Telomere Length and Neighborhood Circumstances: Evaluating Biological Response to Unfavorable Exposures

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Abstract

Background: Multilevel frameworks suggest neighborhood circumstances influence biology; however, this relationship is not well studied. Telomere length (TL) shortening has been associated with individual-level and neighborhood-level exposures and disease and may provide insights into underlying biologic mechanisms linking neighborhood with biology. To support neighborhood–biology investigations, we sought to determine the independent effect of neighborhood exposures on TL using standard multilevel linear regression models and quantile regression, a nonlinear, social science method applicable for testing the biologic hypothesis that extremes of the TL distribution are related to poor outcomes.

Methods: In a multicenter, cross-sectional study, blood TL was measured in 1,488 individuals from 127 census tracts in three U.S. regions using terminal restriction fragment assays. Multilevel linear and quantile regression models were adjusted for individual-level race, education, perceived stress, and depression. Neighborhood exposures included population density, urban/residential crowding, residential stability/mobility, and socioeconomic status.

Results: TL was not associated with any neighborhood variable using linear models, but quantile regression revealed inverse associations between population density and urban crowding at the lower tails of the TL distribution [5th (population density $P = 0.03$; urban crowding $P = 0.002$), 50th (both $P < 0.001$), 75th percentiles (both $P < 0.001$)]. TL was related to residential stability at the upper tail (95th percentile $P = 0.006$).

Conclusions: Findings support the use of nonlinear statistical methods in TL research and suggest that neighborhood exposures can result in biological effects.

Impact: TL may serve as an underlying example of a biologic mechanism that can link neighborhood with biology, thus supporting multilevel investigations in future studies. *Cancer Epidemiol Biomarkers Prev; 26(4); 553–60. ©2017 AACR.*

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Introduction

A growing body of research demonstrates that living in socioeconomically disadvantaged neighborhoods leads to poor health outcomes (1, 2) and higher mortality (3, 4). These associations hold even after consideration of individual-level sociodemographic factors, including income, education, and race/ethnicity (5, 6). Multilevel conceptual frameworks support the collective role of neighborhood circumstances, biologic factors, and individual-level exposures in disease development. However, what is not well understood is whether neighborhood circumstances can impact health at the biologic level.

Blood leukocyte telomere length (TL) has emerged as a biomarker of potential dual relevance to disease processes and social circumstances. Telomeres are long stretches of (TTAGGG)-repeat DNA located at chromosomal ends that protect against DNA degradation (7). Telomeres naturally shorten with age (8, 9) but also shorten prematurely in response to cellular stress (10, 11). Shorter TL has been associated with aging, cancer, diabetes, depression, and cardiovascular disease (1, 2, 8, 10–15). Male gender, age, and Caucasian race consistently relate to shorter TL in literature (16), although associations have been reported between blood leukocyte TL attrition and individual-level socioeconomic variables, including education, income, and employment (16). Studies also show suggested associations between shorter TL and other individual-level exposures that correlate with poor neighborhood circumstances, including lifestyle factors such as smoking, high body mass index (BMI), and low physical activity, as well as psychosocial stressors, including high perceived stress (10, 11) and difficult life circumstances, such as caring for the chronically ill (17).

Previous neighborhood and TL studies demonstrate an inverse relationship between shorter TL and neighborhood socioeconomic

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status (SES; refs. 18, 19), neighborhood disadvantage (20, 21), unfavorable social environment (18), and perceived neighborhood quality (22), even after adjustment for individual-level lifestyle (smoking, BMI, diet, physical activity), biomedical (cardiovascular disease, depression), and socioeconomic (education, income, employment) variables. However, these studies have limitations. Effects of other important risk factors, like cancer diagnosis and perceived stress, were not considered. Studies that investigate neighborhood effects on TL adjusting for relevant psychosocial factors would provide a more comprehensive assessment of the potential independent effect of neighborhood on a biologic outcome in the literature. Furthermore, current studies modeled mean TL in linear regression models so that associations at upper and lower tails of the TL distribution were not distinguished. Given the lower tail of the TL distribution is most biologically relevant (i.e., shorter TL relates to poor health), methodologic approaches looking specifically at the extremes of the TL distribution could provide more clinically relevant insights into TL associations.

