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Research Article

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Posted Date: November 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9016153/v1

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Additional Declarations: No competing interests reported.

Neighborhood cohesion and epigenetic aging: The contribution of daily stressor reactivity

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Abstract

Background: People who perceive their neighborhoods as cohesive (i.e., neighbors can trust and count on one another) have better health, yet questions remain regarding the psychosocial and biological mechanisms for this association. Although greater cohesion has been related to reduced affective reactivity to daily stressors (e.g., arguments with a loved one), whether this reduced reactivity explains cohesion-health links remains unclear. The availability of epigenetic "clocks" in research surveys has allowed for examination of early biological risk for poor health in midlife, a life stage when chronic disease is just becoming apparent. The present study tested the hypotheses that greater perceived cohesion would relate to decelerated aging on three epigenetic algorithms, PhenoAge, GrimAge (v2), and DunedinPACE, and that these links would be partially established through reduced affective reactivity to daily stressors. Using data from the Midlife in the United States national survey, the present study utilized multi-level structural equation models to investigate direct and indirect associations between perceived cohesion and epigenetic aging through affective reactivity to daily stressors. **Results**: People who perceived greater neighborhood cohesion exhibited decelerated epigenetic aging on GrimAge (v2) and DunedinPACE (although not PhenoAge), and these associations were partially explained by reduced affective reactivity to daily stressors. **Conclusions**: These novel findings suggested a unique daily stress pathway linking perceived neighborhood cohesion to epigenetic aging. Fostering neighborhood cohesion, and therapeutic efforts encouraging coping during times of stress, may assist with decelerating epigenetic aging.

Keywords: molecular age; perceived neighborhood characteristics; daily stress processes

Background

The population of older adults in the United States is large, growing rapidly, and predicted to represent 25 percent of the population by 2060.[1] This trend means that the prevalence of chronic diseases responsible for the country's leading causes of death will increase substantially as well, necessitating multi-level efforts to protect the health and well-being of this segment of the population. Rapid growth in discoveries of the biological underpinnings of aging has revealed that changes in the epigenome, particularly via DNA methylation (DNAm), characterize accelerated aging and early risk for morbidity and mortality.[2] The rate of biological aging is thought to vary, in part, from exposure to environmental and psychosocial stressors, with much of this research investigating chronic stressors, lifetime experiences, and traumatic events.[3-4] At a broader level, features of neighborhoods in which people live include risk for chronic disease development, including those that enable older adults to engage physically and socially with their neighborhoods.[5] Indeed, a recent review reported associations between neighborhood socioeconomic status and epigenetic aging.[6] However, neighborhood researchers have long argued that socioeconomic features, aside from being difficult to modify, lie further upstream from more proximal, health-relevant neighborhood features.[7] How residents perceive their neighborhoods, for example, including the degree to which people perceive they can count on and trust their neighbors (i.e., perceived neighborhood cohesion), is associated with chronic health conditions. [8-9] Using a U.S. sample of midlife adults, the current study investigated a mechanism for this association: whether perceptions of neighborhood cohesion would relate to decelerated epigenetic aging on three epigenetic "clocks" or "algorithms." Further, we evaluated whether these links are partially explained through affective responses to daily stressors, which have been highlighted as specific and putative mechanisms linking daily stress to health

outcomes. [10-11]

Perceived Neighborhood Cohesion, Stress, and Health

Neighborhood cohesion is posited to be a fundamental social determinant of health in conceptual frameworks[12-13] and empirical work;[14] it is also featured in the US Healthy People 2030 objectives for health promotion, with a national call for increased research attention on its role in health and well-being across the lifespan.[13] The neighborhoods in which people are embedded shape their health and well-being due in part to the cohesive qualities of the neighborhood.[14] Research on neighborhood cohesion and its impact on health is needed to inform interventions and policies at local and national levels to reduce health risks and promote healthy aging.[13] The term "perceived neighborhood cohesion" captures the connectedness, solidarity, and trust among community members.[14] This shared group characteristic can be drawn on by residents and is distinct from a person's unique social network (e.g., friends and family). Greater neighborhood cohesion often explains why some neighborhoods benefit from less conflict (e.g., crime) and more reciprocity (e.g., cooperation). Greater neighborhood cohesion benefits residents' health through enhanced health behaviors, the appropriation of health services, and the exchange of informational and socioemotional support, the last of which is germane to the present study.

Perceived neighborhood cohesion has been associated with health outcomes ranging from biological status to cardiovascular health.[8-9] Beyond these direct associations, perceptions of cohesion have been demonstrated to offset genetic risk for cardiovascular wear and tear.[15] In addition to these physical health outcomes, perceived neighborhood cohesion has been associated with a host of psychosocial well-being and mental health outcomes. For instance, people residing in more cohesive neighborhoods report greater life satisfaction, happiness, and

optimism, and less depression and loneliness.[16-18] Perceived neighborhood cohesion similarly buffers against other neighborhood risk factors such as safety concerns, particularly in relation to psychological health.[19] Of noteworthy interest for the present analyses, people who perceive their neighborhood as more cohesive also report less perceived stress and exhibit relatively reduced affective reactivity to daily stressors.[20-21]

Taken together, perceived neighborhood cohesion has documented associations with a myriad of health benefits for residents and appears to buffer against daily stress. The latter of these (i.e., daily stress) is a known risk factor for poorer health.[22-23] Yet, no studies have properly investigated whether cohesion-health associations, and certainly not decelerated epigenetic aging, are established at least in part through daily stress processes.

