Journals of Gerontology: Medical Sciences, 2024, **79**(2), 1–8
https://doi.org/10.1093/gerona/glad118
Advance access publication 5 June 2023
Research Article

Association of Neighborhood Deprivation and Depressive Symptoms With Epigenetic Age Acceleration: Evidence From the Canadian Longitudinal Study on Aging

Divya Joshi, PhD,[1,2] Frank J. van Lenthe, PhD,[3,4] Martijn Huisman, PhD,[5] Erik R. Sund, PhD,[6,7] Steinar Krokstad, PhD,[6,8] Mauricio Avendano, PhD,[9] and Parminder Raina, PhD[1,2,*]

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada.
[2]McMaster Institute for Research on Aging, McMaster University, Hamilton, Ontario, Canada.
[3]Department of Public Health, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands.
[4]Faculty of Geosciences, Utrecht University, Utrecht, The Netherlands.
[5]Department of Epidemiology and Data Science and the Amsterdam Public Health Research Institute, Amsterdam University Medical Centers, Amsterdam, The Netherlands.
[6]HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Levanger, Norway.
[7]Faculty of Nursing and Health Sciences, Nord University, Levanger, Norway.
[8]Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway.
[9]Center for Primary Care and Public Health (Unisanté), Department of Epidemiology and Health Systems, University of Lausanne, Lausanne, Switzerland.

*Address correspondence to: Parminder Raina, PhD, Department of Health Research Methods, Evidence, and Impact, McMaster University, 309A McMaster Innovation Park (MIP), 1280 Main St. W., Hamilton, ON L8S 4K1, Canada. E-mail: praina@mcmaster.ca

Decision Editor: Jay Magaziner, PhD, MSHyg

Abstract

Background: Neighborhood deprivation and depression have been linked to epigenetic age acceleration. The next-generation epigenetic clocks including the DNA methylation (DNAm) GrimAge, and PhenoAge have incorporated clinical biomarkers of physiological dysregulation by selecting cytosine–phosphate–guanine sites that are associated with risk factors for disease, and have shown improved accuracy in predicting morbidity and time-to-mortality compared to the first-generation clocks. The aim of this study is to examine the association between neighborhood deprivation and DNAm GrimAge and PhenoAge acceleration in adults, and assess interaction with depressive symptoms.

Methods: The Canadian Longitudinal Study on Aging recruited 51 338 participants aged 45–85 years across provinces in Canada. This cross-sectional analysis is based on a subsample of 1 445 participants at baseline (2011–2015) for whom epigenetic data were available. Epigenetic age acceleration (years) was assessed using the DNAm GrimAge and PhenoAge, and measured as residuals from regression of the biological age on chronological age.

Results: A greater neighborhood material and/or social deprivation compared to lower deprivation ($b = 0.66$; 95% confidence interval [CI] = 0.21, 1.12) and depressive symptoms scores ($b = 0.07$; 95% CI = 0.01, 0.13) were associated with higher DNAm GrimAge acceleration. The regression estimates for these associations were higher but not statistically significant when epigenetic age acceleration was estimated using DNAm PhenoAge. There was no evidence of a statistical interaction between neighborhood deprivation and depressive symptoms.

Conclusions: Depressive symptoms and neighborhood deprivation are independently associated with premature biological aging. Policies that improve neighborhood environments and address depression in older age may contribute to healthy aging among older adults living in predominantly urban areas.

Keywords: CLSA, GrimAge, Neighborhood social deprivation, Neighborhood material deprivation, PhenoAge

The world is currently experiencing 2 unprecedented demographic transitions—rapid aging of the population and urbanization (1). The proportion of the population aged 65 years and older is expected to increase by 16% between 2020 and 2050, and during this time, the proportion of the population living in urban areas is also expected to increase to two thirds of the world's entire population (2). In parallel, there has also been an increased interest in understanding how late-life depression among older adults relates to both urbanization and aging. The hypothesis that the urban environment influences mental health dates back to Faris and Dunham, who proposed the role of "place" as a risk factor for mental health (3). Since then, several empirical studies have examined how urban environments influence depressive symptoms

Received: September 12 2022; Editorial Decision Date: April 16 2023.
© The Author(s) 2023. Published by Oxford University Press on behalf of The Gerontological Society of America. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

Downloaded from https://academic.oup.com/biomedgerontology/article/79/2/glad118/7190263 by Erasmus University Rotterdam user on 07 February 2024

(4–7). Neighborhood characteristics, too, have been linked to the mental health of older adults (8,9). A large and growing body of literature suggests that people living in deprived urban neighborhood with physical, social, and socioeconomic conditions experience more anxiety and depression (5,10,11), and a faster decline in mental health (12). There is also evidence that living in a socially deprived neighborhood is associated with poor mental health, whereas higher neighborhood social cohesion is associated with an improvement in mental health over time (11,12). Further, there is evidence of an interaction between neighborhood deprivation and depression on the risk of cardiovascular disease and multimorbidity (13,14). Based on these findings, we hypothesize that all other factors being equal, neighborhood deprivation may amplify the impact of depressive symptoms on epigenetic age acceleration, for example, because it reinforces the impact of social norms, stress, or other factors associated with age acceleration.

A separate body of research has also reported associations between neighborhood deprivation and markers of biological aging, such as higher allostatic load and shorter telomere length (15,16). These biological markers, too, have been linked to depression in older age. Individuals with major depressive disorder are more likely to show advanced biological aging as assessed using brain imaging and telomere length (17,18). Recently, urban environments and psychopathology have both been linked to epigenetic processes such as DNA modification through methylation (19,20). DNA methylation (DNAm)-based estimators, commonly referred to as "epigenetic clocks," assess DNAm at predetermined cytosine–phosphate–guanine (CpG) sites to estimate biological aging at the cellular level (21,22). An accelerated epigenetic clock, where the epigenetic age is higher than the chronological age, has been associated with age-related declines in health, including faster rates of cognitive decline and higher mortality risk (23,24).