Social frameworks related to neighborhood disorder and chronic physiologic stress have provided useful explanations, from the social science perspective, for the potential link between biology and neighborhood circumstances (23, 24). Under these theories, residents from disadvantaged neighborhoods experience greater emotional stress and poor mental health on a constant basis, leading to continued activation of the physiologic stress response, "wear and tear on the body," and negative effects on health behaviors and outcomes (25). However, in current research studies, there is a lack of focus on how neighborhood can affect the cell and through what biologic mechanisms (19). Therefore, studying neighborhood effects on TL is particularly important because it could provide insight into the underlying biologic mechanism for how neighborhood factors relate to biology. Thus, the goal of this article was to address current methodologic limitations and evaluate the independent effect of neighborhood on TL in a diverse, multineighborhood sample. The main hypothesis was that shorter TL would be related to unfavorable neighborhood sociodemographic circumstances and that this association could provide insights into biologic mechanisms linking neighborhood to biology.

Materials and Methods

Study population

The study sample included data collected at three centers that were originally part of the larger Centers for Population Health and Health Disparities Initiative (26): University of Pennsylvania (UPenn; Philadelphia, PA), the Ohio State University (OSU; Columbus, OH), and the University of Texas Medical Branch (UTMB; Galveston, TX). Each center had its own questionnaire and protocol for recruitment and data collection that has been described previously (27–29). Common data elements from study questionnaires across the three centers were identified, and coding schemes for each variable were standardized (as needed) to harmonize the data for analysis. A previous investigation showed that combining data from these three centers is valid (30), and it increases variation in ethnicity, geography, and neighborhood circumstances. Study participants were recruited from 2004 to 2012. Each center focused on an underserved population (27–29). Briefly, OSU included non-Hispanic white women from rural Appalachia (65% with a high school education or less) who were not pregnant and without cervical cancer at the time of enrollment ($n = 108$; ref. 26). UPenn included mostly urban, more educated (72% with greater than high school education), non-Hispanic white (89%) and African American (11%) prostate cancer patients from urology clinics within the UPenn hospital system ($n = 100$; ref. 28), and UTMB included a population-based sample of non-Hispanic households and a strata sample of Hispanic households (52% of the study population) in Texas City, TX (27), where 32% of the population had greater than a high school education and 37% had less than a high school education ($n = 1,280$). Study participants from all centers provided a blood sample (this sample was collected prior to any cancer treatments), and they completed a questionnaire at study enrollment. Study participants were followed-up for cancer status. Written informed consent was received from all participants, and study protocols were approved by the Institutional Review Boards of each center.

Outcome variable

TL was measured from DNA extracted from blood samples. OSU and UTMB DNA samples were processed using the QIAamp DNA Extraction Kit. UPenn DNA samples were extracted using Chemagen Magnetic Bead technology ($n = 57$) and phenol–chloroform extraction ($n = 36$). Terminal restriction fragment (TRF) or Southern blot assays were used to measure TL on all samples (using duplicate samples), as described previously (31). The overall coefficient of variation (CV%) was 1.25%, where a CV less than 2% is expected (10, 11). Mean TRF in kilobases (kb) was determined using Telorun software (31), and TL was reported in kb units.

Neighborhood variables

Census data from the American Community Survey (ACS) were obtained at the census tract level to ascertain sociodemographic neighborhood variables (http://www2.census.gov/acs2009_5yr/summaryfile/). Neighborhood is defined here by select census tract social and economic conditions. Census variables were linked to geocoded study data by the Federal Information Processing Standard code, which uniquely identifies states, counties, and census tracts (32). To ensure confidentiality, we obtained 5 years of census tract level estimates from the ACS. We used ACS version 2005–2009 as 86% of the study population was accrued between 2004 and 2009. Individuals from the same census tract were assumed to have the same neighborhood characteristics. Our data included 127 unique neighborhood clusters (census tracts). UPenn had the most unique number of clusters ($n = 92$), followed by OSU ($n = 29$) and UTMB ($n = 6$).