Stress, Health, and Aging

At the root of many of the above health outcomes, and indeed in the aging process itself, are lifetime changes in the epigenome.[2] In fact, a series of "clocks" or "algorithms" capturing biological aging have been constructed based on DNAm.[24-25] Recent constructions of such clocks were trained not on chronological age, but rather on biological indices of disease. For instance, 513 CpG sites were identified as having DNAm surrogates related to nine markers representing kidney function, glucose metabolism, and inflammation and immune function in the PhenoAge clock.[26] In the case of GrimAge2, the second and more recent version of this clock, morbidity and mortality were predicted by 1,048 DNAm surrogates for nine plasma proteins including c-reactive protein and hemoglobin A1c as well as for smoking pack years.[27] These two clocks therefore differ fundamentally, both in the input used to define the target "clock" age, and in the way in which DNAm was used: PhenoAge used DNAm to predict clinical biomarkers, and GrimAge2 used DNAm to predict mortality.[26-27]

Further iterations of these constructs have used not a cross-section in clinical markers of disease, but rather change in these markers over time (a 20-year period), including indicators such as body mass index, HbA1c, grip strength, lung and cognitive function, and self-rated health; identification of 173 DNAm predictors of this pace of aging have been quantified in an algorithm referred to as DunedinPACE.[28] Several sociodemographic (e.g., gender, race/ethnicity, education) and behavioral (e.g., BMI, smoking) factors have been related to accelerated epigenetic aging, and accelerated epigenetic aging has, in turn, been associated with poorer physical and cognitive functioning, chronic health conditions, and mortality.[29,2]

Whether subjective experiences of a neighborhood are among the predictors of epigenetic aging has only just begun to be investigated. In a small sample of adults in Detroit (n = 158), perceiving one's neighborhood as more cohesive offset the significant association between neighborhood poverty and accelerated age on the Horvath, Hannum, and PhenoAge clocks.[30] In a larger national sample of U.S. older adults, perceiving one's neighborhoods as less cohesive was related to accelerated PhenoAge and GrimAge, although not on the earlier Hannum or Horvath clocks.[31] While these initial reports show promise, suggesting that neighborhood perceptions are worthy targets for intervention, questions remain. For example, given the utility of these clocks for identifying early risk for poor health, do findings such as those in Choi & Ailshire[31] extend to individuals in earlier stages of life? And, if so, what might account for links between perceived neighborhood cohesion and epigenetic aging? Researchers have long argued that stress lies in the path from neighborhood cohesion to health, rendering this mechanism an attractive starting point.[14] Given the link between daily stressors and long-term physical health outcomes, the present study focused on affective responses to daily stressors, a novel, intervention-ready target, as a potential mechanism linking perceived neighborhood cohesion and epigenetic aging.[11,32]

The Present Study

The present study had two key aims. The first was to test the hypothesis that greater perceptions of neighborhood cohesion would be related to decelerated aging on three epigenetic clocks or algorithms: PhenoAge, GrimAge2, and DunedinPACE. The second was to evaluate the degree to which negative affective reactivity to daily stressors might explain, in part, the hypothesized cohesion-epigenetic aging associations. Data from the second wave of the original cohort and Refresher cohort of the Midlife in the United States study (MIDUS), a sample of U.S. adults in midlife, were used to test these questions.

Methods

Participants and Procedure

The present study used data from MIDUS, a publicly available national study of health and well-being (https://midus.wisc.edu). The analysis included data from two cohorts of MIDUS participants with available data on epigenetic clocks – the second wave of the original longitudinal cohort (2004/2005) and the Refresher cohort (2011). Both MIDUS Wave 2 and MIDUS Refresher cohorts completed a general survey that included questions about neighborhood cohesion (N = 8,540). This general survey was completed before participants were recruited to MIDUS sub-projects. In the National Study of Daily Experiences (NSDE) sub-project, a random subsample of MIDUS participants (N = 2,802) was recruited to complete eight consecutive telephone interviews during which they answered questions about negative affect and stressors. Approximately six months to two years following the initial MIDUS survey, a subsample of participants (N = 2,118) were recruited to a biomarker protocol involving an overnight stay at a clinical research unit. The Biomarker sub-project included blood sample collections that were used for the extraction of DNA methylation and for the construction of

epigenetic algorithms (N = 1,310). The current research made use of all available data from respondents who participated in both the general survey, and the NSDE (N = 2,598) and Biomarker (N = 1,185) sub-projects, to examine the first hypothesis that greater perceived neighborhood cohesion would be related to decelerated epigenetic age. Furthermore, a more restricted sample of participants with data from all sources (N = 645) was used to test the second hypothesis that the predicted cohesion-epigenetic association would be established in part via reactivity to daily stressors.