The aim of this study is to examine how epigenetic age acceleration assessed using the DNAm GrimAge and DNAm PhenoAge relate to both neighborhood deprivation and depressive symptoms, and to assess interactions between these 2 factors between middle-aged and older adults residing in predominantly urban areas in Canada. We hypothesize that both neighborhood deprivation and depressive symptoms are independently associated with epigenetic age acceleration. In addition, we expect a significant interaction so that people with more depressive symptoms experience greater epigenetic age acceleration as a result of living in deprived neighborhoods. Our study addresses a gap in understanding how neighborhood deprivation and depressive symptoms influence epigenetic age acceleration. In addition, most studies have used the first-generation epigenetic clocks such as the original Horvath DNAm and Hannum clocks to estimate the epigenetic age. More recently, second-generation epigenetic clocks such as the DNAm GrimAge and DNAm PhenoAge incorporated clinical biomarkers of physiological dysregulation by selecting CpGs associated with risk factors for disease (25,26). This offers an advantage as depression is associated with changes in inflammatory, metabolic, and endocrine biomarkers.

Methodology

Study Design and Population

The complete study design and methodology for the Canadian Longitudinal Study on Aging (CLSA) have been described in detail previously (27). Briefly, the CLSA is a 20-year population-based, longitudinal cohort study involving a stratified random sample of 51 338 community-living individuals aged 45–85 years at the time of recruitment in 2011–2015. Of these 51 338 participants, 30 097 participants (Comprehensive cohort) were recruited from a 25–50 km area from 1 of 11 data collection sites located across provinces in Canada. The majority of the participants were from urban population centers and a small proportion were from small urban areas with rural populations and medium-sized urban areas. These participants provided data through in-home interviews, physical assessments, and biological samples at data collection sites. Data on epigenetic age measures were obtained from blood samples collected from a random subsample of 1 479 participants who were included in the analysis. Overall, there were no substantial differences in the baseline sociodemographic and health characteristics of participants included in the epigenetic analysis and those not included in the analysis (Supplementary Table 1).

The Canadian Urban Environmental Health Research Consortium (CANUE) is an initiative created to collect and develop standard measures for environmental exposure data and link them to health databases in Canada. For each participant, the environmental data on measures including neighborhood social and material deprivation, air quality, noise and air pollution, weather and climate, built environment, and green spaces were created by CANUE and linked to the CLSA individual participant data using the participant's 6-digit postal code and interview date. For this study, the 2011 environmental exposure data on neighborhood-level material and social deprivation indices available from the CANUE were used. This study was approved by the Hamilton Integrated Research Ethics Board (ethics approval number 09-213 and 10-423). Written consent was obtained from all participants prior to data collection.

Study Measures

DNA methylation age

Genome-wide DNAm in peripheral blood mononuclear cells (PBMCs) was profiled using the Illumina Infinium Methylation EPIC BeadChip microarrays (Illumina, San Diego, CA). The EPIC array quantitatively measures DNAm at 862 927 CpG sites and 2 932 CHH sites across the genome. To obtain the DNAm data, the genomic DNA from the frozen PBMC samples was extracted using QIAsymphony DSP DNA Kits (Qiagen, Hilden, Germany). Bisulfite conversion was performed using the EZ DNA Methylation kit (Zymo, Irvine, CA). For quality control purposes, the raw array data were preprocessed using the GenomeStudio software (Illumina), which transformed the raw methylation values into beta values that range from 0 to 1 and indicate the proportion of methylation at each CpG site. During a quality check of the preprocessed methylation data (RStudio v3.6.3), we identified and excluded 4 samples that had bisulfite-conversion scores of less than 85%. The bisulfite-conversion scores were computed by the bscon function in the wateRmelon package v1.28.0 in R. Further, inconsistently performing nonspecific problems were also excluded. The *wateRmelon* and *lumi* (v23.6.0) packages in R identified 29 additional outlier samples, which were also excluded from further processing procedures. Thus, epigenetic data were available for 1 445

Downloaded from https://academic.oup.com/biomedgerontology/article/79/2/glad118/7190263 by Erasmus University Rotterdam user on 07 February 2024

participants. Complete details about procedures used to generate and process raw data are described in the CLSA Data Support Document (28).

Derivation of Biological Age Estimates From Epigenetic Clocks

Epigenetic aging measures were calculated from the DNAm beta values using the new Horvath online DNA Methylation Age calculator software (https://dnamage.genetics.ucla.edu/home). Epigenetic clocks were derived using weight and beta values that were normalized using the Noob normalization approach (29). The DNAm GrimAge is constructed as a composite of 12 DNAm-based biomarkers and smoking pack years, and estimates mortality risk in unit of years (26). The DNAm PhenoAge was based on a phenotypic age score developed from chronological age and 9 clinically relevant blood biomarkers (25). The unit for DNAm PhenoAge is biological years. The DNAm PhenoAge was trained to predict all-cause mortality and the DNAm GrimAge was trained to predict time-to-death. For both clocks, the residuals from regression of the biological age on chronological age are considered as "age-adjusted" and were used to measure epigenetic age acceleration.

