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The Pace of Biological Aging Partially Explains the Relationship Between Socioeconomic Status and Chronic Low Back Pain Outcomes

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Introduction: Having a lower socioeconomic status (SES) is a predictor of age-related chronic conditions, including chronic low back pain (cLBP). We aimed to examine whether the pace of biological aging mediates the relationship between SES and cLBP outcomes – pain intensity, pain interference, and physical performance.

Methods: We used the Dunedin Pace of Aging Calculated from the Epigenome (DunedinPACE) software to determine the pace of biological aging in adults ages 18 to 85 years with no cLBP (n = 74), low-impact pain (n = 56), and high-impact pain (n = 77).

Results: The mean chronological age of the participants was 40.9 years (SD= 15.1); 107 (51.7%) were female, and 108 (52.2%) were Black. On average, the pace of biological aging was 5% faster [DunedinPACE = 1.05 (SD = 0.14)] in the sample (DunedinPACE value of 1 = normal pace of aging). Individuals with higher levels of education had a significantly slower pace of biological aging than those with lower education levels (F = 5.546, p = 0.001). After adjusting for sex and race, household income level significantly correlated with the pace of biological aging (r = −0.17, p = 0.02), pain intensity (r = −0.21, p = 0.003), pain interference (r = −0.21, p = 0.003), and physical performance (r = 0.20, p = 0.005). In mediation analyses adjusting for sex, race, and body mass index (BMI), the pace of biological aging mediates the relationship between household income (but not education) level and cLBP intensity, interference, as well as physical performance.

Discussion: Results indicate that lower SES contributes to faster biological aging, possibly contributing to greater pain intensity and interference, as well as lower physical performance. Future interventions slowing the pace of biological aging may improve cLBP outcomes.

Pain language summary: Individuals of lower socioeconomic status (SES) experience worse outcomes from age-related chronic conditions, including chronic low back pain (cLBP). This work examines the relationship between SES, pace of biological aging, and cLBP intensity, interference with daily activities, and physical function. Lower SES correlates with a faster pace of biological aging, as well as cLBP pain intensity, pain interference, and physical performance. The pace of biological aging helps explain the relationship between household income and cLBP intensity, interference, as well as physical performance. Interventions targeting SES disparities may slow biological aging and improve cLBP outcomes.

Keywords: socioeconomic status, health disparities, DunedinPACE, pace of biological aging, chronic low back pain, epigenetic clock

Introduction

Socioeconomic status (SES) disparities in healthcare have been well documented for decades and have severe implications.[1] Individuals classified as having a lower SES have a shorter life expectancy and are at increased risk for

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age-related chronic conditions such as chronic pain.[2–4] Among individuals with chronic low back pain (cLBP), those with a lower SES have greater pain intensity and pain-related disability.[4,5] This is relevant because low back pain is a leading cause of years lived with disability. It is estimated that over 840 million people worldwide will have low back pain by 2050.[6] Emerging evidence has linked worse pain outcomes to epigenetically induced alterations in pathways involved in neuroinflammation, hormonal dysregulation, impaired immune function, allostatic loads, and poor metabolic control.[7–9] Interestingly, these major biological pathways overlap with processes that control aging.[10–12] As such, there is growing interest in understanding how socially disadvantaged conditions accelerate the aging process and lead to age-related chronic diseases such as chronic pain.[13,14]

Conceptually, biological aging refers to the progressive cellular and molecular deterioration that occurs with advancing chronological age and exposure to psychosocial, physical, and environmental stressors.[15] Investigators have recently used epigenetic changes as markers of biological aging to test potential underlying mechanisms of health disparities directly.[14,16,17] For instance, DNA methylation (DNAm) is an epigenetic modification that regulates gene expression and changes in DNAm levels at specific Cytosine-phospho-Guanine (CpG) dinucleotide sites across the genome to measure the pace of biological aging, also called epigenetic clocks. Several epigenetic clocks have been developed to predict chronological age,[18,19] morbidity and mortality,[20,21] and the pace of biological aging.[22] Of these clocks, the Pace of Aging Calculated from the Epigenome (DunedinPACE) is the most contemporary epigenetic clock. It estimates the pace of biological aging by measuring DNAm patterns in 173 CpG sites that capture people's rate of physiologic decline over time due to age-related diseases, social determinants of health, and lack of geroprotective interventions.[12,22]

Emerging evidence suggest that accelerated biological aging may be associated with worse pain, reduced physical activity, and cognitive decline.[23,24] A DunedinPACE score of one reflects normal aging, and scores > 1 reflect accelerated aging, such that a score of 1.05 represents a 5% faster pace of biological aging. We and others demonstrated differences in the pace of biological/epigenetic aging among individuals with various chronic pain conditions.[25–29] Individuals with cLBP had a faster pace of biological aging than pain-free controls (PFCs), and the DunedinPACE epigenetic clock was a stronger predictor of cLBP severity than chronological age.[25] After controlling for confounding variables, the odds of having cLBP were 14.9 points higher than PFC for every 0.1 unit increase in DunedinPACE scores. Also, the pace of biological aging positively correlated with both pain intensity and pain interference with daily activities. Furthermore, the pace of biological aging partially mediates the relationship between sleep disorders and pain-related disability.[26] Other investigators have reported that individuals living with sickle cell disease (commonly associated with chronic pain) have faster biological aging.[27] To our knowledge, very limited studies have examined the relationship between biological aging and pain disparities in the context of non-specific cLBP.