Measures

Perceived neighborhood cohesion. Perceived neighborhood cohesion was measured using two items: "I could call on a neighbor for help if I needed it" and "My neighbors trust each other."[33] Responses (1=a lot, 2=a little, 3=some, and 4=not at all) were reverse coded so that higher values indicate greater perceived neighborhood cohesion. A composite score was obtained by taking the average of responses across the two items. The measure demonstrated adequate internal consistency in the present study (α = .62).

Daily negative affect. Over eight consecutive days, participants were presented with a list of six negative emotions (e.g., everything was an effort, fidgety, nervous) and asked to indicate how frequently they felt each emotion in the past 24 hours. Responses ranged from 0 (*none of the time*) to 4 (*all of the time*). Daily negative affect scores were computed by averaging across items for each day.[34]

Daily stressors. Over eight consecutive days, participants also completed the Daily Inventory of Stressful Events (DISE), consisting of six questions that assess whether certain types of stressors had been experienced in the past 24 hours (e.g., In the past 24 hours, did you have an argument or disagreement with someone?). A dichotomous variable was used to

characterize days as either non-stress days (0=n*o stressor was reported*) or stress days (1=*at least 1 stressor was reported*.[35]

Epigenetic aging. GrimAge2, PhenoAge, and DunedinPACE were used to operationalize epigenetic aging.[26-28] Blood samples were tested for suitable DNA yield and integrity and subjected to genome-wide DNAm profiling using the Illumina Methylation EPIC v1 microarray. GrimAge2 was created with surrogate DNAm biomarkers (including plasma protein adrenomedullin, CRP, PAI-1, GDF15, C-reactive protein, and HbA1c) and years of smoking packs.[27] PhenoAge was created with a host of 20,169 CpGs sites predicting levels of nine clinical biomarkers.[26] DunedinPACE was created based on 18 biomarkers and 46 CpG sites.[28] Training models used established algorithms to inform and determine each epigenetic clock or algorithm.[26-28] Higher values of PhenoAge and GrimAge2 indicated older biological age. Higher values of DunedinPACE indicated a faster pace of biological aging. Additional details on clock generation, quality control, assaying procedures, and training models are available at https://midus.colectica.org/.

Covariates. Several covariates were included in our analyses, given their known associations with epigenetic aging.[29,2] First age was coded in years since birth and was included to isolate epigenetic age acceleration. Gender was coded as 0 (*male*) or 1 (*female*). Education, coded as 0 (*high school or less*) or 1 (*some college or more*), was included as an indicator of socioeconomic position, given that an individuals' highest educational attainment is stable, predicts income and occupational prestige, and is more reliable than income as a measure of socioeconomic position among samples of midlife-older adults who may have retired. Race/ethnicity was self-reported by participants as White, Black and/or African American, Native American or Alaska Islander, Native Hawaiian or Pacific Islander, or Other. Due to small

sample sizes across most non-White groups, race/ethnicity in the present study was coded as 0 (*non-Hispanic White*) or 1 (*racialized as not White*). Smoking status was coded as 0 (*never smoked regularly*) or 1 (e*ver smoked regularly*). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Cohort was coded as 0 (*MIDUS 2 core sample*) or 1 (*MIDUS Refresher sample*).

Analytic Strategy

A description of all analytic variables was conducted by requesting means and standard deviations of all variables. As such, means for categorical variables represented the proportion of participants in the group coded 1. These descriptions are provided in Table 1 separately by samples that completed the general survey and 1) the Biomarker sub-project, 2) the NSDE sub-project, and 3) those that completed both sub-projects to compare samples of successively smaller size that nevertheless allow for a test of both key hypotheses.

To investigate the first hypothesis that people who perceived their neighborhoods as more cohesive would exhibit decelerated epigenetic age, a series of multiple linear regressions were conducted predicting each separate clock by perceived neighborhood cohesion, adjusting for age, gender, highest education attainment, race/ethnicity, smoking status, BMI, and cohort (MIDUS 2 or Refresher). Each set of regressions (one for each clock) was conducted for the participants who completed the general survey and 1) the biomarker sub-project, and 2) the subset of participants who also completed the NSDE sub-project to compare coefficients across successively smaller sample sizes.

Finally, a multilevel structural equation modeling (MSEM) framework was used to handle the hierarchically structured data from the daily diary design and permit a multivariate examination of the mediating effect of daily stress reactivity in the path between neighborhood

cohesion and epigenetic clocks across levels of analysis.[36-38] An important feature of the MSEM approach is that random effects from the within-person level (Level 1) can be modeled as both exogenous and endogenous variables at the between-person level (Level 2). That is, the latent random slopes (i.e., the departure of individual stress reactivity scores from the overall group mean of stress reactivity) can be specified to represent individual differences in the within-person associations, and these individual differences can be included as a mediator of the effect of cohesion on epigenetic aging. Daily measurement occasions are nested within people, resulting in two levels of analysis.