Depressive Symptoms

The 10-item Center for Epidemiologic Studies Short—Depression Scale (CES-D10) was used to assess depressive symptoms in the past 7 days (30). The CES-D10 includes items on depressed affect, positive affect, and somatic symptoms. Each item is scored on an ordinal scale from 0 (never or rarely, <1 day) to 3 (all of the time, 5–7 days a week). After reverse coding the positive affect items, scores can range from 0 to 30, with higher scores indicating higher depressive symptoms. The CES-D10 has good reliability and validity, with an internal consistency of 0.86, test–retest reliability of 0.85, and convergent and divergent validity of 0.91 and 0.89, respectively, in the adult population (31,32).

Neighborhood Deprivation

Material and social deprivation refers to characteristics of individuals in the neighborhood, and the indices were based on socioeconomic factors that were known to be associated with health. The deprivation indices are based on the dissemination areas, which are the smallest geographical units for which Canadian census data are disseminated. These indices were developed by CANUE and were constructed from 5 socioeconomic factors taken from the 2011 Statistics Canada's census program (33,34). These indices measure deprivation among Canadians and assess inequalities in accessing material and social resources in the communities (33,34). Material deprivation was assessed based on the proportion of individuals without a high school diploma, the employment-to-population ratio, and the average personal income of individuals. Material deprivation is an indicator of people's inability to access or afford goods and conveniences that are part of modern life, such as proper housing, nutritious meals, high-speed internet, a car, or a neighborhood with recreational facilities. It reflects economic hardships and is an indicator of the consequences associated with low educational achievement, job insecurity, unemployment, and lack of sufficient income (33). Social deprivation reflects the presence of weak social networks in the family and the community. This index is an indication of the proportion of people who live alone, are separated, divorced or widowed, or are a lone parent (33). Data on the socioeconomic indicators are obtained for people aged 15 years and older, and except for the proportion of people who are single-parent families, have been adjusted for the age and sex distribution of the Canadian population. Data on material and social deprivation were available as quintiles with the highest quintile representing the most deprivation. When cross-tabulated, the material and social components of neighborhood deprivation will result in 25 different deprivation groups. A combined deprivation index from the quintiles was created to overcome the limitation of having a smaller number of participants in these groups. Participants in the upper 2 quintiles for material and/or social deprivation were considered as being high "materially and/or socially deprived" (35).

Covariates

The analysis was adjusted for individual-level covariates including sex (male or female), income (less than $20 000, $20 000–<$50 000, $50 000–<$100 000, $100 000–<$150 000, and $150 000 or more, treated as a continuous variable), number of people currently living in the household not including the participant, number of poor health behaviors, and number of chronic health conditions. Smoking intensity was assessed by calculating total pack years (number of cigarettes smoked per day divided by 20 cigarettes per pack, and multiplied by the number of years smoked), and dichotomized as "never or less than 20 pack years" or "20 or more pack years." The Physical Activity Scale for the Elderly (PASE) was used to assess the physical activity levels (36). Participants meeting the World Health Organization's age-specific cutoff of at least 75 minutes of vigorous intensity or at least 150 minutes of moderate intensity of physical activity per week were considered as "adequate," otherwise "inadequate" (37). Nutritional risk was assessed using the validated "Seniors in the Community: Risk Evaluation for Eating and Nutrition (SCREEN-II)" tool, and scores were dichotomized as "high risk" (total score <32) or "not at-risk" (total score ≥32) (38). Alcohol consumption was grouped as "did not drink alcohol in the past 12 months" or "occasional and regular drinker." The number of poor health behaviors tend to co-occur and therefore were summed to create a score ranging between 0 and 4. Participants were presented with a list of chronic conditions including musculoskeletal problems, respiratory diseases, cardiovascular disease, endocrine disorders, neurological diseases, gastrointestinal disorders, genitourinary problems, ophthalmologic disorders, kidney disease, back problems, and cancer, and asked to report only those chronic conditions diagnosed by a health professional that are expected to last or have already lasted at least 6 months. The number of conditions endorsed by each participant was summed for inclusion in the analysis. In the analysis, number of poor health behaviors and chronic conditions were modeled as continuous variables to improve statistical power. These covariates were identified a priori and were included in the analysis as they are known to be associated with depressive symptoms, neighborhood deprivation, and epigenetic age.

Statistical Analysis

All analyses were adjusted for the sampling design. Descriptive analysis was performed using the inflation weights, and regression analysis was performed using the analytical weights provided by the CLSA to ensure that the results are generalizable to the target population. A multilevel regression model was tested to examine the effect of neighborhood-level material and/or social deprivation after adjusting for individual-level

Downloaded from https://academic.oup.com/biomedgerontology/article/79/2/glad118/7190263 by Erasmus University Rotterdam user on 07 February 2024

socioeconomic factors. The results produced an intraclass correlation coefficient of less than 2% indicating lack of presence of multilevel effect by neighborhood deprivation (39). Therefore, multivariable linear regression models were used to examine the association of neighborhood material deprivation and/or social deprivation and depressive symptoms with each epigenetic age acceleration measure after adjusting for the above-mentioned covariates. Total household income, number of poor health behaviors, and number of chronic conditions were included in the analysis as potential confounders of the associations between neighborhood deprivation and depressive symptoms and epigenetic age acceleration measures (Supplementary Figure 1). A 2-way interaction between neighborhood deprivation and depressive symptoms was tested to assess if the association between neighborhood deprivation and epigenetic age acceleration differed by depressive symptoms. We reported unstandardized coefficients with 95% confidence intervals (95% CIs). Data management and analyses were performed on SAS version 9.4 software (SAS Institute, Cary, NC). Post-hoc power calculation was performed using GPower statistical program version 3.1.9.7. A multivariable linear regression model for an effect size (Cohen's f2) of 0.008, sample size of 1 315, type 1 error rate of 5%, 1 tested predictor, and 7 total number of predictors resulted in a power of 89%.