The role of the pace of biological aging in the link between SES and cLBP remains to be clearly understood. This knowledge gap is concerning because SES (education, income, wealth, and neighborhood deprivation) impacts one's opportunities, experiences, and health, contributing to health disparities.[30] Lower SES has been associated with epigenetically induced increased systemic inflammation and other markers of allostatic load,[31] and epigenetic aging.[32,33] Living below the poverty level has been associated with accelerated epigenetic aging.[34] Using the Health and Retirement Study (HRS) and Multi-Ethnic Study of Atherosclerosis (MESA) data, Schmitz et al found a strong association between SES and epigenetic aging (GrimAge and DunedinPoAm) clocks.[32] In a large multi-national dataset, Fiorito et al also reported a relationship between lower SES and accelerated intrinsic epigenetic aging.[13] Also, several studies have linked accelerated epigenetic aging from first and second-generation epigenetic clocks with lower SES in adults with chronic knee pain.[28,29] Specifically, accelerated GrimAge mediates the relationship between individual level[28] and neighborhood SES[29] and knee pain, leading to the question of whether biological aging affects the relationship between SES and cLBP outcomes.

This study fills these gaps by comprehensively investigating the relationships between SES, the pace of biological aging, and non-specific cLBP symptoms: pain intensity, pain interference, and physical performance. Specifically, the aims of the current study were to establish 1) whether SES correlates with the pace of biological aging and 2) whether the pace of biological aging mediates the relationship between SES and cLBP symptoms. Based on data from studies of individuals with knee pain, we hypothesized that lower SES is associated with a faster pace of biological aging and worse

pain outcomes. Also, we hypothesize that the faster pace of biological aging mediates the relationship between SES and pain outcome.

Methods

Study Population

A convenient sample of community-dwelling adults with and without non-specific cLBP was recruited as part of a cross-sectional studies sponsored by the National Institutes of Health (NIH grant# R01AR079178 & R01MD010441) examining epigenomic changes, racial and SES disparities in nonspecific cLBP. Details of the study protocol have previously been described.[4,35] Briefly, participants included 116 adults with cLBP and 91 pain-free controls (PFCs) who self-identified as non-Hispanic Black (NHB, n = 108) or non-Hispanic White (NHW, n = 99). Recruitment was done primarily with flyers posted at pain clinics and the surrounding community in Birmingham, Alabama, USA. The study staff screened potential participants to determine eligibility based on the following: 1) ages 18 to 85 years, 2) self-identified racial category was NHB or NHW, 3) speak and write English, and 4) non-specific cLBP as the primary pain that has lasted for at least six (6) consecutive months. The diagnosis of non-specific cLBP was confirmed with medical records and guidelines from the American Colleges of Physicians and the American Pain Society.[36] Exclusion criteria included 1) cLBP related to ankylosing spondylitis, infection, malignancy, compression fracture, or other trauma, 2) systematic rheumatic diseases, 3) uncontrolled hypertension, 4) neurological diseases, 5) serious psychiatric disorder requiring hospitalization in the past 12 months and 6) pregnancy. The same eligibility criteria were applied to PFCs, except for the diagnosis of non-specific cLBP or any chronic pain condition.

This study followed the Research Task Force of the NIH Pain Consortium's cLBP research standards.[37] All participants provided written informed consent, and Ethical approval was obtained from the Institutional Review Board (IRB) at the University of Alabama at Birmingham. This study complies with the Declaration of Helsinki.

Measures

During their initial laboratory visit, participants completed all self-report measures described below via a research electronic data capture (REDCap) system.

Sociodemographic Characteristics

Baseline sociodemographic data included age, sex, race/ethnicity, body weight, and height. Per the National Institutes of Health guidelines, participants self-identified their race/ethnicity. Participants self-reported their sex as male, female, transgender (male to female), or transgender (female to male). Height and weight measurements were used to calculate the body mass index (BMI).

Socioeconomic Status (SES)

Participants self-reported their SES using questionnaires about their education, household income level after taxes, and highest degree earned. Education was classified into eight categories: 1) Not applicable or unknown, 2) Less than 7th grade, 3) Junior high, including 9th grade, 4) Partial high school (10th or 11th grade), 5) High school graduate, 6) Partial college, at least one year of college, 7) Standard college or University graduate, and 8) Graduate or professional training.

Household income level after taxes was collected based on the following categories: $0–$9999; $10,000–$14,999; $15,000–$19,999; $20,000–$24,999; $25,000–$29,999; $30,000–$34,999; $35,000–$39,999; $40,000–$44,999; $45,000–$49,999; $50,000 - $74,999; $75,000 - $99,000 and $100,000 or higher. Because of small cell counts, household income was re-coded as follows for data analysis: 1 = 0–24,999; 2 = 25k - 49,999; 3 = 50k - 74,999; 4 = 75k - 99,999 and 5 = > 100k.

