0.198, 99%CI: [-1.482, -0.660]), and DunedinPACE pace of aging (B = -0.021, SE = 0.004, Beta = -0.152, 99%CI: [-0.032, -0.011]).

After adjusting for chronological age and sex (Model 2), the EAA Hovarth scores no longer retained statistical significance, but the significant associations with epigenetic aging were still evident for EAA GrimAge2 (B = -1.062, SE = 0.162, Beta = -0.196, 99%CI: [-1.480, -0.645]) and DunedinPACE pace of aging (B = -0.027, SE = 0.004, Beta = -0.193, 99%CI: [-0.038, -0.016]). Those significant associations were observed even after adjusting for educational attainment and marital status in Model 3 (EAA GrimAge2: B =-0.601, SE = 0.159, Beta = -0.111, 99%CI: [-1.012, -0.190]; DunedinPACE page of aging: B = -0.014, SE = 0.004, Beta = -0.099, 99%CI: [-0.024, -0.003]). After adjusting for potential mediators, BMI and smoking history, the associations between neighborhood factors and variation in those measures were no longer significant for GrimAge2 EAA(B =-0.294, SE = 0.144, Beta = -0.054, 99%CI: [-0.666, 0.079]), but not for DunedinPACE pace of aging (B = -0.006, SE = 0.004, Beta = -0.043, 99%CI: [-0.016, 0.004]).

The Moderating Effect of Neighborhood Social Cohesion on the Association Between ADI and Epigenetic Aging

The results incorporating the interaction terms between ADI and perceived neighborhood social cohesion are presented in Table 4. After adjusting for chronological age, sex, educational attainment, and marital status, the interaction between ADI and perceived neighborhood social cohesion was significant for EAA GrimAge2 (B = -0.018, SE = 0.005, 99%CI: [-0.032, -0.004]) and DunedinPACE (B = -0.000, SE = 0.000, 99%CI: [-0.001, 0.000]).

The results of the simple slope analyses are presented in Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/B193, and the graphical representations are shown in Figure S4A and S4B, Supplemental Digital Content, http://links.lww.com/PSYMED/B193. Simple slopes analysis revealed that, for individuals reporting lower perceived social cohesion (-1 SD), the association between ADI and EAA GrimAge2 was significant (Est. = 0.05, SE = 0.01, 99% CI: 0.03, 0.07). However, for those reported higher social cohesion (+1 SD), this association was significantly attenuated and no longer reached significance (Est. = 0.01, SE = 0.01, 99%CI: -0.00, 0.03). For individuals reporting lower perceived social cohesion (-1 SD), the association between ADI and DunedinPACE was significant (Est. = 0.001, SE = 0.000, 99%CI: 0.001, 0.002). This association remained significant even among those who reported higher social cohesion (+1 SD) (Est. = 0.001, SE = 0.000, 99%CI: 0.000, 0.001).

The Johnson-Neyman plots in Figures S4C and S4D, Supplemental Digital Content, http://links.lww.com/PSYMED/B193, illustrate the regions of significance for the level of social cohesion where the associations between the ADI and EAA GrimAge2 and DunedinPACE pace of aging were significant. In EAA GrimAge2, the downward slope of the line demonstrates that as perceived neighborhood social cohesion increased, the strength of the relationship between ADI and EAA GrimAge2 declined, eventually losing statistical significance at high levels of social cohesion (threshold value = 6.14). In other words, the conditional effect of ADI on EAA GrimAge2 was significant when the score of social cohesion was below the threshold value, but the greater the social cohesion level, the weaker the effect of ADI on EAA GrimAge2. Once social cohesion reached the threshold value, the association was no longer statistically significant. Similarly, the downward slope of the conditional effect was observed for the DunedinPACE pace of aging, indicating that as perceived neighborhood social cohesion increased, the strength of the

relationship between ADI and DunedinPACE pace of aging declined, eventually losing statistical significance at a threshold of 6.89.