Results

The descriptive characteristics of participants in the study sample are shown in Table 1. The mean chronological age of participants was 59.7 years (standard error [*SE*] = 0.3 years, range 45–85 years), 49.7% were males, and 92.6% were of European ethnic background. At the individual level, 78.8% of participants had attained a post-secondary or higher education and 40.9% had a total annual household income of CAD$100 000 or higher. The average depressive symptom score was 5.5 (*SE* = 0.2) and 59.1% resided in neighborhoods that were materially and/or socially deprived. The average DNAm GrimAge (mean = 56.3, *SE* = 0.3 years) was closer to the chronological age and much higher than the epigenetic age estimated using the DNAm PhenoAge estimator (mean = 42.8, *SE* = 0.3 years). The correlations of each epigenetic clock with chronological age are presented in Figure 1. Both epigenetic clocks were significantly positively correlated with chronological age, with strong correlations observed for DNAm GrimAge (r = 0.90) and DNAm PhenoAge (r = 0.82).

Results from models examining the association of depressive symptoms and material and/or social deprivation with epigenetic age acceleration measures are reported in Table 2. On average, higher depressive symptoms score showed a positive association with epigenetic age acceleration estimated by DNAm GrimAge after adjusting for covariates (b = 0.07; 95%

Table 1. Descriptive Characteristics at Baseline for Participants in the Canadian Longitudinal Study on Aging (n = 1 479)

	n	Mean or Frequency	*SE* or Percentage*
Chronological age, mean (*SE*)	1 479	59.73	(0.32)
Male sex, *n* (%)	1 479	732	(49.68)
European ethnic background, *n* (%)	1 476	1 371	(92.64)
Post-secondary education or higher, *n* (%)	1 479	1 107	(78.81)
Annual household income, *n* (%)			
<$20 000	1 400	94	(5.75)
≥$20 000-<$50 000	1 400	364	(20.08)
≥$50 000–<$100 000	1 400	458	(33.28)
≥$100 000–<$150 000	1 400	248	(20.20)
≥$150 000	1 400	236	(20.69)
Depressive symptoms, mean (*SE*)	1 474	5.47	(0.16)
Neighborhood material and/or social deprivation, *n* (%)†	1 427	857	(59.10)
DNAm GrimAge, mean (*SE*)	1 445	56.32	(0.29)
DNAm PhenoAge, mean (SE)	1 445	42.81	(0.34)
Total number of poor health behaviors, mean (*SE*)	1 479	1.69	(0.03)
Smoking, *n* (%)	1 474	305	(18.93)
Inadequate physical activity, *n* (%)	1 403	988	(64.94)
Nutritional risk, *n* (%)	1 362	213	(14.52)
Alcohol consumption, *n* (%)	1 442	1059	(74.88)
Number of people living in the same household, mean (*SE*)	1 479	1.48	(0.04)
Chronic conditions			
Number of chronic conditions, mean (*SE*)	1 479	2.33	(0.07)
None, *n* (%)	1 479	244	(21.86)
One, *n* (%)	1 479	303	(23.20)
Two, *n* (%)	1 479	265	(18.30)
Three or more, *n* (%)	1 479	667	(36.65)

Notes: CLSA = Canadian Longitudinal Study on Aging; DNAm = DNA methylation; *SE* = standard error.
*Estimates are weighted by the inflation weights provided by the CLSA.
†With the exception of neighborhood material and/or social deprivation, all variables were assessed at the individual level.

Downloaded from https://academic.oup.com/biomedgerontology/article/79/2/glad118/7190263 by Erasmus University Rotterdam user on 07 February 2024

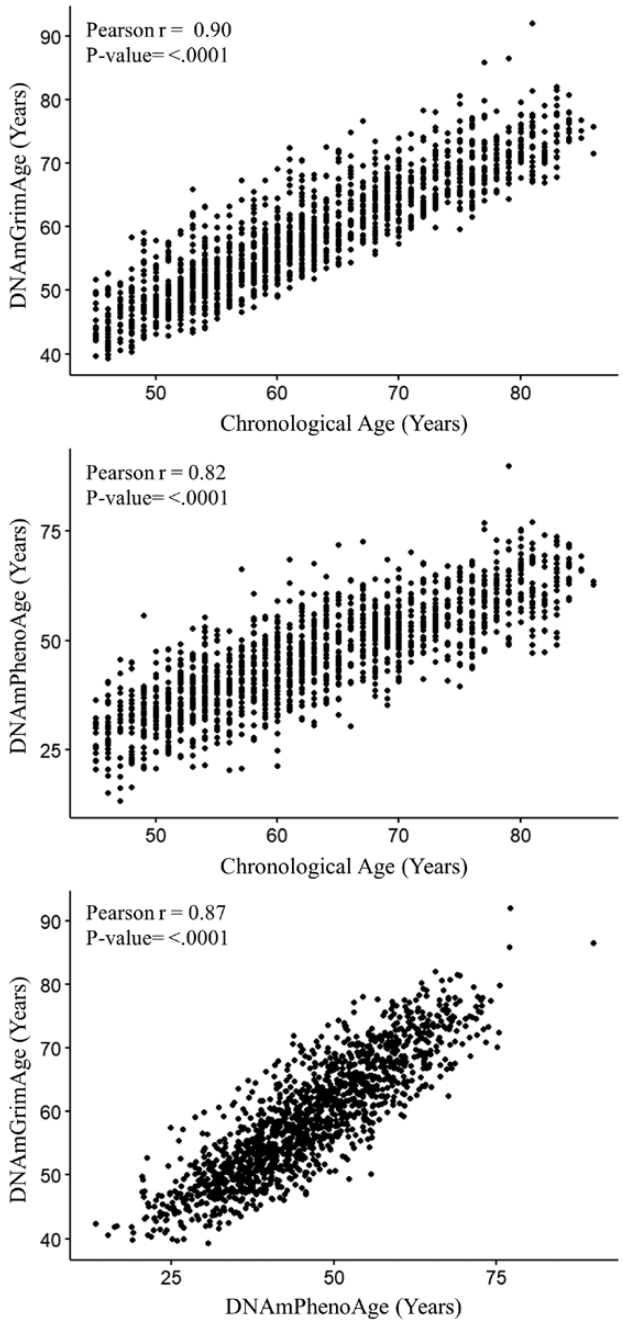

Figure 1. Scatterplot between chronological age and epigenetic age measures.