Participants also reported their highest degree earned from the following categories: less than high school; high school diploma or Graduate Educational Development (GED); some college; Associate degree, Bachelor degree; Graduate or Professional training. The highest degree attained was re-coded as follows for analysis: 1 = high school/GED or less; 2 = Associate or Bachelor degree; 3 = graduate or professional training. SES variables were dummy coded numerically for analyses: education 1–8, household income 1–5, and highest degree 1–3.

Pain Intensity and Pain Interference

Pain intensity and pain-related disability were assessed through the graded chronic pain scale (GCPS).[38] For pain intensity, participants rated the current, worst, and average pain over the past 6-month period on an 11-point Likert scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). Pain intensity scores (0 to 100) were calculated as the mean of these three items, multiplied by 100. For pain disability, participants rated how pain interfered with their performance of daily, social, work, and family activities from 0 (do not interfere) to 10 (completely interfere). Pain disability scores (0–100) were calculated from the mean of the seven (7) items multiplied by 100. Higher scores indicate greater pain intensity and pain-related disability. In addition, participants responded to the following open-ended question: "How many days in the last six (6) months have you been kept from your usual activities because of pain" (ie, disability days)? To operationalize the impact of cLBP, we employed the GCPS pain grades categories as previously reported:[38] Grade 0 = PFCs; Grades 1–2 = low impact pain; and Grades ≥ 3 = high impact pain. In our sample, GCPS has an excellent internal consistency reliability Cronbach's alpha r = 0.97.

Physical Performance

Physical performance was assessed using the short physical performance battery (SPPB), a valid measure of lower extremity mobility that is predictive of adult mortality.[39] Participants performed three tests consisting of (1) three standing-balance trials, (2) five continuous chair stands, and (3) a 4-meter walk test. The performance time of each participant on the task was graded on a scale of 0 to 4 and summed. Total SPPB scores range from 0 (worst) to 12 (best function), with higher scores indicating better lower body function. In our sample, SPPB had an excellent internal consistency reliability Cronbach's alpha r= 0.92.

Pace of Biological Aging and Epigenetic Aging

Details of genomic DNA extraction and sequencing have previously been reported.[40] Briefly, blood-based genomic DNA was extracted using the *Gentra Puregene* DNA Purification Protocol (Qiagen, Valencia, CA, USA) and sent to the University of Minnesota Genomic Center for sequencing. DNAm data was generated twice using the Illumina Infinium v1 and v2 human MethylationEPIC BeadChip arrays (Illumina, Inc). Five samples were randomly selected and run in duplicate for quality control. For each CpG site, the methylation level was analyzed as the beta values, based on published algorithms. Then, we selected the beta values associated with CpG sites required for each epigenetic clock based on published algorithm. Selected beta values were input into the online DNA Methylation Age Calculator developed by the Horvath laboratory,[41] which calculated various epigenetic ages, including the Horvath age,[18] Hannum age,[19] and PhenoAge.[21] Finally, DunedinPACE scores were calculated from the beta values using R-software as described by Belsky et al.[22] The pace of biological aging, and epigenetic aging calculations included participants' chronological ages at the time of the blood collection.

Data Analyses

Following data cleaning and checking for missingness, all statistical analysis was performed using SPSS v29.0 (IBM Corp, Armonk, NY). Only samples with all variables of interest were included in the analyses. Descriptive statistics were used to summarize sociodemographic data, and the Chi-square test was used to determine pain group differences between categorical variables. Analysis of variance (ANOVA) was used to test pain group differences between continuous variables. Post-hoc analyses were done using Bonferroni correction. Next, a partial correlation matrix between study variables was constructed using Pearson's correlation, controlling for the effects of sex, race, and sample batch (potentially caused by reagents, microarray chips, and other equipment). Then, mediation analysis was conducted using Hayes' model 4 of the SPSS PROCESS macro bootstrapping method.[42] In the mediation analyses, the outcome variables were pain intensity and physical performance, the predictor was SES (income and education levels), and the mediator was the pace of biological aging derived from DunedinPACE. The covariates were sex, race, and BMI. The bootstrap samples were set to 5000. p-values < 0.05 and 95% confidence interval (CI) for the effect did not include zero were considered statistically significant.

Results

Participant Characteristics

Of the 213 individuals who participated in the study, 207 had a complete set of pain, sociodemographic, and DNAm age data. Overall, the average chronological age of the participants was 40.99 (SD = 15.09) years. Most participants self-identified as NHB (n = 108, 52.2%) and female (n=107, 51.7%). Participants' household income levels ranged from less than $24,000 to over $100,000 per year, with the majority making less than $50,000 (51.7%).