At the within-person level, daily stressor exposure$_{ij}$ was included as a predictor of daily levels of NA$_{ij}$ (where NA refers to negative affect). The subscript *ij* indicates that both stressor exposure and NA could vary across days (*j*), and individuals (*i*). Stress reactivity was modeled as the daily within-person association between stressor exposure and NA. Because stressor exposure was a dichotomous variable, stress reactivity was defined as the difference in NA on stressor days compared to non-stressor days. This daily within-person association between stressor exposure and NA (i.e., stress reactivity) was modeled as a random slope and permitted to vary across individuals.

At the between-person level, individual differences in *stress reactivity*$_i$ were modeled as latent slopes, indicating that they are estimated from the model and reflect the strength of daily stress reactivity for individual *i*. Individual differences in stress reactivity were included as a mediator (e.g., indirect effect) of the effect of perceived neighborhood cohesion in relation to epigenetic age. All effects were estimated simultaneously using the Bayes estimator in Mplus version 8.10,[39] which makes use of all available data. Each epigenetic clock was estimated in a separate model.

Results

Table 1 provides descriptive statistics for the primary study variables across samples defined as those who completed the general survey and 1) the Biomarker sub-project, 2) the NSDE sub-project, and 3) those that completed both sub-projects. Demographic characteristics of these three samples, despite differing size, were similar. For instance, participants across these three samples were, on average, in their early 50s and consisted of slightly more women than men. Roughly three-quarters of all three samples were college-educated, and one-quarter or less were racial/ethnic minorities. There was a smaller proportion of Refresher participants in the sample of participants in the survey + NSDE sub-project relative to those in the survey + Biomarker sub-project. In terms of behavioral covariates, about two-fifths of the participants in these three samples had smoked in their lives, and body mass index was about 28 across all three samples. Critically, perceived neighborhood cohesion was quite similar across the three samples. When comparing participants in the larger Biomarker sub-project to those in the smaller sample of participants with NSDE data as well, epigenetic age as assessed on DunedinPACE, GrimAge2, and PhenoAge were similar. Finally, when comparing participants in the larger NSDE sub-project to those with Biomarker sub-project data as well, values of daily negative affect (NA) and the proportions of days in which a stressor was reported were similar.

Table 2 reports results of multiple linear regressions testing our first hypothesis that people who perceived their neighborhoods as more cohesive would exhibit decelerated epigenetic aging. Among participants in the Biomarker sub-project (N = 1,185), perceiving greater neighborhood cohesion was significantly associated with a slower pace of aging on DunedinPACE (est. = -.009, p = .027) and decelerated epigenetic age on GrimAge2 (est. = -.441, p = .008), but was not significantly associated with PhenoAge. Similarly, among the smaller

subset of participants who participated in the NSDE sub-project as well (N = 645), perceiving greater neighborhood cohesion was significantly associated with a slower pace of aging on DunedinPACE (est. = -.015, p = .020) and decelerated epigenetic age on GrimAge2 (est. = -.708, p = .006), but was not significantly associated with PhenoAge.

Finally, Table 3 reports results of mediation models testing the second hypothesis that reduced daily stressor reactivity would partially mediate the link between perceptions of neighborhood cohesion and decelerated epigenetic age. At the within-person level and across all models, on days when individuals reported a stressor, they also reported significantly higher NA compared to non-stress days (est. = 0.137, pSD = 0.005, p < .001). At the between-person level, perceived neighborhood cohesion consistently predicted individual differences in stress reactivity, where those who reported greater cohesion were less reactive to daily stressors than individuals who reported lower cohesion (est. = -0.052, pSD = 0.007, ps < .001).

Significant direct effects of neighborhood cohesion on DunedinPACE and GrimAge2 remained but were attenuated when stress reactivity was included as a mediator. Stress reactivity predicted DunedinPACE and GrimAge2, such that individuals who were more reactive to daily stressors had accelerated epigenetic age compared to those who were less reactive. Importantly, there was a significant indirect effect from perceived neighborhood cohesion through stress reactivity to both DunedinPACE (see Figure 1A) and GrimAge2 (see Figure 1B), indicating that stress reactivity significantly mediated the association between perceived neighborhood cohesion and the respective epigenetic clocks.

The direct effect of neighborhood cohesion on PhenoAge remained non-significant after including the direct and indirect effects of stress reactivity. Similarly, stress reactivity was not significantly related to PhenoAge, nor was there evidence of an indirect effect of perceived

neighborhood cohesion predicting PhenoAge through stress reactivity.

Discussion

The current study examined whether one aspect of a neighborhood—perceived social cohesion—was associated with an indicator of biological aging. Results revealed that greater perceived neighborhood cohesion was associated with decelerated epigenetic age, as measured by the GrimAge2 clock and DunedinPACE algorithm. Importantly, these associations were significantly mediated by reduced reactivity to daily stressors. Findings extend previous research on the links between neighborhoods and health and speak to the importance of interventions that reduce affective responses to daily stressors and that foster neighborhood social cohesion.