CI = 0.01, 0.13). Greater neighborhood material and/or social deprivation compared to lower neighborhood deprivation were associated with higher DNAm GrimAge acceleration (b = 0.66; 95% CI = 0.21, 1.12). The associations between depressive symptoms, neighborhood material and/or social deprivation, and epigenetic age acceleration estimated using DNAm PhenoAge were positive, but not statistically significant.

Engaging in greater number of poor health behaviors including smoking, inadequate physical activity, poor nutrition, and alcohol consumption was positively associated with DNAm GrimAge acceleration only. Each additional poor health behavior was associated with a 1-year higher epigenetic age acceleration (b = 1.06; 95% CI = .77, 1.34). Compared to females, males had higher epigenetic age acceleration, and having a greater number of chronic conditions was positively associated with higher epigenetic age acceleration using both DNAm GrimAge and PhenoAge clocks (Table 2).

Two-way interactions between depressive symptoms and neighborhood material and/or social deprivation were not statistically significant for both clocks (Table 2). In sensitivity analysis, we examined associations between depressive symptoms, material and/or social deprivation, and epigenetic age acceleration using the first-generation Horvath DNAm Age and Hannum DNAm Age, and found no evidence of a statistically significant interaction or main effects (Supplementary Table 2). We also examined the associations after restricting the sample to individuals of European ethnicity. The results remained similar to those obtained from the overall sample for all 4 age acceleration measures (results not shown).

Discussion

This study sought to examine how living in a deprived neighborhood and having depressive symptoms are associated with epigenetic age acceleration in a community-based sample of middle-aged and older adults residing in predominantly urban areas. The results showed that neighborhood deprivation and depressive symptoms were positively associated with the acceleration of the epigenetic age estimated using the DNAm GrimAge clock. As DNAm GrimAge estimates mortality risk in units of years, our results indicate an acceleration in the risk of mortality by 1 month for every point increase in depressive symptom score, and by almost 1 year for those exposed to greater neighborhood deprivation (upper 2 quintiles for material and/or social deprivation) compared to lower neighborhood deprivation. We did not find evidence, however, of a statistically significant interaction between neighborhood deprivation and depressive symptoms.

Consistent with prior literature, we found that a greater number of depressive symptoms was associated with acceleration of epigenetic aging estimated using DNAm GrimAge after adjusting for all covariates, suggesting that the association is above and beyond individual- and neighborhood-level factors (20,40). Emotional distress caused by depression may result in biological wear and tear and dysregulation of the physiological systems, and in turn lead to accelerated epigenetic aging (41). Dysregulation of the hypothalamic–pituitary–adrenal axis, and inflammatory, neurological, and immune processes have been implicated in the pathophysiology of mood disorders, including major depressive disorder (42). Changes in glucocorticoid receptor activity, cortisol levels, and presence of inflammatory biomarkers have been noted in individuals with exposure to chronic stress and/or depression, and may be linked with cellular aging (42). Evidence also suggests that differences in the methylation levels of the aryl hydrocarbon receptor repressor gene and the associated immune and neuroinflammatory processes may be associated with the pathophysiology of psychiatric diseases and aging (26,43,44). Individuals with depressive symptoms may also have had exposure to environmental stressors such as childhood trauma, poor lifestyle and health behaviors, and weaker social networks; thus, accumulation of stressors over the life course may explain the observed epigenetic changes among these individuals (20). However, longitudinal studies are needed to understand the causal nature of these associations.

Downloaded from https://academic.oup.com/biomedgerontology/article/79/2/glad118/7190263 by Erasmus University Rotterdam user on 07 February 2024

Table 2. Association Between Neighborhood Material and/or social Deprivation, Depressive Symptoms, and Epigenetic Age Acceleration Measures

	DNAm GrimAge Acceleration		DNAm PhenoAge Acceleration	
	b	95% CI	*b*	95% CI
Unadjusted models				
Depressive symptoms (*n* = 1 440)	0.11*	(0.05, 0.16)	0.06	(−0.03, 0.15)
High material and/or social deprivation versus low deprivation (*n* = 1 393)	1.13*	(0.65, 1.60)	0.39	(−0.43, 1.20)
Adjusted model† (*n* = 1 315)				
Depressive symptoms	0.07*	(0.01, 0.13)	0.07	(−0.03, 0.17)
High material and/or social deprivation versus low deprivation	0.66*	(0.21, 1.12)	0.20	(−0.64, 1.04)
Male versus female	2.99*	(2.53, 3.44)	3.90*	(3.07, 4.72)
Annual household income	−0.55*	(−0.79, −0.32)	−0.20	(−0.62, 0.23)
Number of people living in the same household	0.14	(−0.06, 0.35)	−0.17	(−0.53, 0.18)
Number of poor health behaviors	1.06*	(0.77, 1.34)	0.46	(−0.02, 0.94)
Number of chronic conditions	0.18*	(0.07, 0.28)	0.21*	(0.03, 0.40)
Interaction Model† (*n* = 1 315)				
Depressive symptoms × High material and/or social deprivation	−0.10	(−0.22, 0.02)	−0.07	(−0.27, 0.13)

Notes: CI = confidence interval; DNAm = DNA methylation.
†Model is adjusted for individual level covariates including sex, annual household income, number of people living in the same household, number of chronic conditions, and number of poor health behaviors.
*p Value of <.05.