Nineteen sociodemographic variables, which relate to five main domains (i.e., population density, urban crowding, residential crowding, residential stability, and residential mobility), were chosen *a priori* and extracted from the ACS database based on their association with chronic stress, poor health outcomes, and their correlation with previously tested neighborhood variables from TL association studies (33–37). A principal components analysis was completed, identifying the 5 domains as uncorrelated components. Within each domain, the variable with the highest correlation coefficient was selected to represent that domain. For instance, for the residential crowding domain, percent households that are not crowded (people/room $\leq$ 1.00), percent households that are crowded (people/room > 1.00), percent households that are severely crowded (people/room > 1.50), and average household size were extracted, and percent

households that have more than one occupant per room was selected to represent residential crowding in the analysis (0.91). The representative variables for the remaining domains included population density (overall population/total land area in square miles), urban crowding (housing units/square mile, 0.81), residential stability (percent living in the same house for the past year, 0.89), and residential mobility [percent who moved their residence within the same state (not county) as of 1 year ago, 0.92]. There was a low degree of correlation (<0.4) among the variables selected to represent each domain for analysis.

To evaluate neighborhood SES, a neighborhood SES (NSES) index, previously developed by the RAND corporation, was utilized and included the following variables: education (percent adults over 25 with less than a high school education), employment (percent male unemployment), poverty (percent households with income below the poverty line, percent households receiving public assistance, percent female-headed households with children), and income (median household income; ref. 37). The method of selection for these six variables has been described previously (37). Briefly, they were the best representatives of SES in a factor analysis that originally started with 12 U.S. census variables (loading factor alpha between 0.80 and 0.93) in a previous RAND corporation study (37) that utilized national data from National Health and Nutrition Examination Survey. Each of the six variables were summed after being transformed (i.e., higher values corresponded to higher SES). This total score was then standardized to a mean of zero and an SD of one. Thus, an index score greater than zero denotes a tract with SES above the sample average (37).

Individual-level covariates

Variables common to all three centers (30) were included as covariates in statistical models: gender (male/female), age at enrollment (continuous); race/ethnicity (white/non-Hispanic, African American/non-Hispanic, and Hispanic), educational status [<high school, a high school education (12 years of schooling/GED), or >high school education], cigarette smoking status (ever/never), disease status (cancer; yes/no), total perceived stress score dichotomized at the median (38, 39), as measured from the Perceived Stress Scale (40, 41); and depression dichotomized at a clinical cutoff point of 16 (40, 42, 43), as measured from questions from Center for Epidemiological Studies-Depression (CES-D) scale (44) and the CES-D revised (R) scale (45). Laboratory factors known to affect TL measures in prior studies, including DNA extraction method (30, 46) and date of blood draw [given potential seasonal (47) and storage effects (48) on TL measures], were also included as covariates in statistical models.

Statistical analysis

The distributions of TL and neighborhood variables were examined for nonnormality, and appropriate data transformations were conducted. Natural log-transformed TL was used as the outcome variable for all analyses. For ease of interpretation, continuous neighborhood variables (with the exception of the NSES index) were scaled by dividing by their SD (18). We used linear mixed effect models to account for the multilevel nature of the data; likelihood ratio tests demonstrated that models including neighborhood and center information improved model fit. Thus, linear mixed effect models were used to allow for clustering of individuals within neighborhoods and centers and to estimate associations between neighborhood variables and TL before and after adjustment for individual-level covariates (18). Quantile regression was also used to assess associations with neighborhood factors within segments of the TL distribution, accounting for clustering by census tract and by center, similar to linear mixed effect models (49, 50). Quantile regression coefficients at the 5th, 10th, 25th, 50th, 75th, 90th, and 95th TL percentiles were considered. The coefficients at each TL percentile are interpreted as the change in log-transformed TL, given each unit increase in the neighborhood variable SD. Interactions among covariates were evaluated in stratified analysis and by taking the cross-product terms of each variable in both multilevel linear regression and quantile regression models. Individual-level and neighborhood-level covariates were assessed for multicollinearity before inclusion in statistical models using correlation matrices (51). Robust SEs are reported and all tests were two-sided. A P <0.05 was considered to be statistically significant. In quantile regression, postestimation tests were conducted to account for multiple comparisons across quantiles (52). Bootstrapping techniques were applied to quantile regression models, and results were similar to standard P values. Findings were similar in a subset of participants without cancer, in center specific-analysis, and when restricting the study population to those accrued between 2004 and 2009 (data not shown). All analyses were performed using Stata 12.1 (StataCorp LP; ref. 53).