Of the 207 participants in the final study sample, 74 (35.7%) were PFCs, 56 (27.1%) had low-impact pain, and 77 (37.2%) had high-impact pain. Table 1 summarizes the differences between the pain group categories in sociodemographic and study variables. There were no significant differences in sex (p = 0.51), household income level (p = 0.085), and level of education (0.123). There was a significant difference in race distribution across the pain groups, with more NHBs in the high-impact pain category and more NHWs in the no-pain category (p = 0.003). On average, participants with high-impact pain were older than those with low-impact pain and no pain. Group differences in chronological age, PhenoAge, and pace of biological aging derived from DunedinPACE were statistically significant (p < 0.001). There were no significant group differences in Horvath and Hannum epigenetic Ages. As expected, individuals with high-impact pain reported greater pain intensity and pain interference compared to low-impact pain and no-pain groups (p<0.001).

Table 1 Characteristics of Study Participants and Measures

	No Chronic (n = 74)	Low Impact (n = 56)	High Impact (n = 77)	p-value
Race, N (%)				0.003 [a,b]
Black	27 (36.5)	34 (60.7)	47 (61)	
White	47 (63.5)	22 (39.3)	30 (39)	
Sex, N (%)				0.51
Male	36 (48.7)	30 (53.6)	34 (44.2)	
Female	38 (51.3)	26 (46.4)	43 (55.8)	
Income, N (%)				
0–24,999	16 (27.2)	14 (23.7)	29 (49.1)	0.085
25k - 49,999	19 (39.6)	16 (33.3)	13 (27.1)	
50k - 74,999	12 (33.3)	7 (19.4)	17 (47.2)	
75k - 99,999	5 (26.3)	5 (26.3)	9 (47.4)	
> 100k	17 (45.9)	13 (35.1)	7 (18.9)	
Education, N (%)				0.123
High school or less	13 (30.9)	8 (19.1)	21 (50)	
Partial college or at least one year of college	27 (38.0)	16 (22.5)	28 (39.4)	
Standard college or university	12 (30.8)	17 (43.6)	10 (25.6)	
Graduate/professional training	22 (40)	15 (27.3)	18 (32.7)	
Age, mean (SD)	35.7 (14.8)	42.4 (13.8)	45.1 (15.0)	< 0.001 [a,b]
Horvath Age, mean (SD)	40.8 (17.2)	45.5 (15.5)	46.7 (15.4)	0.066
Hannum Age, mean (SD)	32.1 (22.09)	35.2 (21.2)	36.8 (21.6)	0.412
PhenoAge, mean (SD)	32.8 (13.2)	40.6 (13.3)	43.1 (14.4)	< 0.001 [a,b]
DunedinPACE, mean (SD)	1.0 (0.1)	1.1 (0.2)	1.1 (0.1)	< 0.001 [a,b]
BMI, mean (SD)	29.0 (13.4)	30.8 (6.6)	32.6 (7.8)	0.097
GCPS Intensity, mean (SD)	0	39.2 (20.9)	70.6 (15.4)	< 0.001 [b]
GCPS Interference, mean (SD)	0	19.3 (18.6)	63 (22.3)	< 0.001 [b]
SPPB, mean (SD)	11.1 (1.1)	10.1 (1.6)	8.9 (1.8)	< 0.001 [a,b,c]

Notes: [&]denotes chi-square for categorical variable and F-statistic for continuous. In pairwise comparison [a]denotes significant difference between no pain and low-impact pain groups; [b]denotes significant difference no pain and high-impact pain group, and [c]denotes significant differences between low-impact and high-impact pain groups.

Abbreviations: SD, standard deviation; GCPS, Graded Chronic Pain Scale; BMI, body mass index; SPPB, short physical performance battery; DunedinPACE, Dunedin Pace of Aging Calculated from Epigenome.

Socioeconomic Status, DunedinPACE, and Pain

Table 2 contains a partial correlation matrix for associations between sociodemographic variables, epigenetic ages, and various measures of pain. When examining income level, significant associations were found with the pace of biological aging derived from DunedinPACE (r = −0.173, p =0.016), pain intensity (r = −0.210, p = 0.003), pain interference (−0.208, p = 0.004), and SPPB (r = 0.203, p = 0.005). DunidinPACE scores were significantly associated with chronological age (r = 0.340, p < 0.001), HorvathAge (r = 0.292, p < 0.001), HannumAge (r = 0.250, p < 0.001), PhenoAge (r = 0.435, p < 0.001), pain intensity (0.326, p < 0.001), pain interference (r = 0.342, p < 0.001), SPPB (r= −0.313, p < 0.001), and pain impact (r = 0.247, p = 0.001).

Regarding the level of education, an ANOVA revealed a significant difference in the pace of biological aging between various levels of education (F = 5.55, df = 3, p = 0.001). A pairwise comparison of education level revealed that those with no more than high school education had a significantly faster pace of aging than those with standard college or university (mean diff. = 0.11, p = 0.001) or partial college/at least one-year college (mean diff = 0.08, p = 0.017). However, there was no statistically significant difference between those with graduate or professional education and standard college or university (mean diff = 0.06, p = 0.129), partial college/ at least one-year college (mean diff = 0.03, p = 1.00), as well as high school or less (mean diff = −0.05, p = 0.419). There was no significant difference in pain intensity, physical performance, and impact between various levels of education (p > 0.05). Figure 1 depicts the relationship between DunedinPACE-derived pace of biological aging and various measures of SES.