The findings also add to the growing body of evidence that exposure to urban environment and neighborhood deprivation is associated with accelerated epigenetic aging (19,45). Neighborhood social environment is associated with DNAm of both stress- and inflammation-related genes (46). Adults who lived in neighborhoods characterized by lower aesthetic quality, safety, and social cohesion had shorter telomere length (another marker of biological aging) than those who lived in a more socially advantaged neighborhood (16). Likewise, material deprivation is also associated with the epigenetic age acceleration measured using epigenetic clocks, shorter telomere length, and DNAm of genes involved in stress and inflammation processes (19,47). Because the material deprivation index in the current study is based on the dissemination area-level indicators, this finding highlights the potential associations of biological aging with residing in neighborhoods characterized by lower-income households, high unemployment rate, and lower education rates. The association between material and social deprivation and epigenetic age acceleration could be reflective of poor childhood environment, lifestyle and health behaviors, stress of experiencing economic hardship, weaker social networks, and fewer opportunities for social participation, which may result in premature biological aging (47–49). Our results showed that the effect of neighborhood deprivation on epigenetic age acceleration was similar regardless of depressive symptoms, suggesting that depression influences epigenetic age acceleration through mechanisms that are unrelated to neighborhood deprivation.

There was no statistical association between depressive symptoms, material and/or social deprivation, and epigenetic age acceleration measured using the PhenoAge. The differences in findings between the 2 epigenetic clocks may be explained by the differences in the number and type of DNAm-based estimators included in the algorithm. There is also a little overlap of CpG sites between clocks, which may indicate that the different epigenetic clocks may be measuring different aspects of biological aging. The DNAm GrimAge may be more sensitive and may outperform other clocks, as its estimation is based on a greater number of CpG sites (1 030 CpGs) compared with the DNAm PhenoAge (513 CpGs), Horvath DNAm Age (353 CpGs), and Hannum DNAm Age (71 CpGs) (50).

The findings of our study should be considered in light of some limitations. The cross-sectional study design prevents us from determining the temporal sequences between urban environment attributes, depressive symptoms, and epigenetic aging. Evidence suggests that the association between depressive symptoms and epigenetic age may be bidirectional. Therefore, longitudinal studies are needed to examine these associations further. This study also did not assess the age of onset or duration of depression. Further, information regarding the length of exposure or how long individuals lived in their neighborhood was not available. It may be possible that individuals who spend more time in deprived neighborhoods have a higher epigenetic age. Another limitation is that our sample was predominantly of European ethnic background; in addition, individuals residing in the Canadian territories, on First Nation reserves, in long-term care homes, and those with cognitive impairment were excluded from the study, which limits the generalizability of our findings to community-dwelling older adults of European ethnicity.

Conclusion

Taken together, these findings suggest that living in urban environments with higher levels of neighborhood deprivation and having depressive symptoms are both associated with premature biological aging, even after accounting for individual-level health and behavioral risk factors. DNAm GrimAge estimates mortality risk in unit of years; therefore, these results may indicate an acceleration in the risk of mortality for those with depressive symptoms as well as those exposed

Downloaded from https://academic.oup.com/biomedgerontology/article/79/2/glad118/7190263 by Erasmus University Rotterdam user on 07 February 2024

to neighborhood material and social deprivation. However, longitudinal studies are needed to confirm these associations. Future studies are also needed to examine whether the associated epigenetic changes are stable or reversible over time. As the next steps, future research should focus on identifying and examining the underlying biological mechanisms linking depression, neighborhood material and social deprivation, epigenetic age acceleration, and increased risk of morbidity and mortality.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

This research was made possible using the data/biospecimens collected by the Canadian Longitudinal Study on Aging (CLSA). Funding for the Canadian Longitudinal Study on Aging (CLSA) is provided by the Government of Canada through the Canadian Institutes of Health Research (CIHR) under grant reference: LSA 94473 and the Canada Foundation for Innovation, as well as the following provinces, Newfoundland, Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia. This research has been conducted using the CLSA dataset Baseline Comprehensive Dataset version 4.0, Tracking Baseline version 3.4, CLSA Sample Weights version 1.2, and CANUE, under Application Number 171013. The CLSA is led by Drs. Parminder Raina, Christina Wolfson and Susan Kirkland. Parminder Raina holds the Raymond and Margaret Labarge Chair in Optimal Aging and Knowledge Application for Optimal Aging, is the Director of the McMaster Institute for Research on Aging and the Labarge Centre for Mobility in Aging and holds a Tier 1 Canada Research Chair in Geroscience. This study was partly supported by the European Union Horizon2020 Programme (667661; Promoting depressed affect in the aging population-MINDMAP).

Conflict of Interest

None declared.

Author Contributions

D.J., F.J.v.L., M.H., E.R.S., S.K., M.A., and P.R. were involved in the conceptualization and design of the study. D.J. and P.R. conducted the data analyses. D.J. drafted the manuscript. All authors contributed to the interpretation of the data, provided critical revisions of the manuscript, and approved the final version to be published.

Ethics Approval and Consent to Participate

This study was approved by the Hamilton Integrated Research Ethics Board (ethics approval number 09-213 and 10-423). The participant data were de-identified at the CLSA Data Curation Centre prior to their release to the study team. Written consent was obtained from all participants prior to data collection.