Results

Baseline characteristics of the study sample are presented in Table 1. Of the 1,488 participants, 58.8% were female, 15.7% had a cancer diagnosis, and the median age was 51 years [interquartile range (IQR) = 38–63]. The sample was comprised of 45.6% non-Hispanic whites, 45.0% Hispanics, and 9.4% African Americans. The overall sample reported mild levels of stress on the Perceived Stress Scale (median score = 19; IQR = 17–22) and low levels of depressive symptoms (median score = 6, IQR = 1–15). The distribution of most population characteristics in Table 1 (with the exception of cigarette smoking status) differed significantly across centers; thus, statistical models were adjusted for confounding and clustering effect by center, as reported previously (30). The study sample had a relatively low median NSES index overall (−0.11; IQR = −0.68–0.48), although neighborhood SES was different by region [UPenn = 0.80 (IQR = 0.38–1.11); OSU = −0.35 (IQR = −0.61to −0.17); UTMB = −0.10 (IQR = −0.68–0.48)]. We report a median population density (total population/total area of land use in square miles) of 3,857.3 (IQR = 1,694–5,101). The United States reports a population density of 87.5 (54). Galveston, TX, reports 1,158.2, Appalachian Ohio reports 127.8, and Philadelphia county reports 11,379.4 (54). The median percent of households considered to be crowded (i.e., greater than one occupant per room) was 2.6% for the overall study population, which is lower than the national average (55). The median percent of the population still living in the same house as of 1 year was 86.7%, and the median percent of the population that moved within the same state in the past year was 2.9%.

No associations were found between any neighborhood factor and log-transformed TL in multilevel linear regression models. These findings did not change when adjusting for individual level covariates and psychosocial factors (Table 2). In quantile regression models, associations were seen between log-transformed TL and population density and urban crowding at lower tails of the

Table 1. Study characteristics including neighborhood and individual-level psychosocial factors

	All centers	UPenn	OSU	UTMB	P[a]
Population characteristics					
Total population (*N*)	1,488	100	108	1280	
Median TL (kb)[b]	6.4 (4.3–8.3)	8.7 (4.2–11.8)	6.3 (5.1–7.9)	6.3 (4.2–8.3)	0.0001
Median age[b]	51 (38–63)	58 (53–63)	30 (26–43)	51 (38–64)	0.0001
Male gender (%)	41.2	100	0	40.1	0.0001
Cancer diagnosis (%)	15.7	100	0	10.5	<0.001
Ever cigarette smokers (%)	51.0	57.4	42.3	51.2	0.08
Race (%)					
Non-Hispanic white	45.6	89.0	98.2	37.8	
African American	9.4	11.0	1.8	9.9	
Hispanic	45.0	0	0	52.3	<0.001
Education (%)					
>High school	37.0	72.3	11.7	31.8	
High school/GED	29.8	23.7	23.4	30.8	
<High school	33.2	4.0	64.9	37.4	<0.001
Median total perceived stress[c]	19 (17–22)	20 (18–22)	22 (19–24)	19 (16–22)	0.0001
Median depressive symptoms[c]	6 (1–15)	8 (3–13)	12 (7–22)	5 (0–14)	0.0001
Neighborhood factors					
Median NSES index	−0.11 (−0.68–0.48)	0.80 (0.38–1.11)	−0.35 (−0.61 to −0.17)	−0.11 (−0.68–0.48)	0.0001
Median population density [population/ square (sq) mile]	3,857.3 (1,694–5,101)	2,305.8 (1,221–5,132)	54.9 (40–126)	4,405.8 (1,694–5,101	0.0001
Median urban crowding (housing units/sq. mile)	1,755.8 (695–1,833)	952.8 (455–2,086)	24.9 (18.2–53.1)	1,755.8 (695–1,833)	0.0001
Residential crowding (%)					
Median % households that are crowded (people per room >1)	2.6 (0.6–11)	0.5 (0–1.0)	1.1 (0.4–2.0)	3.6 (2.7–11.3)	0.0001
Residential stability (%)					
Median % living in the same house for the past year	86.7 (78–91)	90.3 (87–93)	86.9 (82–89)	79.0 (79–91)	0.0001
Residential mobility (%)					
Median % moved within the same state (not county) as of one year ago	2.9 (1.2–2.9)	1.7 (0.71–3.3)	2.3 (1.4–3.9)	2.9 (1.2–2.9)	0.02

[a]*P* values comparing characteristics across each of the three centers using Kruskal–Wallis test or Fisher exact test. Range from low to high for Depression (0–60) and Perceived Stress Scale (0–40).
[b]Medians (IQR for the median).
[c]Range from low to high for Depression (0–60) and Perceived Stress Scale (0–40).