Neighborhoods and Health

Neighborhoods have long been associated with several self-reported mental and physical health outcomes,[40] but only recently have they been linked to accelerated biological aging.[6] For example, in a study of 1,064 individuals aged 45-84 years, experiencing daily discrimination was associated with shortened telomere length, but only among those living in neighborhoods perceived as having low social cohesion.[41] To our knowledge, however, only two studies have examined the link between more subjective aspects of a neighborhood (i.e., social cohesion) and epigenetic aging. Martin and colleagues[30] examined this question in a relatively small sample of individuals living in Detroit, and Choi and Ailshire[31] analyzed data from individuals aged 56 and over from the Health and Retirement Survey. Both studies found that lower perceived neighborhood social cohesion was associated with accelerated epigenetic aging. The current study replicated these findings in a slightly larger sample with a broader age range (i.e., 35-86) and extended this work by showing that the link between neighborhood cohesion and epigenetic aging is partially mediated by lower affective reactivity to daily stressors. Thus, this study not

only provides further evidence of the importance of neighborhood social cohesion for decelerated epigenetic aging but also identifies one explanatory mechanism, that is an accessible intervention target, for this association.[11,32]

Direct and indirect effects of neighborhood social cohesion on epigenetic aging. Our findings revealing direct and indirect effects of neighborhood social cohesion on epigenetic aging are akin to the main and stress buffering models of social support.[42] This seminal model highlights two processes by which social support exerts effects on mental and physical health. The main effects model posits that social support directly contributes to an individual's health and well-being, regardless of stress level, by providing positive social interactions, a sense of belonging, and access to resources. Similar to this model, in neighborhoods where perceived social cohesion is high, residents feel connected and supported by others,[43] which is not only protective for mental and physical health,[44] but as the current study suggests, may be beneficial for epigenetic aging, as well.

In addition to finding a direct effect of neighborhood social cohesion on epigenetic aging, the current study also revealed that this association was partially mediated by how people react to the daily stressors in their lives. Specifically, higher levels of perceived neighborhood social cohesion were related to lower affective reactivity to daily stressors, which, in turn, was related to decelerated epigenetic aging. This finding is akin to the stress-buffering model of social support, which states that social support acts as a buffer to mitigate the effects of stress.[42] Similar to this model, in cohesive neighborhoods, an individual can draw upon their social capital to assist them during times of stress, which may reduce how they react to stressors. For example, the impact of a stressful day at work may be ameliorated after coming home and talking to a supportive neighbor. Similarly, problems in the house, such as a plumbing emergency, may be

less impactful if there are neighbors to call for assistance. Because heightened affective reactivity to daily stressors is related to worse mental and physical health outcomes,[45,22] factors that reduce this reactivity may also reduce the occurrence of adverse health outcomes. Existing studies indicate that higher perceived neighborhood cohesion is related to lower daily stressor reactivity;[21] however, this is the first study to demonstrate stressor reactivity as a mediating variable in the relationship between neighborhood cohesion and epigenetic aging. Based on these findings, it is possible that the trajectory of aging among residents of less socially cohesive neighborhoods could be set, in part, through daily stressor reactivity. Thus, interventions aimed at fostering social cohesion in neighborhoods could result in concomitant decreases in how a person reacts to stressors in their lives.

Is neighborhood social cohesion just social support? In the current study, neighborhood social cohesion refers to the extent to which an individual can trust and count on their neighbors in times of need. As such, one question that may arise is whether neighborhood social cohesion is a proxy for social support, particularly since both are associated with indices of mental and physical health. This hypothesis, however, was tested in a previous study indicating that neighborhood social cohesion predicted improved daily well-being even when adjusting for other types of social support.[21]

Epigenetic aging—Does the clock matter? Another question that may arise from our findings is why our hypotheses were supported when using GrimAge2 and DunedinPACE, but not PhenoAge. The answer to that question may lie in how these clocks are constructed. Although all three clocks use DNAm patterns to estimate biological age, they differ in how they are trained. GrimAge2 uses DNAm patterns linked to behavioral and biological processes (i.e., smoking history and plasma proteins,[27] and DunedinPACE is constructed using longitudinal

changes in biomarkers.[28] In contrast, PhenoAge is constructed using methylation sites associated with clinical biomarkers that reflect an individual's *current* physiological state.[26] Thus, whereas DunedinPACE and GrimAge2 are centered on rate of aging and life left to live, respectively, PhenoAge is centered on assessing health status and disease risk. These distinctions may be why perceived social cohesion was significantly associated with GrimAge2 and DunedinPACE but not PhenoAge, either directly or indirectly. More work, however, is needed to test this hypothesis.