Data Availability

Data are available from the Canadian Longitudinal Study on Aging (www.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data.

References

1. World Health Organization. *Global Age-friendly Cities: A Guide*. World Health Organization; 2007.
2. Michel J-P. Urbanization and ageing health outcomes. *J Nutr Health Aging*. 2020;24(5):463–465. doi:10.1007/s12603-020-1360-1
3. Faris R, Dunham H. *Mental Disorders in Urban Areas: An Ecological Study of Schizophrenia and Other Psychoses*. University of Chicago Press; 1939.
4. Galea S, Ettman CK, Vlahov D. *Urban Health*. Oxford University Press; 2019:xv, 437.
5. Mair C, Diez Roux AV, Galea S. Are neighbourhood characteristics associated with depressive symptoms? A review of evidence. *J Epidemiol Community Health*. 2008;62(11):940–946, 8 p following 946. doi:10.1136/jech.2007.066605
6. Galea S, Vlahov D. Urban health: evidence, challenges and directions. *Annu Rev Public Health*. 2005;26:341–365. doi:10.1146/annurev.publhealth.26.021304.144708
7. Galea S, Bresnahan M, Susser E. Mental health in the city. In: Freudenberg N, Galea S, Vlahov D, eds. *Cities and the Health of the Public*. Vanderbilt University Press; 2006:247–274.
8. Evans GW. The built environment and mental health. *J Urban Health*. 2003;80(4):536–555. doi:10.1093/jurban/jtg063
9. Julien D, Richard L, Gauvin L, Kestens Y. Neighborhood characteristics and depressive mood among older adults: an integrative review. *Int Psychogeriatr*. 2012;24(8):1207–1225. doi:10.1017/S1041610211002894
10. Beard JR, Cerdá M, Blaney S, Ahern J, Vlahov D, Galea S. Neighborhood characteristics and change in depressive symptoms among older residents of New York City. *Am J Public Health*. 2009;99(7):1308–1314. doi:10.2105/AJPH.2007.125104
11. Generaal E, Timmermans EJ, Dekkers JEC, Smit JH, Penninx B. Not urbanization level but socioeconomic, physical and social neighbourhood characteristics are associated with presence and severity of depressive and anxiety disorders. *Psychol Med*. 2019;49(1):149–161. doi:10.1017/s0033291718000612
12. Fone D, White J, Farewell D, et al. Effect of neighbourhood deprivation and social cohesion on mental health inequality: a multilevel population-based longitudinal study. *Psychol Med*. 2014;44(11):2449–2460. doi:10.1017/S0033291713003255
13. Prigge R, Wild SH, Jackson CA. The individual and combined associations of depression and socioeconomic status with risk of major cardiovascular events: a prospective cohort study. *J Psychosom Res*. 2022;160:110978. doi:10.1016/j.jpsychores.2022.110978
14. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37–43. doi:10.1016/S0140-6736(12)60240-2
15. Geronimus AT, Hicken M, Keene D, Bound J. "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. *Am J Public Health*. 2006;96(5):826–833. doi:10.2105/AJPH.2004.060749
16. Needham BL, Carroll JE, Diez Roux AV, Fitzpatrick AL, Moore K, Seeman TE. Neighborhood characteristics and leukocyte telomere length: the Multi-Ethnic Study of Atherosclerosis. *Health Place*. 2014;28:167–172. doi:10.1016/j.healthplace.2014.04.009
17. Ridout KK, Ridout SJ, Price LH, Sen S, Tyrka AR. Depression and telomere length: a meta-analysis. *J Affect Disord*. 2016;191:237–247. doi:10.1016/j.jad.2015.11.052
18. Koutsouleris N, Davatzikos C, Borgwardt S, et al. Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of

Downloaded from https://academic.oup.com/biomedgerontology/article/79/2/glad118/7190263 by Erasmus University Rotterdam user on 07 February 2024