TL distribution (the 5th, 50th, and 75th percentiles for population density and from the 5th through 75th percentiles for urban crowding) and between residential crowding and TL at the 50th percentile ($P = 0.03$; Table 3). For both population density and urban crowding, magnitudes of effect were small, but included a 2-fold difference between the 5th percentile (−0.10 for population density; −0.11 for urban crowding) and the 75th percentile of the log-transformed TL distribution (−0.05 for population density; −0.04 for urban crowding). Postestimation tests further confirm that the difference between the point estimates for the 5th and 75th percentile are significant for both population density ($P = 0.02$) and urban crowding ($P = 0.03$). This variation in effect, going from higher to lower percentiles, suggests the main association between neighborhood and TL lies at the lower tail of the distribution (49, 50). For residential crowding, an association at the 50th percentile suggests modeling about the median is appropriate and that the tails of the TL distribution are unlikely to contribute to this association (49, 50). For neighborhoods where residents remained in the same house in the past year, there was a positive association between TL and residential stability at the highest levels of the TL distribution (95th percentile $P < 0.001$; 90th percentile $P = 0.002$). For neighborhoods where residents

Table 2. Associations reported in terms of beta estimates and SEs between log-transformed TL (kb) and independent neighborhood factors [scaled by SD, before and after adjustment for covariates ($n = 1,488$) in linear mixed effect models]

	Neighborhood factors scaled by SD			
	Model 1 (estimate, SE)	P	Model 2 (estimate, SE)	P
Increasing NSES index	−0.01, 0.04	0.90	−0.01, 0.04	0.91
Increasing population density (population/sq. mile)	−0.02, 0.02	0.32	−0.03, 0.02	0.33
Increasing urban crowding (housing units/sq. mile)	−0.02, 0.02	0.36	−0.02, 0.02	0.30
Increasing residential crowding				
% Crowded households	−0.05, 0.07	0.52	−0.05, 0.08	0.54
Increasing residential stability (%)				
% Same house for the past year	0.06, 0.05	0.18	0.05, 0.05	0.27
Increasing residential mobility (%)				
% Moved within same state (not county) as of one year ago	−0.01, 0.04	0.89	−0.001, 0.04	0.99

NOTE: Model 1 is the crude analysis without covariates. Model 2 includes adjustment for age, gender, cancer status, race/ethnicity, perceived stress (high/low), depression (high/low), smoking (ever/never), date of blood draw (month and year), education level, DNA extraction, and the interactions of gender and cancer status, and race/ethnicity and educational level.

Table 3. Associations with independent neighborhood factors (SD adjusted) across the log-transformed TL distribution (kb)

	Log-transformed TL distribution						
	5th Percentile	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	95th Percentile
	Coeff (SE)	Coeff (SE)	Coeff (SE)	Coeff (SE)	Coeff (SE)	Coeff (SE)	Coeff (SE)
Neighborhood factor	***P***	***P***	***P***	***P***	***P***	***P***	***P***
Increasing neighborhood SES	0.03 (0.02) 0.19	0.02 (0.02) 0.48	0.02 (0.03) 0.38	0.005 (0.02) 0.80	0.01 (0.02) 0.79	−0.02 (0.03) 0.55	0.01 (0.02) 0.71
Increasing population density (population/sq. mile)	−0.10 (0.05) 0.04[a]	−0.07 (0.04) 0.11	−0.06 (0.05) 0.24	−0.04 (0.01) <0.001[a]	−0.05 (0.02) <0.001[a]	−0.05 (0.04) 0.20	−0.01 (0.02) 0.71
Increasing urban crowding (housing units/sq. mile)	−0.11 (0.05) 0.03[a]	−0.08 (0.05) 0.04[a]	−0.06 (0.01) <0.001[a]	−0.05 (0.01) <0.001[a]	−0.05 (0.03) <0.001[a]	−0.04 (0.04) 0.29	−0.03 (0.02) 0.21
Increasing residential crowding							
% Crowded households	−0.02 (0.02) 0.29	−0.03 (0.01) 0.12	−0.04 (0.02) 0.22	−0.01 (0.02) 0.02[a]	−0.01 (0.02) 0.97	0.03 (0.03) 0.30	0.03 (0.02) 0.07
Increasing residential stability (%)							
% in the same house for the past year	0.03 (0.04) 0.49	0.03 (0.04) 0.44	0.04 (0.03) 0.26	0.03 (0.02) 0.12	0.04 (0.02) 0.09	0.04 (0.01) 0.002[a]	0.03 (0.01) <0.001[a]
Increasing residential mobility (%)							
% Moved within same state (not county) as of one year ago	0.02 (0.02) 0.53	0.02 (0.03) 0.25	0.01 (0.02) 0.26	−0.01 (0.02) 0.52	−0.01 (0.01) 0.26	−0.03 (0.01) 0.01[a]	−0.02 (0.01) 0.001[a]