DISCUSSION

Our analyses demonstrate that neighborhood context, including neighborhood socioeconomic deprivation and perceived neighborhood social cohesion, is associated with several different indices of epigenetic age acceleration. We also examined whether perceptions of neighborhood social cohesion moderate the association between neighborhood socioeconomic deprivation and an acceleration of the pace of epigenetic aging. We found significant associations between neighborhood socioeconomic deprivation and perceived neighborhood social cohesion, particularly with the more recent indices of epigenetic age acceleration: EAA GrimAge2 and DunedinPACE pace of aging. These associations were observed even after accounting for sociodemographic and economic factors, highlighting the potential biological processes of aging shaped by neighborhood context. In addition, we found that perceived neighborhood social cohesion moderated the association between neighborhood socioeconomic deprivation and epigenetic aging based on EAA GrimAge2 and DunedinPACE pace of aging. The findings suggest that the association between neighborhood socioeconomic deprivation and epigenetic age is weaker among those who report greater neighborhood cohesion. Interestingly, the association between neighborhood disadvantage (ADI) and GrimAge2 was attenuated at high levels of perceived social cohesion, suggesting a threshold above which social cohesion may buffer some aspects of the biological impact of disadvantage. Further, an exploratory analysis revealed that these associations did not differ significantly among non-Hispanic Black and white adults.

Our findings are consistent with previous research indicating an association between adverse neighborhood socioeconomic contexts and epigenetic aging when measured by two widely employed DNA methylation-based epigenetic aging measures: GrimAge2 and DunedinPACE pace of aging[24,30,31]. The associations were not as clearly evident for the Horvath and Hannum indices, which were developed in the early stages of epigenetic aging research and are now considered to be first-generation clocks. PhenoAge and GrimAge2 are considered to be second-generation epigenetic clocks and their algorithms were trained with respect to mortality and health indicators[44]. DunedinPACE is a third-generation epigenetic clock, which was generated to quantify within-person pace of aging (relative to chronological time) from biomarkers and health status in young adults who had been followed longitudinally[44]. It is designed to capture the rate of epigenetic change with respect to biomarkers of health rather than current age. The second and third generation clocks appear to be more closely associated with lifetime socioeconomic status, health behavior, and health outcomes[6]. Thus, our observation that the pattern of association differed between first-generation clocks (Horvath, Horvath Skin and Blood, and Hannum) and GrimAge2 and DunedinPACE, was not surprising.

The difference in results between PhenoAge, GrimAge2, and DunedinPACE could be attributed to their intrinsic structures, leading to different sensitivities to the neighborhood socioeconomic contexts. DunedinPACE is distinct from the other two clocks. It focuses on the current pace of aging, so its algorithms may reflect be more reflective of current environmental conditions than are the other two clocks measuring the cumulative effects of aging across the life course[24,59]. Both PhenoAge and GrimAge2 were trained on multiple biomarkers, but they have different developmental methods and therefore emphasize different biological pathways. The development of GrimAge2 also incorporates DNA methylation-based surrogates for smoking

and specific plasma proteins that are sensitive to chronic stress and lifestyle behaviors, tuned to predict time-to-death[6]. In contrast, PhenoAge was developed to predict a composite phenotypic age based on ten clinical blood markers and was trained to predict phenotypic age[60], which may capture gross organ-system function and may be relatively less responsive to wear-and-tear associated with neighborhood environments. Indeed, previous studies also reported similar differences in sensitivity, with GrimAge2 and DunedinPACE being more closely linked to neighborhood socioeconomic deprivation[24,31].

Our findings add to the growing evidence for the important ways that societal and socio-economic factors can lead to epigenetic alterations and influence both physical and psychological well-being. Findings from Cuevas et al. (2025) showed that lower neighborhood opportunities based on Childhood Opportunity Index were associated with faster epigenetic aging as indexed by an accelerated DunedinPACE pace of aging[24]. Similarly, among American and Puerto Rican women, Lawrence et al. (2020) found that higher neighborhood socioeconomic deprivation (also based on ADI) was associated with faster epigenetic aging, as reflected by the GrimAge index[61]. In our study of middle-aged and older American adults, we found that higher ADI scores were associated with faster epigenetic aging, especially as captured by two epigenetic clocks: GrimAge2 and DunedinPACE pace of aging. Furthermore, we demonstrated that neighborhood cohesion significantly contributes to epigenetic aging. Conversely, our findings indicate that higher social cohesion was linked to slower epigenetic aging as reflected by both GrimAge2 and DunedinPACE scores.