Mediation Analysis of Socioeconomic Status, DunedinPACE, and Pain Intensity

In the mediation model adjusting for the impact of BMI, race, and sex, household income level significantly negatively affected the DunedinPACE-derived pace of biological aging (β = −0.014; 95% CI [−0.027 to −0.002]). The pace of biological aging also significantly positively affected pain intensity (β = 71.89; 95% CI [37.17 to 106.63]). The direct effect of income level on pain intensity adjusting for pace of biological aging was negatively significant (β = -3.733; 95% CI [−6.748 to −0.719]). The indirect effect of household income on pain intensity through DunedinPACE was significant (β = -1.021; 95% boots CI [−2.097 to −0.071]), and the total effect of income level on pain intensity was negatively significant (β = -4.754; 95% CI [−7.849 to −1.659]), indicating partial mediation. Non-standardized estimates of the coefficients of the associated variables are shown in Figure 2.

Table 2 Partial Correlation of Sociodemographic and Study Variables, Adjusting for Batch, Sex, and Race

		1	2	3	4	5	6	7	8	9	10	11	12
1	Age	1.000											
2	Horvath Age	0.882**	1.000										
3	Hannum Age	0.705**	0.897**	1.000									
4	PhenoAge	0.883**	0.792**	0.569**	1.000								
5	DunedinPACE	0.334**	0.322**	0.318**	0.429**	1.000							
6	BMI	0.053	0.049	0.064	0.028	0.119	1.000						
7	Pain Intensity	0.223**	0.099	0.043	0.277**	0.322**	0.082	1.000					
8	Pain Interference	0.241**	0.150*	0.117	0.286**	0.343**	0.100	0.887**	1.000				
9	SPPB	−0.290**	−0.166*	−0.080	−0.286**	−0.315**	−0.117	−0.569**	−0.552**	1.000			
10	Income	0.111	0.093	0.049	0.102	−0.174*	−0.057	−0.227**	−0.237**	0.205**	1.000		
11	Education	0.157*	0.075	0.025	0.091	−0.088	0.070	−0.175*	−0.169*	0.103	0.362**	1.000	
12	Pain Impact	0.169*	0.030	−0.026	0.245**	0.237**	0.101	0.895**	0.824**	−0.497**	−0.133	−0.131	1.000

Notes: **Correlation is significant at 0.01 level; *Correlation is significant at 0.05 level; Pain intensity and pain interference scores were obtained from the Graded Chronic Pain Scale.

Abbreviations: SPPB, short physical performance battery; DunedinPACE, Dunedin Pace of Aging Calculated from the Epigenome.

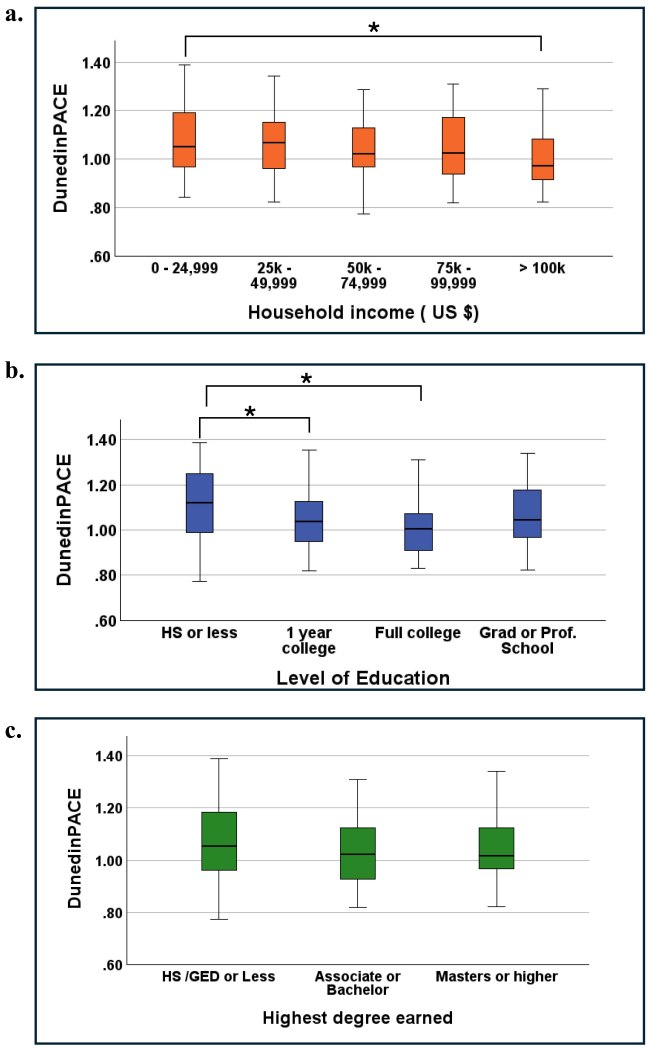

Figure 1 Comparative analysis of the differences in the pace of biological aging according to DunedinPACE as a function of (**a**) household income after taxes, (**b**) level of education, and (**c**) highest degree earned in adults with no, low-impact, and high-impact chronic pain. The boxplot represents median values, the first and third quartiles, and ranges.

Note: *p < 0.05.