NOTE: Model includes adjustment for age, gender, cancer status, ever cigarette smoking, race/ethnicity, perceived stress (high/low), depression (high/low), center, educational level, date of blood draw (month and year) and DNA extraction, and the interactions of gender and cancer status, and race/ethnicity and educational level.

[a]*P* value less than 0.05.

moved within the same state (but not the same county) in the past year, there was an inverse relationship with TL at the 90th ($P = 0.01$) and 95th percentiles ($P < 0.001$).

Discussion

This is the first study to evaluate the relationship between TL and neighborhood, using nonlinear statistical methods and including adjustments for measures of psychosocial stress. We found associations between shorter TL and increases in population density and urban crowding. We also observed associations between longer TL and residential stability and mobility. These associations are in the direction we expect (18, 20, 21); however, associations were only noted in nonlinear, quantile regression models.

Our findings are similar to results from previous neighborhood and TL studies, using different neighborhood variables, confounders, and analytic approaches (18, 22). Previous studies investigated the relationship between TL and composite scores of NSES (from year 2000 U.S. Census variables), self-reported neighborhood social factors (e.g., social cohesion, aesthetics, and safety; ref. 18), and neighborhood quality (22). We chose population density, urban crowding, residential crowding, residential stability and mobility variables, and a NSES index to represent sociodemographic neighborhood circumstances for this analysis because they have been considered surrogates for self-reported measures of unfavorable neighborhood exposures that were investigated in previous TL studies (18). Specifically, they provide insight into the social norms and disorder of a neighborhood, as well as provide general insights into the neighborhood physical landscape (56, 57). For instance, urban and residential crowding are related to increases in social stress (58, 59), can negatively affect family and social relationships (60), and impact social cohesion (56, 57, 59). Urban and residential crowding can be affected by an individual's race/ethnicity and socioeconomic status (61); thus, statistical models were adjusted for these individual-level factors. Residential stability is related to neighborhood safety (i.e., safer neighborhoods are related to increases in residential stability; ref. 62) and can also affect social cohesion (56, 57), particularly when a number of well-established residents or families leave a neighborhood, causing destabilization of social norms and a disruption of social networks (56, 57). Both impoverished and flourishing neighborhoods can have a high level of residential stability, yet impoverished neighborhoods often have poorer health (57). To test whether neighborhood deprivation could confound or modify findings, particularly findings related to residential stability, we adjusted statistical models for NSES, and associations with TL remained unchanged (data not shown). Furthermore, despite using U.S. Census variables (an approach that is generally considered less specific than self-reported data) for measures of neighborhood, our findings are consistent with previous neighborhood and TL studies. This suggests that more readily available census variables could be reasonable measures of social and environmental phenomena and could be used to justify more in-depth neighborhood investigations.

Previous neighborhood and TL studies modeled mean TL in linear statistical models. Biologic literature suggests that lower tails or short TL is related to unfavorable health outcomes. Thus, we used quantile regression to investigate potential associations at the extremes of the TL distribution (49, 50). Quantile regression allows for the study of predictors across the entire TL distribution, without having to categorize a continuous outcome variable (with concomitant reduction in statistical power). It has been used in the obesity literature to identify potential cutoff points in BMI where clinically significant changes in risk occur (63). It would be premature to use quantile regression to establish clinically significant cutoff points of TL, but findings in urban crowding and population density, which show greater magnitudes of effect in the lower tails of the distribution, and significant, but lesser magnitudes of effect in the 75th percentile, suggest that further investigations into potentially clinically relevant TL cutoff points are warranted. Our findings demonstrate that using an approach like quantile regression may identify associations that are

otherwise missed by modeling simple linear relationships. Findings also suggest when considering the relationship between complex exposures, including neighborhood, and biological variables such as TL, novel statistical modeling tools may be required to obtain relevant insights into these relationships.