Limitations. Findings of the current study must be placed within the context of its limitations. First, the analytic sample in the present analyses was small, given that only 1,310 participants had epigenetic clock data, and only 645 of those had daily diary. This limited the sample size used to test the hypothesis that daily stressor reactivity partially explains links between perceived neighborhood cohesion and epigenetic age. Relatedly, the MIDUS sample is primarily non-Hispanic White and well-educated, and these combined factors limit generalizability. Studies have shown that the effects of neighborhood social cohesion vary across race/ethnicity, something we were unable to examine due to the sample representing primarily non-Hispanic White participants. Second, the cohesion scale used in the current study was limited to two items that focused on trust and reciprocity. Although it has been validated using large samples and confirmatory factor analysis,[33] it is important to note that cohesion is a multi-faceted construct. As such, this work should be replicated using a more comprehensive assessment of perceived neighborhood social cohesion. Third, although all participants answered questions about neighborhood social cohesion before participating in either the NSDE or biomarker sub-projects from whence the mediator and outcome variables originated, respectively, some participants could have completed the biomarker sub-project prior to

completing the NSDE sub-project. Concerns about temporal ordering are somewhat small, however, given that epigenetic clock/algorithm change is not expected to be observed in intervals as short as days or weeks. Finally, our results are based on cross-sectional data. Although informative, longitudinal studies are warranted to examine the relationship between neighborhood cohesion and epigenetic aging over time. This may be particularly important for people who experience residential movements and/or significant social mobility. An additional benefit of the longitudinal design is to minimize concern having to do with potential reverse causation, or that accelerated epigenetic aging could influence stressor reactivity or perceptions of neighborhood cohesion.

Public policy implications. Accelerated epigenetic age predicts increased morbidity and mortality.[2] Its ability to detect risk for poor health at earlier ages stresses the importance of designing interventions before end-stage illness manifests. The current study thus underscores the importance of policy-level strategies that improve neighborhood social cohesion, particularly should future research confirm these associations longitudinally. This includes community investment in spaces that build social infrastructure and encourage residential interaction.[46] For example, the creation of third spaces, such as parks and recreation facilities, has been shown to increase neighborhood social cohesion.[47] In contrast, factors that impede social interaction, such as decreased walkability and heavy traffic, are related to decreased social cohesion.[48] In addition, communities should provide events and gatherings designed to foster interaction among residents. Not only could that increase neighborhood social cohesion, but it could also foster the exchange of important information.[49] Finally, implementing communication platforms that keep residents informed and involved in local governance can also strengthen participation and accountability, which can enhance social cohesion.[50]

Conclusions

Neighborhoods are vital to our health and well-being. The current study documented the unique contribution of daily stress reactivity in the link between perceived neighborhood cohesion and epigenetic aging. Findings suggest that fostering neighborhood cohesion, and implementing strategies to cope with daily stress, may slow the pace of aging inherent in disease risk.

Declarations

Ethics approval and consent to participate. This study was approved by the Institutional Review Board of the institution responsible for data collection, and all respondents consented to their participation.

Consent for publication. Not applicable

Availability of data and materials. The datasets analyzed during the current study are available in the MIDUS Colectica Portal, https://midus.colectica.org/Account/Login?returnUrl=%2F

Competing interests. The authors declare they have no competing interests.

Funding. Publicly available data from the MIDUS study was used for this research. 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), 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), 1UL1RR025011 (UW). This work was further supported by the National Institute on Minority Health and Health Disparities (U54 MD012388 to E.S.C.).

Authors' contributions. JWR, JR, ESC, RSS and JRP conceived the analysis plan. JR performed the analysis. JWR, JR, ESC, and JRP were responsible for the drafting of the manuscript. JWR, JR, ESC, RSS and JRP were responsible for critical revisions of paper. All authors read, reviewed, and approved the final manuscript.

Acknowledgements. Not applicable

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Table 1. *Description of study variables in the Biomarker, Daily Diary, and combined Biomarker and Diary Samples, Midlife in the United States Survey (MIDUS 2) and MIDUS Refresher*

	Biomarker Subproject (N = 1,185)			*Diary Subproject (N = 2,598)*			*Biomarker + Diary Sample (N = 645)*		
Variable	*M*	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range
Demographics									
Age, years	51.84	12.51	25–82	54.12	12.82	25–84	50.22	11.67	25–82
Gender	0.55	0.50	0–1	0.57	0.50	0–1	0.58	0.49	0–1
Education	0.78	0.41	0–1	0.72	0.45	0–1	0.78	0.41	0–1
Race/Ethnicity	0.24	0.43	0–1	0.15	0.36	0–1	0.25	0.43	0–1
Smoking status	0.42	0.49	0–1	0.44	0.50	0–1	0.39	0.49	0–1
BMI	28.63	6.48	16–66	28.43	6.40	14–93	28.46	6.47	17–66
Cohort	0.58	0.49	0–1	0.28	0.44	0–1	0.47	0.50	0–1
Neighborhood cohesion	3.19	0.79	1–4	3.27	0.72	1–4	3.20	0.77	1–4
Day-level variables									
Daily NA[a]	–	–	–	0.19	0.37	0–4	0.20	0.38	0–4
Daily Stressor[b]	–	–	–	0.40	0.49	0–1	0.43	0.49	0–1
Epigenetic Clocks									
DunedinPACE	0.99	0.14	0.53–1.45	–	–	–	0.98	0.14	0.53-1.45
GrimAge2	62.68	10.74	33.01–94.14	–	–	–	61.64	10.35	34.60-94.14
PhenoAge	43.64	12.99	10.27–85.00	–	–	–	42.70	12.26	11.69-85.00

Note. Gender (0=male; 1=female). Education (high school or less = 0; some college or more = 1). Race/Ethnicity (non-Hispanic White = 0; not white = 1). Smoking status (never smoked regularly = 0; ever smoked regularly = 1). Cohort (MIDUS 2 core sample = 0; MIDUS Refresher sample = 1). BMI = Body Mass Index. NA = negative affect.
[a] Aggregated across daily assessments. [b] Proportion of stress days.