Abbreviations: HS, high school; GED, general educational diploma; Grad, graduate school; and Prof, post-baccalaureate professional training.

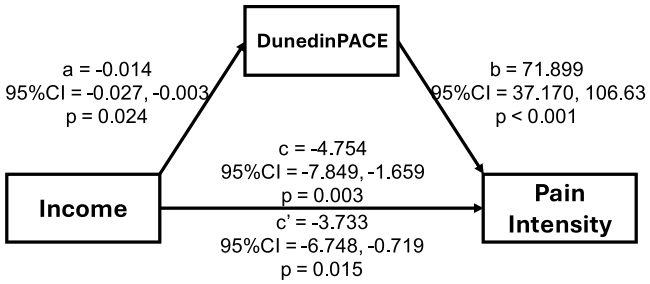

Figure 2 Mediating effect of the pace of biological aging (mediator) on the relationship between income (predictor)and pain intensity (outcome). a = effect of income on pace of biological aging; b = effect of pace of biological aging on pain intensity; c = total effect of income on pain intensity; c′ = direct effect of income on pain intensity, controlling for mediator and covariates (sex, race, and BMI). Bootstrap Indirect effect of income on pain intensity through the pace of biological aging: β = −1.021(0.524), 95% Boot CI = −2.097 to −0.071.

However, the indirect effects of education on pain intensity through DunedinPACE-derived pace of biological aging was not statistically significant (β = -1.069; 95% boots CI [−2.549 to 0.203]). The total effect of education level on pain intensity was negatively significant (β = -4.927; 95% CI [−9.094 to −0.759]). Figure 3 depicts non-standardized estimates of the coefficients of the model.

Mediation Analysis of Socioeconomic Status, DunedinPACE, and Pain Interference

In the third mediation model, we included SES (income level and level of education) as predictors, DunedinPACE as mediator, pain interference as outcome, and BMI, race, and sex as covariates. Household income level significantly negatively affected the DunedinPACE-derived pace of biological aging (β = −0.014; 95% CI [−0.027 to −0.002]). The pace of biological aging also significantly positively affected pain interference (β = 73.858; 95% CI [40.366 to 107.35]). The direct effect of income level on pain intensity adjusting for pace of biological aging (β = -3.820; 95% CI [−6.727 to −0.913]), and the indirect effect of household income on pain interference through the pace of biological aging (β = -1.049; 95% boots CI [−2.113 to −0.113]) were significant, indicating partial mediation. The total effect of income level on pain interference was negatively significant (β = -4.869; 95% CI [−7.870 to −1.867]). Non-standardized estimates of the coefficients of the associated variables are shown in Figure 4.

Furthermore, the indirect effects of education on pain interference through DunedinPACE-derived pace of biological aging was not statistically significant (β = -1.085; 95% boots CI [−2.586 to 0.247]. The total effect of education level on pain intensity was negatively significant (β = -4.724; 95% CI [−8.741 to −0.707]). Figure 5 depicts non-standardized estimates of the coefficients of the model.

Mediation Analysis of Socioeconomic Status, DunedinPACE, and Physical Performance

In this model, we controlled for BMI, race, and sex. Household income level significantly negatively affected DunedinPACE's pace of biological aging (β = -0.014; 95% CI [−0.026 to −0.001]). Income-adjusted DunedinPACE-derived pace of biological aging also significantly negatively affects SPPB (β = -3.754; 95% CI [−5.563 to −1.945]). The

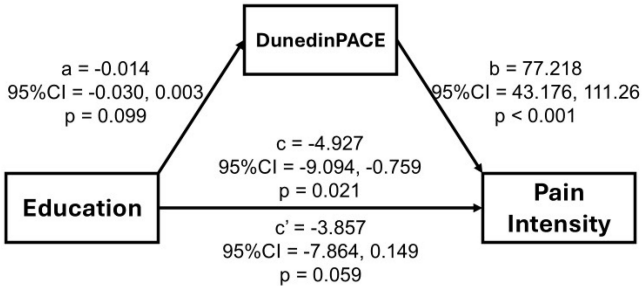

Figure 3 Mediating effect of the pace of biological aging (mediator) on the relationship between education level (predictor) and pain intensity (outcome). a = effect of education level on the pace of biological aging; b = effect of pace of biological aging on pain intensity; c = total effect of education level on pain intensity; c′ = direct effect of education level on pain intensity, controlling for mediator and covariates (sex, race, and BMI). Bootstrap Indirect effect of education level on pain intensity through the pace of biological aging: β = −1.069(0.705), 95% Boot CI = −2.549 to 0.203.

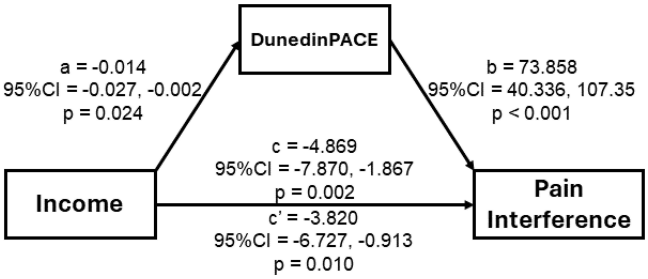

Figure 4 Mediating effect of the pace of biological aging (mediator) on the relationship between income (predictor)and pain interference (outcome). a = effect of income on pace of biological aging; b = effect of pace of biological aging on pain interference; c = total effect of income on pain interference; c′ = direct effect of income on pain interference, controlling for mediator and covariates (sex, race, and BMI). Bootstrap Indirect effect of income on pain interference through the pace of biological aging: β = −1.049(0.513), 95% Boot CI = −2.113 to −0.113.