In addition, our findings suggest further that the perceptions of neighborhood social cohesion can moderate the association between neighborhood socioeconomic deprivation and epigenetic aging acceleration. Previous studies have reported a moderating role of social cohesion on the association between neighborhood socioeconomic deprivation and adverse health outcomes, including on coronary heart disease and stroke[18,62] and mortality[19–21]. Collectively, the research conveys a strong influence of social and physical features of neighborhoods that affect health and the temporal aspects of aging. For example, a previous analysis using data from the Detroit Neighborhood Health Study found that social cohesion could exert a buffering role, lessening the impact of neighborhood poverty on epigenetic aging[43]. However, their analysis was limited to only including three measures of epigenetic aging: Horvath, Hannum, and PhenoAge. In our analysis, we were able to evaluate a larger sample of middle-aged and older American adults, as well as include more recent indices of epigenetic aging. We found the moderating role of social cohesion was evident only for the two newer epigenetic clocks, GrimAge2 and DunedinPACE pace of age. This difference may be because both clocks were generated by training algorithms that focused on physiological biomarkers of health, whereas the early generation of epigenetic clocks had been trained with respect to chronological age [44].

Notwithstanding the uniqueness of our analyses, several limitations should be acknowledged. First, the cross-sectional design limits our ability to infer the directionality of the relationship between perceived neighborhood social cohesion and the pace of epigenetic aging, although reverse causation, from epigenetic biomarkers to perceptions of social cohesion, seems unlikely. Nevertheless, it is important to consider that because epigenetic aging could also be the result of detrimental health outcomes, determination of the direct pathway between deprivation and health outcomes is challenging. Second, our use of the 2015 ADI has limitations. The 2015 ADI, based on the 5-year ACS estimates (2011-2015), may not reflect participants' residential environments at the time of MIDUS 2 data collection (2004-2009). Thus, our analyses assume

that the relative neighborhood environment did not dramatically change over the period since the biomarker data collection. This assumption likely does not hold, as neighborhoods may change due to several forces that shape the area-level sociodemographic profiles used in the ADI. Additionally, due to limitations in data availability, we cannot account for the duration of time participants resided in these areas. However, there are several factors that partially mitigate this concern. Research on longer-term neighborhood change suggests that the extremes of the deprivation distribution (i.e. the most and least deprived areas) show the highest persistence over time[63]. In addition, changes in neighborhood disadvantage among older adults were known to be relatively uncommon[64]. In addition, the ranking measures for neighborhood socioeconomic deprivation may not fully capture the absolute magnitude of the socioeconomic differences between areas. For example, the difference in neighborhood quality between areas ranked 50th and 51st could be larger than that between areas ranked 1st and 2nd, and there could be within-neighborhood heterogeneity. The ADI ranking from 2015 was used because it was closest to the MIDUS data collection time among available measures. Third, our data lacked a multilevel structure that would have enabled us to disentangle the contribution of cohesion at the neighborhood level from individual perceptions of cohesion. We do not have access to participants' addresses, including region, state, and county/city. Consequently, the exposure variable (i.e., perceived cohesion) may partly reflect unobserved individual characteristics, such as personality or subtle mental health differences, rather than actual differences in neighborhood context. Fourth, the inability to apply population weighting restricts the generalizability of our estimates to a larger population, even though the insights are likely broadly applicable. Fifth, the non-Hispanic Black participants were largely recruited via oversampling from a single city, Milwaukee, WI, which has highly segregated communities, limiting the generalizability of findings to non-Hispanic Black adults in other geographical areas. Finally, the demographic composition of the MIDUS sample did not permit comparisons across other racial and ethnic groups, constraining our ability to conclude whether the benefits of neighborhood quality and perceived social cohesion extend beyond the populations represented in our sample. While we aimed to investigate the moderating effect of race, we lacked sufficient statistical power to obtain meaningful estimates and inferences. Given growing evidence of racial inequities in neighborhood experiences, we recommend analyzing three-way interactions between cohesion, deprivation, and race/ethnicity in future research within larger cohorts.

To address some of these limitations, future research should include a more diverse cohort and prioritize longitudinal and multilevel studies with repeated measures of epigenetic aging. The follow-up data on these epigenetic clocks from the next wave of assessment in the MIDUS study will soon be made available to the public. Thus, the current results are formative and foundational for a subsequent analysis of the longitudinal associations among neighborhood socioeconomic deprivation, social cohesion, and epigenetic aging. Future studies can also address that DNA methylation at specific CpG sites is only one of the methodological approaches that can be employed to capture how the social realm influences gene regulation and protein transcription

Conclusion

Our analyses focused on the association between socioeconomic deprivation and social cohesion and their influence on the pace of epigenetic aging. The findings indicated that both socioeconomic deprivation and perceived neighborhood social cohesion are associated with epigenetic aging, especially when investigating this association with the two more recently developed epigenetic clocks, GrimAge2 and DunedinPACE. The buffering effects of perceived

cohesion on the association between socioeconomic deprivation and epigenetic aging were evident among both non-Hispanic Black and non-Hispanic white adults. However, the variation in conclusions when employing different epigenetic clocks conveys some of the complexities of employing the epigenome to index the pace of biological aging.