Table 2. *Regression models of neighborhood cohesion predicting epigenetic age clocks, MIDUS 2 and MIDUS Refresher cohorts*

Biomarker Sub-project

	DunedinPACE		GrimAge2		PhenoAge	
Variable	Estimate (*SE*)	*p*-value	Estimate (*SE*)	*p*-value	Estimate (*SE*)	*p*-value
Neighborhood cohesion	−0.009 (.004)	.027	−0.441 (.166)	.008	−0.251 (.226)	.268
Age	0.002 (.000)	<.001	0.729 (.010)	<.001	0.913 (.014)	<.001
Gender	−0.017 (.006)	.008	−1.552 (.252)	<.001	−0.419 (.344)	.223
Education	−0.034 (.008)	<.001	−2.036 (.318)	<.001	−0.010 (.434)	.982
Race/Ethnicity	0.067 (.008)	<.001	1.756 (.305)	<.001	0.113 (.417)	.787
Smoking status	0.071 (.007)	<.001	4.498 (.259)	<.001	1.690 (.354)	<.001
BMI	0.006 (.000)	<.001	0.093 (.018)	<.001	0.121 (.025)	<.001
Cohort	−0.021 (.007)	.002	−0.155 (.260)	.550	0.462 (.355)	.194

Daily Diary + Biomarker Sub-projects

	DunedinPACE		GrimAge2		PhenoAge	
Variable	Estimate (*SE*)	*p*-value	Estimate (*SE*)	*p*-value	Estimate (*SE*)	*p*-value
Neighborhood cohesion	−0.015 (.007)	.020	−0.708 (.220)	.006	−0.191 (.292)	.534
Age	0.003 (.000)	<.001	0.742 (.015)	<.001	0.917 (.020)	<.001
Gender	0.001 (.010)	.460	−0.883 (.351)	.014	0.318 (.466)	.494
Education	−0.011 (.012)	.190	−1.281 (.457)	<.001	1.013 (.608)	.074
Race/Ethnicity	0.065 (.012)	<.001	1.420 (.468)	.006	−0.696 (.622)	.240
Smoking status	0.071 (.010)	<.001	4.215 (.397)	<.001	1.279 (.527)	.006
BMI	0.006 (.001)	<.001	0.103 (.025)	<.001	0.163 (.033)	<.001
Cohort	−0.024 (.010)	<.001	−1.675 (.351)	<.001	−1.417 (.467)	<.001

Note. Gender (0=male; 1=female). Education (high school or less = 0; some college or more = 1). Race/Ethnicity (non-Hispanic White = 0; not white = 1). Smoking status (never smoked regularly = 0; ever smoked regularly = 1). Cohort (MIDUS 2 core sample = 0; MIDUS Refresher sample = 1). BMI = Body Mass Index. Estimates are reported as unstandardized regression coefficients.

Table 3. *MSEM mediation model of neighborhood cohesion predicting epigenetic age clocks through daily stress reactivity, MIDUS 2 and MIDUS Refresher cohorts*

Variable	DunedinPACE		GrimAge2		PhenoAge	
	Estimate (*pSD*)	*p*-value	Estimate (*pSD*)	*p*-value	Estimate (*pSD*)	*p*-value
Fixed effects						
Within-person variables (Level 1)						
NA intercept	0.138 (.005)	<.001	0.138 (.005)	<.001	0.138 (.006)	<.001
Daily stress reactivity intercept	0.137 (.005)	<.001	0.137 (.005)	<.001	0.137 (.005)	<.001
Between-person variables (Level 2)						
Neighborhood cohesion → Stress reactivity	−0.052 (.007)	<.001	−0.052 (.007)	<.001	−0.053 (.006)	<.001
Neighborhood cohesion	−0.013 (.006)	.026	−0.619 (.218)	<.001	−0.166 (.309)	.560
Stress reactivity	0.071 (.035)	<.001	2.512 (1.304)	.020	1.709 (1.751)	.350
Age	0.003 (.000)	<.001	0.745 (.015)	<.001	0.917 (.022)	<.001
Gender	0.001 (.008)	.443	−0.919 (.317)	.006	0.316 (.434)	.450
Education	−0.004 (.013)	.403	−1.199 (.453)	<.001	0.916 (.654)	.140
Race/Ethnicity	0.065 (.012)	<.001	1.359 (.438)	<.001	−0.713 (.563)	.250
Smoking status	0.070 (.010)	<.001	4.168 (.353)	<.001	1.214 (.440)	<.001
BMI	0.006 (.001)	<.001	0.101 (.026)	<.001	0.169 (.032)	<.001
Cohort	−0.022 (.009)	.018	−1.639 (.447)	<.001	−1.334 (.494)	.010
Random effects						
Within-person residual	0.056 (.001)		0.056 (.001)		0.056 (.001)	
Between-person						
NA	0.056 (.002)		0.056 (.002)		0.056 (.002)	
Daily stress reactivity	0.032 (.002)		0.032 (.002)		0.033 (.002)	
Age clock	0.013 (.001)		17.607 (1.082)		31.801 (1.879)	
Indirect effect	−0.004 (.002)	<.001	−0.132 (.038)	.020	−0.082 (.092)	.350

