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Neighborhood characteristics and leukocyte telomere length: The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Telomeres are the protective caps at the ends of eukaryotic chromosomes. Telomeres get shorter each time a cell divides, and critically shortened telomeres trigger cellular senescence. Thus, telomere length is hypothesized to be a biological marker of aging. The purpose of this study was to examine the association between neighborhood characteristics and leukocyte telomere length. Using data from a subsample ($n=978$) of the Multi-Ethnic Study of Atherosclerosis, a population-based study of women and men aged 45–84, we found that neighborhood social environment (but not neighborhood socioeconomic disadvantage) was associated with telomere length. Respondents who lived in neighborhoods characterized by lower aesthetic quality, safety, and social cohesion had shorter telomeres than those who lived in neighborhoods with a more salutary social environment, even after adjusting for individual-level socioeconomic status and biomedical and lifestyle factors related to telomere length. Telomere length may be one biological mechanism by which neighborhood characteristics influence an individual's risk of disease and death.

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1. Introduction

People who live in socioeconomically disadvantaged neighborhoods tend to have greater morbidity (Diez Roux and Mair, 2010) and mortality (Meijer et al., 2012) than those who live in more advantaged neighborhoods, even after controlling for individual-level socioeconomic status (SES). Previous research suggests that this may be due, in part, to differences in physical and social features of neighborhoods, such as aesthetic quality, safety, and social cohesion, that shape exposure and vulnerability to stress (Diez Roux and Mair, 2010; Hill et al., 2005; Ross and Mirowsky, 2001). Several theoretical models propose that the chronic stress associated with social disadvantage contributes to wear and tear on the body, which accelerates the rate of decline in physiological functioning (Geronimus et al., 2006; McEwen, 1998).

Leukocyte telomere length (LTL) has recently emerged as a potential biomarker of cell aging (Der et al., 2012) and exposure to chronic stress (Epel, 2009). Telomeres cap the ends of chromosomes and promote chromosomal stability. Telomere shortening, which tends to occur with advancing chronological age (Aubert and Lansdorp, 2008; Frenck et al., 1998; Iwama et al., 1998), triggers cellular senescence (Blasco, 2005; Hayflick, 1965), a component of biological aging (Campisi and d'Adda di Fagagna, 2007). In support of the role of telomere length in aging and disease, a number of studies have found that shorter telomere length is associated with increased morbidity (e.g., Demissie et al., 2006; Fitzpatrick et al., 2007; Samani et al., 2001; Zee et al., 2010) and mortality (e.g., Bakaysa et al., 2007; Cawthon et al., 2003; Fitzpatrick et al., 2011; Weischer et al., 2012), independent of chronological age.

A growing body of evidence suggests that exposure to stressful life circumstances is associated with shorter telomere length (Damjanovic et al., 2007; Drury et al., 2011; Epel et al., 2004; Kananen et al., 2010; Tyrka et al., 2010). However, we are aware of only one previous study that investigated whether exposure to neighborhood stressors is associated with telomere length. In a small sample ($n=99$) of African–American children in New Orleans, Theall et al. (2013) found that neighborhood socioeconomic disadvantage and neighborhood disorder were associated with shorter telomeres. Observing a link between neighborhood stressors and telomere length would suggest that the chronic stress associated with neighborhood conditions has measurable biological consequences with possible implications for a range of health outcomes. In this study, we used data from the Multi-Ethnic Study of Atherosclerosis (MESA) to examine the association

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between neighborhood conditions and telomere length in a population-based sample of US adults.

1.1. Hypotheses

We hypothesized that (1) individuals living in socioeconomically disadvantaged neighborhoods would have shorter telomeres than those living in more advantaged neighborhoods and (2) individuals living in neighborhoods with poorer social environments, as indicated by lower aesthetic quality, safety, and social cohesion, would have shorter telomeres than those living in neighborhoods with more salutary social environments.

2. Data and methods

2.1. Data

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based longitudinal study designed to identify risk factors for the progression of subclinical cardiovascular disease (CVD) (Bild et al., 2002). Between July 2000 and August 2002, 6814 white, African–American, Hispanic, and Chinese–American women and men aged 45–84 without clinically apparent CVD were recruited from six regions in the US, including Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles County, CA. Each Field Center recruited from locally available sources, which included lists of residents, lists of dwellings, and telephone exchanges, with the goal of obtaining balanced recruitment across strata defined by gender, race/ethnicity, and age. Additional information on study recruitment has been published elsewhere (Bild et al., 2002). Paper-based questionnaires were interviewer-administered. Field Center staff were responsible for data entry, and data are stored electronically at the MESA Coordinating Center at the University of Washington. Telomeres were assessed on a subsample of 978 white, African–American, and Hispanic MESA participants aged 45–84 years from the New York and Los Angeles sites who agreed to participate in an ancillary study examining the effects of stress on cardiovascular outcomes (the MESA Stress Study). Participants were enrolled in the order in which they attended the MESA exam, until approximately 500 participants were enrolled at each site. This resulted in an approximately random sample of white, African–American, and Hispanic participants from the New York and Los Angeles sites. This study was approved by the Institutional Review Boards of all MESA Field Centers and the MESA Coordinating Center.