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Table 1. Descriptive statistics of sociodemographic characteristics, epigenetic aging acceleration, and perceived neighborhood social cohesion of participants with complete responses (N = 1111).

		Missing (n)	M (SD) or % (N = 1,111)
Neighborhood Context	Perceived Neighborhood Social Cohesion	2	5.35 (1.00)
	ADI National Rank	74	48.02 (27.43)
Epigenetic Aging Acceleration	Hovarth	0	0.00 (4.45)
	Hovarth Skin and Blood	0	0.00 (3.52)
	Hannum	0	0.00 (4.42)
	PhenoAge	0	0.00 (6.05)
	GrimAge2	0	0.00 (5.39)
	DunedinPACE	0	0.99 (0.14)
Covariates	Chronological Age	0	54.13 (12.55)
	Sex	0	
	Female		614 (55.27%)
	Male		497 (44.73%)
	Educational Attainment	0	
	Bachelor's degree or higher		525 (47.25%)
	Lower than bachelor's degree		586 (52.75%)
	Marital Status	0	
	Married		650 (58.56%)
	Not Married Currently		460 (41.44%)
	BMI	0	30.35 (7.10)
	History of Tobacco Use	0	508 (45.72%)

Note: a = p-values < .05 indicate significant differences between non-Hispanic Black and non-Hispanic white groups.

Table 2. Summary of results from regression analyses on the association between neighborhood socioeconomic deprivation and measures of epigenetic aging acceleration among all participants (*N* = 1111).

	Model 1			Model 2		
EAA	B (SE)	99%CI	Beta	B (SE)	99%CI	Beta
Hovarth	0.004 (0.005)	[-0.009, 0.017]	0.025	0.005 (0.005)	[-0.007, 0.018]	0.033
Hovarth Skin and Blood	0.002 (0.004)	[-0.008, 0.012]	0.014	0.002 (0.004)	[-0.008, 0.012]	0.017
Hannum	-0.003 (0.005)	[-0.015, 0.010]	-0.018	-0.001 (0.005)	[-0.014, 0.011]	-0.008
PhenoAge	0.017 (0.007)	[0.000, 0.034]	0.079	0.018 (0.007)	[0.001, 0.035]	0.082
GrimAge2	0.054 (0.006)	[0.039, 0.069]	0.275	0.057 (0.006)	[0.042, 0.071]	0.288
DunedinPACE	0.002 (0.000)	[0.001, 0.002]	0.313	0.002 (0.000)	[0.001, 0.002]	0.34

	Model 3			Model 4		
EAA	B (SE)	99%CI	Beta	B (SE)	99%CI	Beta
Hovarth	0.007 (0.005)	[-0.007, 0.021]	0.043	0.006 (0.005)	[-0.008, 0.020]	0.037
Hovarth Skin and Blood	0.002 (0.004)	[-0.009, 0.013]	0.018	0.002 (0.004)	[-0.009, 0.013]	0.013
Hannum	0.003 (0.005)	[-0.011, 0.016]	0.018	0.001 (0.005)	[-0.012, 0.015]	0.009
PhenoAge	0.014 (0.007)	[-0.004, 0.033]	0.066	0.008 (0.007)	[-0.010, 0.027]	0.038
GrimAge2	0.035 (0.006)	[0.019, 0.050]	0.177	0.026 (0.005)	[0.012, 0.039]	0.13
DunedinPACE	0.001 (0.000)	[0.001, 0.002]	0.224	0.001 (0.000)	[0.001, 0.001]	0.174

Note: B = unstandardized regression coefficient, SE = standard error, Beta = standardized regression coefficient. Standardized regression coefficients are calculated β×SD(ADI National Rank) / SD(EAA measures).

Model 1: no covariates included; Model 2: adjusted for chronological age (years) and sex (0 = male, 1 = female); Model 3: adjusted for chronological age (years) and sex (0 = male, 1 = female), educational attainment (0 = less than a bachelor's degree, 1 = bachelor's degree or higher), marital status (0 = not married, 1 = married); Model 4: adjusted for chronological age (years) and sex (0 = male, 1 = female), educational attainment (0 = less than a bachelor's degree, 1 = bachelor's degree or higher), marital status (0 = not married, 1 = married), BMI, and smoking history (0 = No, 1 = Yes).