Note. Gender (0=male; 1=female). Education (high school or less = 0; some college or more = 1). Race/Ethnicity (non-Hispanic White = 0; not white = 1). Smoking status (never smoked regularly = 0; ever smoked regularly = 1). Cohort (MIDUS 2 core sample = 0; MIDUS Refresher sample = 1). *pSD* = posterior standard deviation. BMI = Body Mass Index. NA = negative affect. Estimates of fixed effects are reported as unstandardized regression coefficients. Estimates of random effects are reported as variances.

Figure 1. Indirect path from perceived neighborhood cohesion to epigenetic age via daily stressor reactivity, Midlife in the United States (MIDUS 2) and MIDUS Refresher

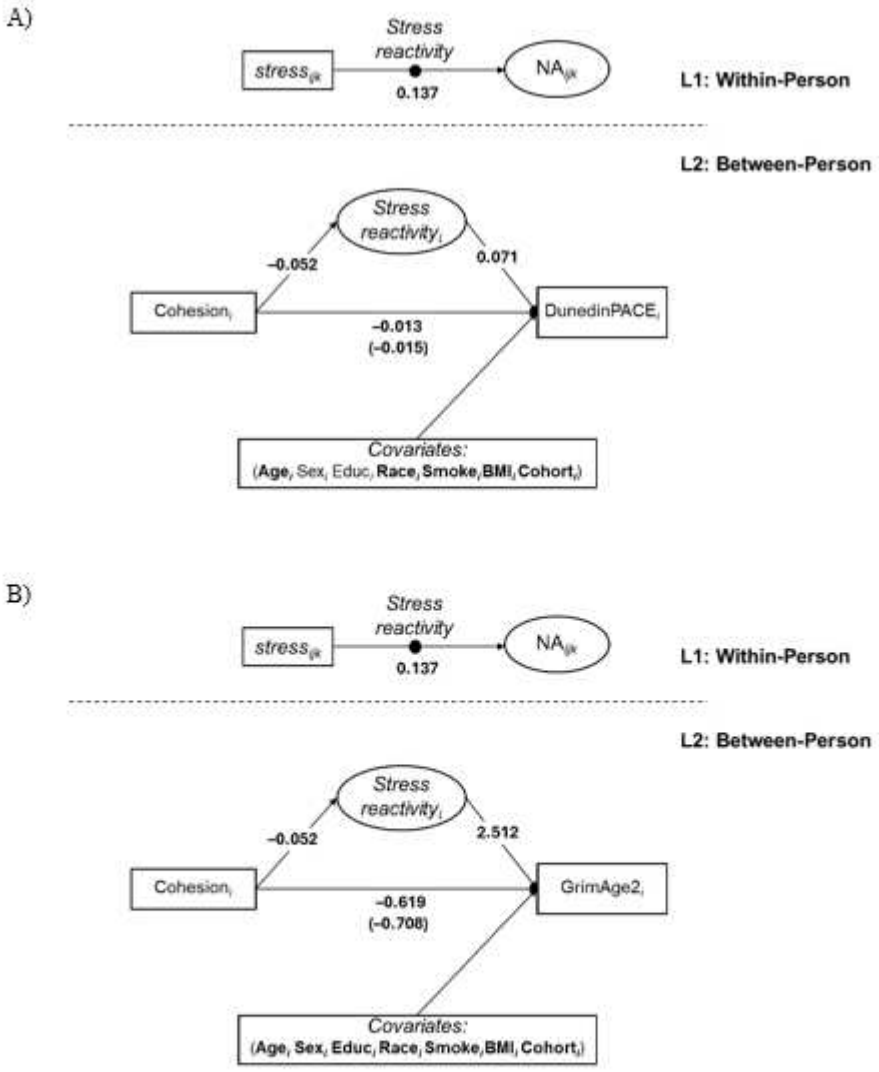


Figure 1. Multilevel mediation model of neighborhood cohesion predicting A) DunedinPACE and B) GrimAge2 epigenetic age clocks through daily stress reactivity. *Note*. Ovals indicate variables that were estimated within the model. Black dots indicate that pathway was modeled as a random slope. Bold values are statistically significant, *ps* < .05. Values in parenthesis are from initial models that only examined the direct effect of neighborhood cohesion on epigenetic age clocks. NA = negative affect. stress = stress exposure day. Educ = education.