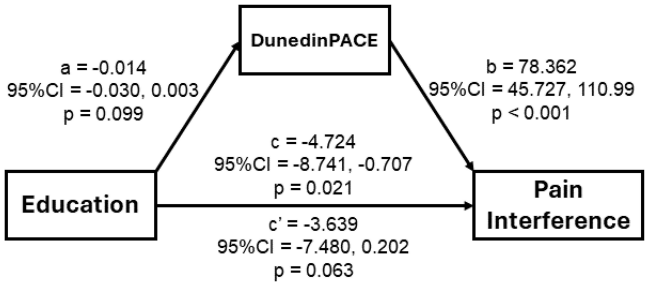

Figure 5 Mediating effect of the pace of biological aging (mediator) on the relationship between education level (predictor) and pain interference (outcome). a = effect of education level on the pace of biological aging; b = effect of pace of biological aging on pain interference; c = total effect of education level on pain interference; c′ = direct effect of education level on pain interference, controlling for mediator and covariates (sex, race, and BMI). Bootstrap Indirect effect of education level on pain interference through the pace of biological aging: β = −1.085(0.703), 95% Boot CI = −2.568 to 0.247.

direct effect of income level on SPPB (β = 0.166; 95% CI [0.009 to 0.323]), and the indirect impact of income level on SPPB via DunedinPACE (β = 0.051; 95% boots CI [0.003 to 0.101]) were statistically significant, indicating a partial mediation. The total effect of income level on SPPB was positively significant (β = 0.217; 95% CI [0.056 to 0.379]). Figure 6 depicts the non-standardized estimates of the coefficients of the associated variables.

Similarly, the indirect effects of education on physical performance through DunedinPACE-derived pace of biological aging was not statistically significant (β = 0.061; 95% boots CI [−0.011 to 0.142]). Also, the direct effect of education level on physical performance with DunedinPACE was not significant (β = 0.145; 95% CI [−0.067 to 0.357]). The total effect of education level on physical performance was positively significant (β = 0.206; 95% CI [−0.016 to 0.429]). Figure 7 depicts non-standardized estimates of the coefficients of the model.

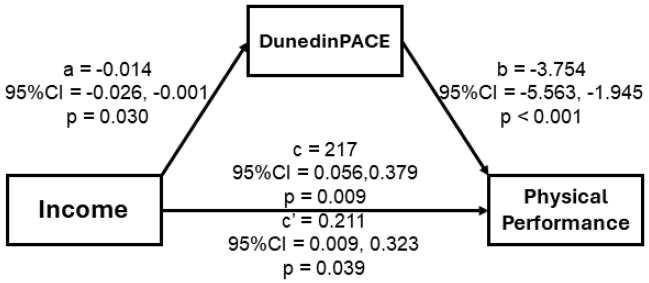

Figure 6 Mediating effect of the pace of biological aging (mediator) on the relationship between income (predictor) and physical performance (outcome). a = effect of income on the pace of biological aging; b = effect of pace of biological aging on physical performance; c = total effect of income on physical performance; c′ = direct effect of income on physical performance, controlling for mediator and covariates (sex, race, and BMI). Bootstrap Indirect effect of income on physical performance through the pace of biological aging: β = 0.051(0.025), 95% Boot CI = 0.003 to 0.101.

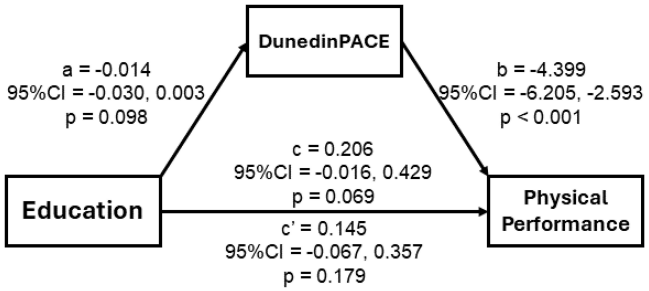

Figure 7 Mediating effect of the pace of biological aging (mediator) on the relationship between income (predictor) and physical performance (outcome). a = effect of education level on the pace of biological aging; b = effect of pace of biological aging on physical performance; c = total effect of education level on physical performance; c′ = direct effect of education level on physical performance, controlling for mediator and covariates (sex, race, and BMI). Bootstrap Indirect effect of education level on physical performance through the pace of biological aging: β = 0.061(0.038), 95% Boot CI = −0.011 to 0.142.