Table 3. Summary of results from regression analyses on the association between perceived neighborhood social cohesion and measures of epigenetic aging acceleration among all participants (*N* = 1111).

	Model 1			Model 2		
EAA	B (SE)	99%CI	Beta	B (SE)	99%CI	Beta
Hovarth	-0.304 (0.134)	[-0.649, 0.041]	-0.068	-0.265 (0.136)	[-0.615, 0.084]	-0.059
Hovarth Skin and Blood	-0.172 (0.106)	[-0.445, 0.101]	-0.049	-0.170 (0.108)	[-0.449, 0.109]	-0.048
Hannum	-0.121 (0.133)	[-0.464, 0.223]	-0.027	-0.058 (0.134)	[-0.404, 0.288]	-0.013
PhenoAge	-0.282 (0.182)	[-0.752, 0.188]	-0.046	-0.283 (0.186)	[-0.764, 0.198]	-0.047
GrimAge2	-1.071 (0.159)	[-1.482, -0.660]	-0.198	-1.062 (0.162)	[-1.480, -0.645]	-0.196
DunedinPACE	-0.021 (0.004)	[-0.032, -0.011]	-0.152	-0.027 (0.004)	[-0.038, -0.016]	-0.193

	Model 3			Model 4		
EAA	B (SE)	99%CI	Beta	B (SE)	99%CI	Beta
Hovarth	-0.281 (0.141)	[-0.643, 0.082]	-0.063	-0.261 (0.142)	[-0.627, 0.105]	-0.058
Hovarth Skin and Blood	-0.181 (0.112)	[-0.470, 0.109]	-0.051	-0.171 (0.113)	[-0.463, 0.122]	-0.048
Hannum	-0.139 (0.139)	[-0.497, 0.219]	-0.031	-0.099 (0.140)	[-0.460, 0.262]	-0.022
PhenoAge	-0.187 (0.193)	[-0.684, 0.311]	-0.031	-0.004 (0.191)	[-0.497, 0.488]	-0.001
GrimAge2	-0.601 (0.159)	[-1.012, -0.190]	-0.111	-0.294 (0.144)	[-0.666, 0.079]	-0.054
DunedinPACE	-0.014 (0.004)	[-0.024, -0.003]	-0.099	-0.006 (0.004)	[-0.016, 0.004]	-0.043

Note: B = unstandardized regression coefficient, SE = standard error, Beta = standardized regression coefficient. Standardized regression coefficients are calculated β×SD(social cohesion score) / SD(EAA measures).

Model 1: no covariates included; Model 2: adjusted for chronological age (years) and sex (0 = male, 1 = female); Model 3: adjusted for chronological age (years) and sex (0 = male, 1 = female), educational attainment (0 = less than a bachelor's degree, 1 = bachelor's degree or higher), marital status (0 = not married, 1 = married); Model 4: adjusted for chronological age (years) and sex (0 = male, 1 = female), educational attainment (0 = less than a bachelor's degree, 1 = bachelor's degree or higher), marital status (0 = not married, 1 = married), BMI, and smoking history (0 = No, 1 = Yes).

Table 4. Summary results of regression analysis with an interaction term for EAA GrimAge2 and DunedinPACE.

	GrimAge2			DunedinPACE		
	B (SE)	99% CI	Beta	B (SE)	99% CI	Beta
Neighborhood socioeconomic deprivation (centered)	0.032 (0.006)	[0.017, 0.048]	0.164	0.001 (0.000)	[0.001, 0.001]	0.214
Perceived social cohesion (centered)	-0.471 (0.158)	[-0.878, -0.063]	-0.087	-0.010 (0.004)	[-0.020, 0.000]	-0.072
Deprivation (centered) × Cohesion (centered)	-0.018 (0.005)	[-0.032, -0.004]	-0.094	-0.000 (0.000)	[-0.001, 0.000]	-0.056

Note: B = unstandardized regression coefficient, SE = standard error; Models were adjusted for chronological age (years) and sex (0 = male, 1 = female), educational attainment (0 = less than a bachelor's degree, 1 = bachelor's degree or higher), and marital status (0 = not married, 1 = married).