psychiatric disorders. *Schizophr Bull*. 2014;40(5):1140–1153. doi:10.1093/schbul/sbt142
19. Lawrence KG, Kresovich JK, O'Brien KM, et al. Association of neighborhood deprivation with epigenetic aging using 4 clock metrics. *JAMA Netw Open*. 2020;3(11):e2024329. doi:10.1001/jamanetworkopen.2020.24329
20. Han LKM, Aghajani M, Clark SL, et al. Epigenetic aging in major depressive disorder. *Am J Psychiatry*. 2018;175(8):774–782. doi:10.1176/appi.ajp.2018.17060595
21. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet*. 2018;19(6):371–384. doi:10.1038/s41576-018-0004-3
22. Hannum G, Guinney J, Zhao L, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol Cell*. 2013;49(2):359–367. doi:10.1016/j.molcel.2012.10.016
23. Marioni RE, Shah S, McRae AF, et al. The epigenetic clock is correlated with physical and cognitive fitness in the Lothian Birth Cohort 1936. *Int J Epidemiol*. 2015;44(4):1388–1396. doi:10.1093/ije/dyu277
24. Chen BH, Marioni RE, Colicino E, et al. DNA methylation-based measures of biological age: meta-analysis predicting time to death. *Aging (Albany NY)*. 2016;8(9):1844–1865. doi:10.18632/aging.101020
25. Levine ME, Lu AT, Quach A, et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany NY)*. 2018;10(4):573–591. doi:10.18632/aging.101414
26. Lu AT, Quach A, Wilson JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging (Albany NY)*. 2019;11(2):303–327. doi:10.18632/aging.101684
27. Raina P, Wolfson C, Kirkland S, et al. Cohort profile: the Canadian Longitudinal Study on Aging (CLSA). *Int J Epidemiol*. 2019;48(6):1752–1753. doi:10.1093/ije/dyz173
28. Lin DTS, MacIsaac JL, Ramadori KE, et al. The Canadian Longitudinal Study on Aging: Genome-Wide DNA Methylation Profiling on 1,479 Participants Using Illumina Infinium MethylationEPIC BeadChip Microarray Technology Data Support Document. ProMED-mail. Accessed April 24, 2023. https://www.clsa-elcv.ca/doc/3491
29. Triche TJ, Jr, Weisenberger DJ, Van Den Berg D, Laird PW, Siegmund KD. Low-level processing of Illumina Infinium DNA methylation bead arrays. *Nucleic Acids Res*. 2013;41(7):e90. doi:10.1093/nar/gkt090
30. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med*. 1994;10(2):77–84.
31. Björgvinsson T, Kertz SJ, Bigda-Peyton JS, McCoy KL, Aderka IM. Psychometric properties of the CES-D-10 in a psychiatric sample. *Assessment*. 2013;20(4):429–436. doi:10.1177/1073191113481998
32. Miller WC, Anton HA, Townson AF. Measurement properties of the CESD scale among individuals with spinal cord injury. *Spinal Cord*. 2008;46(4):287–292. doi:10.1038/sj.sc.3102127
33. Pampalon R, Hamel D, Gamache P, Philibert MD, Raymond G, Simpson A. An area-based material and social deprivation index for public health in Québec and Canada. *Can J Public Health*. 2012;103(8 Suppl 2):S17–S22. doi:10.1007/BF03403824
34. *CanMap Postal Code Suite v2015.3. [computer file]* Markham: DMTI Spatial Inc.; 2015.
35. Gamache P, Hamel D, Blaser C. Material and Social Deprivation Index: A Summary—INSPQ Website. ProMED-mail. www.inspq.qc.ca/en/publications/2639
36. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. *J Clin Epidemiol*. 1999;52(7):643–651. doi:10.1016/s0895-4356(99)00049-9
37. World Health Organization. *Global Recommendations on Physical Activity for Health [Internet]*. World Health Organization; 2010.
38. Keller HH, Goy R, Kane SL. Validity and reliability of SCREEN II (Seniors in the community: risk evaluation for eating and nutrition, Version II). *Eur J Clin Nutr*. 2005;59(10):1149–1157. doi:10.1038/sj.ejcn.1602225
39. Raudenbush SW, Bryk AS. *Hierarchical Linear Models: Applications and Data Analysis Methods*. 2nd ed. Vol. 1. Sage Publications; 2002.
40. Protsenko E, Yang R, Nier B, et al. "GrimAge," an epigenetic predictor of mortality, is accelerated in major depressive disorder. *Transl Psychiatry*. 2021;11(1):193. doi:10.1038/s41398-021-01302-0
41. Verhoeven JE, Révész D, Epel ES, Lin J, Wolkowitz OM, Penninx BW. Major depressive disorder and accelerated cellular aging: results from a large psychiatric cohort study. *Mol Psychiatry*. 2014;19(8):895–901. doi:10.1038/mp.2013.151
42. Beydoun MA, Hossain S, Chitrala KN, et al. Association between epigenetic age acceleration and depressive symptoms in a prospective cohort study of urban-dwelling adults. *J Affect Disord*. 2019;257:64–73. doi:10.1016/j.jad.2019.06.032
43. Smith AK, Ratanatharathorn A, Maihofer AX, et al. Epigenome-wide meta-analysis of PTSD across 10 military and civilian cohorts identifies methylation changes in AHRR. *Nat Commun*. 2020;11(1):5965. doi:10.1038/s41467-020-19615-x
44. Reynolds LM, Wan M, Ding J, et al. DNA methylation of the Aryl hydrocarbon receptor repressor associations with cigarette smoking and subclinical atherosclerosis. *Circ Cardiovasc Genet*. 2015;8(5):707–716. doi:10.1161/CIRCGENETICS.115.001097
45. Barber S, Hickson DA, Kawachi I, Subramanian SV, Earls FD. The joint impact of neighborhood disadvantage and low social cohesion on cumulative risk of disease among African American men and women in the Jackson Heart Study. *Soc Sci Med*. 2016;153:107–115. doi:10.1016/j.socscimed.2016.02.001
46. Smith JA, Zhao W, Wang X, et al. Neighborhood characteristics influence DNA methylation of genes involved in stress response and inflammation: the Multi-Ethnic Study of Atherosclerosis. *Epigenetics*. 2017;12(8):662–673. doi:10.1080/15592294.2017.1341026
47. Simons RL, Lei MK, Beach SR, et al. Economic hardship and biological weathering: the epigenetics of aging in a U.S. sample of black women. *Soc Sci Med*. 2016;150:192–200. doi:10.1016/j.socscimed.2015.12.001
48. Hughes A, Smart M, Gorrie-Stone T, et al. Socioeconomic position and DNA methylation age acceleration across the life course. *Am J Epidemiol*. 2018;187(11):2346–2354. doi:10.1093/aje/kwy155
49. Quach A, Levine ME, Tanaka T, et al. Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. *Aging (Albany NY)*. 2017;9(2):419–446. doi:10.18632/aging.101168
50. Li X, Ploner A, Wang Y, et al. Longitudinal trajectories, correlations and mortality associations of nine biological ages across 20-years follow-up. *Elife*. 2020;9:e51507–e51526. doi:10.7554/eLife.51507

Downloaded from https://academic.oup.com/biomedgerontology/article/79/2/glad118/7190263 by Erasmus University Rotterdam user on 07 February 2024