Discussion

Despite consistent evidence showing that SES is strongly related to chronic pain intensity and related disabilities,[2,43] the potential mechanisms through which social status gets "under the skin" remain relatively unknown. To our knowledge, this is the first study to formally examine the complex interplay between SES disparities, the pace of biological aging, pain intensity, pain interference, and physical performance in adults with non-specific cLBP. Results indicate that lower SES, is associated with a faster pace of biological aging, as measured by the DunedinPACE, as compared with those of higher SES. Moreover, the pace of biological aging mediated a portion of the total effect of household income level on cLBP outcomes (pain intensity, pain interference, and physical performance).

This study builds on a growing body of past research examining the association between SES and chronic pain, and epigenetic aging.[5,28,29,43] Our findings are consistent with prior studies that suggest second generation (GrimAge) are more consistently associated chronic pain, potentially because the GrimAge was trained to predict morbidity and mortality and more consistently associated with age-related chronic condition.[28,29,] Among patients with knee osteoarthritis, Strath et al reported that accelerated epigenetic aging (measured with GrimAge) partially mediated the relationship between SES and the impact of knee pain.[28] Using the same data, Jackson et al found that accelerated epigenetic aging partially explained the effect of neighborhood deprivation on knee pain intensity.[29] Other investigators have reported that lower SES is associated with accelerated decline in age-related functional and phenotypic processes.[44] Our findings build in this body of work and report that higher income level correlate with a slower pace of biological (from a third generation clock), which in turn predicted lower cLBP severity and interference with daily activity. It is possible that income-related disparities in pain intensity may partly be attributable to differences in the rate of biological aging among individuals with cLBP. While these findings do not establish causality, they underscore the importance of considering biological aging processes when examining socioeconomic determinants of pain outcomes.

Our findings suggest that epigenetic effects of lower SES and biological aging influence functional performance. We found that the pace of biological aging mediates the relationship between SES (income) and physical performance in individuals with cLBP. Several studies have reported that individuals with lower SES exhibit lower cognitive and physical performance and accelerated epigenetic aging.[44,45] Other investigators have reported that exercise-induced epigenetic modifications can reduce inflammation and the pace of biological aging.[46–49] However, individuals of lower SES are less likely to engage in exercise and physical activity, perhaps because of limited access to facilities or an impaired neighborhood-built environment.[50–52] Also, SES may shape one's health by influencing access to resources for healthy living.[30] Thus, the limited access to health-promoting resources, lack of exercise, and a faster pace of aging in those with lower SES may predispose them to loss of muscle strength and mass, unsteady gait, and decreased physical functioning,[53] with resultant worse pain outcomes.

In our study there was no significant relationship between SES and first (Horvath[18] and Hannum[19]) and second (PhenoAge[21]) clocks. This may be a function of the ways in which different epigenetic clocks were developed. Horvath[18] and Hannum[19] clocks are trained to predicts chronological age, while PhenoAge was trained to predict mortality risk based primarily on immune function and tissue markers. These biomarker may not be sensitive to the impact of SES and cLBP outcomes, compared to biomarkers used to train DunedinPACE (rate of change in markers associated with aging).[22] Consistent with our prior findings, DunedinPACE is a more sensitive indicator of cLBP outcomes.[25] Similarly, in mediation analyses, educational level was not a significant predictor of the pace of biological aging (mediator) and cLBP outcomes. This may be the result of the fact that households income and wealth may be stronger predictors of access to health promoting amenities such as healthy neighborhood compared to educational level. Differences in individual epigenetic clocks and measures of SES underscore the need for comprehensive studies, like this one, clarifying what epigenetic clocks and SES measures are most responsive and predictive to pain outcomes.

These findings should be interpreted in the context of the study's strengths and limitations. The study's strengths include high-quality pain phenotyping using a well-established pain measure (GCPS) and functional performance assessments (SPPB). Furthermore, we used a third-generation epigenetic clock (DunedinPACE) that is a more precise measure of the pace of biological aging than the first and second-generation clocks.[22] However, our study has some limitations as well. First, the findings cannot be generalized to all adults, as our sample included only NHB and NHW

Americans. Future studies should aim to include individuals from more diverse racial and ethnic groups. Second, the cross-sectional design limits temporal understanding of the nature of the relationship between variables. However, mediation analysis provides a robust statistical approach to maximize power for generating hypotheses and exploring associations that can be investigated using a longitudinal design to establish causality.[42,54] Finally, other unmeasured confounding or mediating factors may affect the associations between SES and chronic pain outcomes, including medication use, access to care, and provider bias. Thus, our findings should be replicated and validated in additional, more diverse populations to address these concerns.

Conclusion

Lower SES has previously been linked with poor health outcomes, including worse cLBP, and elucidating potential mechanisms would reduce health disparities. The findings from this study provide important information regarding the potential role of accelerated biological aging in pain that could form the basis of interventions to promote equity in pain outcomes. As studies of biological aging, social determinants of health, and pain disparities are in their infancy, further studies are needed to advance our understanding of the biological mechanisms behind worse pain outcomes for individuals of lower SES and to directly test whether interventions to slow biological aging can improve pain outcomes and other age-related chronic conditions.

Author Contributions

Edwin N Aroke and Burel R Goodin share Senior Authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no competing interests.

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