A previous study did not collect data related to perceived stress and was unable to investigate effects of neighborhood on TL in the context of psychosocial stressors, citing this as a study limitation (18). This study also did not report potential effects of DNA extraction method or date of blood draw on TL, when previous studies suggest that seasonal effects (date of blood draw) and type of laboratory methods used could influence TL measures (30, 46, 47). We found that neighborhood effects remained even after adjustment for individual-level covariates and psychosocial factors. Thus, our study contributes new and compounding evidence that neighborhood can exert independent effects on TL. Furthermore, these findings across neighborhood and TL studies suggest that individual-level factors are limited in their capacity to fully explain changes at the biologic level. This indicates that other unexplored biologic or social explanations (22) should be considered. For example, although out of the scope of this particular analysis, investigations into joint effects or gene–environment interaction studies could shed light on TL and neighborhood associations (64). Most gene–environment studies to date have been limited to traditional, often geo-atmospheric measures of environment and much less so to the social and population measures of neighborhood environments used here. Although this has not been tested, it is possible that individuals at the lower tails of the TL distribution in this study (for instance, the 5th and 10th percentiles) could be genetically predisposed to having shorter TL, and those in the upper tails of the TL distribution (the 90th and 95th percentiles) could be genetically predisposed to having longer TL. Thus, based on our findings, neighborhood effects related to residential stability may only be relevant in those who have inherently longer TL. Furthermore, although linking telomere biology to evolutionary influences is still in the early stages, natural selection pressures could call for TL shortening in the presence of certain environments, like crowding (48, 65). This is because overcrowding correlates with limited resources (i.e., food and shelter; ref. 66) and poor health outcomes (stress, mental health; ref. 67) that can impact lifespan, and TL shortening may be a conditioned response to this environment (65). Thus, future studies that focus on the relationship between neighborhood, TL and a disease outcome, as well as on gene–neighborhood effects on TL, in the context of other relevant genetic-, individual-, and neighborhood-level factors, appear warranted (64).

Our study had some limitations. This was a cross-sectional study; we were not able to investigate change in TL or neighborhood characteristics. Studies that include longitudinal follow-up of TL and changes in residential stability, neighborhood gentrification, and in–out migration of neighborhood residents and families over time could shed light into our findings (57). Our study population comes from three U.S. regions, and each center had its own ascertainment strategy. Therefore, our study population is not a nationally representative sample. This sampling strategy could affect generalizability of results; however, our data did include multiple geographic regions and racial/ethnic groups. Although our study did not collect and evaluate previously studied disease states (hypertension and diabetes) and other risk factors related to TL, including smoking duration/intensity, BMI, etc. (18), we were able to evaluate neighborhood effects on TL in the context of perceived stress, which was a limitation in other studies (18). Furthermore, although our blood TL measures in this study were broad, that is, compiled on the basis of an individual's average TL from a combined mixture of various white blood cells that are known to have varying TL (i.e., granulocytes, lymphocytes, and monocytes report different average TL across cell types; ref. 68), the reporting of average TL in population studies is standard, and we did consider other laboratory factors (i.e., DNA extraction), which other neighborhood and TL studies have not evaluated. There is not a standard, agreed upon approach to defining neighborhoods, and although the utility of predefined boundaries to define neighborhoods, such as census tract, has been questioned, it is a commonly used approach and has the benefit of allowing for standardized assessments of neighborhoods with readily available data (69, 70). Future studies could consider so-called boundary-free geographic methods to measure environments that are more complex, yet are an improvement upon more commonly used polygon-based methods (71). Despite these limitations, our findings were similar to a population-based study with comparable sample demographics (18).

The results of this study provide evidence to support the hypothesis that neighborhood circumstances can have biologic consequences and that TL should continue to be investigated as a marker of the biological influences of neighborhood circumstances on human health and disease. However, our findings would need to be replicated in other studies, given associations varied by statistical method used. We conclude that neighborhood-level factors may contribute to TL under both social and biologic frameworks (34, 72), but that the effect of neighborhood on TL is complex.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Telomere Length and Neighborhood Circumstances: Evaluating Biological Response to Unfavorable Exposures

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