2.2. Measures

2.2.1. Dependent variable

Telomere length was measured from baseline blood samples by quantitative PCR (Q-PCR) (Cawthon, 2002). Blood was collected by venipuncture and stored at -80° at the University of Vermont and the University of Minnesota. Each sample was amplified for telomeric DNA and for 36B4, a single-copy control gene that provided an internal control to normalize the starting amount of DNA. A four-point standard curve (2-fold serial dilutions from 10 to 1.25 ng DNA) was used to transform cycle threshold into nanograms of DNA. Baseline background subtraction was performed by aligning amplification plots to a baseline height of 2% in the first 5 cycles. The cycle threshold was set at 20% of maximum product. All samples were run in triplicate and the median was used for calculations. The amount of telomeric DNA (T) was divided by the amount of single-copy control gene DNA (S), producing a relative measurement of the telomere length (T/S ratio). Two control samples were run in each experiment to allow for normalization between experiments and periodical reproducibility experiments were performed to guarantee correct measurements. The intra- and inter-assay variability (coefficient of variation) for Q-PCR was 6 and 7%, respectively.

2.2.2. Independent variables

Neighborhood socioeconomic disadvantage scores for each neighborhood were created based on a principal components analysis of 16 census-tract level variables from the 2000 US Census. These variables reflect dimensions of education, occupation, income and wealth, poverty, employment, and housing. The neighborhood SES score is the weighted sum of the following six standardized variables, which accounted for 49% of the variance and loaded on the first factor: percent in census tract with a bachelor's degree; percent with a managerial/professional occupation; percent with a high school education; median home value; median household income; and percent with household income greater than $50,000 per year. Higher values on the scale indicate greater neighborhood socioeconomic disadvantage.

Neighborhood social environment is the sum of standardized conditional empirical Bayes estimate (CEB) scales for aesthetic quality, safety, and social cohesion. Information on neighborhood characteristics was obtained from questionnaires administered to MESA participants and to an auxiliary sample of other neighborhood residents in the New York site (Mujahid et al., 2007). Responses were aggregated across respondents in census tracts to create neighborhood-level measures of aesthetic quality, safety, and social cohesion. The CEB estimates are more reliable than the census-tract crude means because they borrow information from other census tracts in cases where the sample size per tract is very small. In addition, the CEB estimates adjust for important factors in survey response, including site, participant sex and age, and survey type (MESA or auxiliary sample).

The aesthetic quality scale was created by summing responses to three questions. Respondents were asked to report their level of agreement (1=strongly agree—5=strongly disagree) with the following statements: (1) there is a lot of trash and litter on the street in my neighborhood; (2) there is a lot of noise in my neighborhood; and (3) my neighborhood is attractive. Item (3) was reverse coded so that higher values on this scale indicate better aesthetic quality. Cronbach's alpha for the aesthetic quality scale was.67.

The safety scale was created by summing responses to two questions. Respondents were asked to report their level of agreement (1=strongly agree—5=strongly disagree) with the following statements: (1) I feel safe walking in my neighborhood day or night; and (2) violence is a problem in my neighborhood. Item (1) was reverse coded so that higher values on this scale indicate greater perceptions of safety. Cronbach's alpha for the safety scale was.64.

The social cohesion scale was created by summing the responses to four questions. Respondents were asked to report their level of agreement (1=strongly agree—5=strongly disagree) with the following statements: (1) people around here are willing to help their neighbors; (2) people in my neighborhood generally get along with each other; (3) people in my neighborhood can be trusted; and (4) people in my neighborhood share the same values. All items were reverse coded so that higher values on this scale indicate greater social cohesion. The Cronbach's alpha for the social cohesion scale was.72.

Higher values on the original neighborhood social environment scale, which combines information from the aesthetic quality, safety, and social cohesion scales, indicate a better overall social environment. For this analysis, we multiplied the original scale

by −1 so that higher values indicate poorer neighborhood social environment.

2.2.3. Covariates

We control for the following potential confounders of the association between neighborhood characteristics and telomere length: age (in years), sex (1=female), race/ethnicity (dummy variables for African–American and Hispanic, with white as the reference category), nativity (1=foreign born), education (dummy variables for high school or less and some college, with college as the reference category), adjusted income (income/number of people supported), home ownership (1=home owner) (Carroll et al., 2013), and marital status (1=currently married or living with a partner). We also control for percent Hispanic in the census tract (a proxy for the proportion of foreign-born residents in the neighborhood) because areas with a high concentration of immigrants may have different resources than areas with similar levels of socioeconomic deprivation but a lower concentration of immigrants.

Biomedical and lifestyle factors have been linked to telomere length in previous research and could confound or mediate any observed differences in telomere length by neighborhood conditions. Therefore, models were also adjusted for the following: body mass index (BMI; kg/m^2) (Tzanetakou et al., 2012), systolic and diastolic blood pressure (mmHg) (Jeanclos et al., 2000), cholesterol medication (1=yes) (Saliques et al., 2011), LDL and HDL cholesterol (mg/dL) (Chen et al., 2009), interleukin-6 (IL-6; pg/L) (O'Donovan et al., 2011), pack-years of smoking (the average number of cigarettes smoked per day times the number of years smoked, divided by 20) (Strandberg et al., 2011; Valdes et al., 2005), consumption of processed meats (servings per day) (Nettleton et al., 2008), and moderate/vigorous physical activity (MET-minutes per week) (Ludlow and Roth, 2011).

2.3. Analysis

We used linear multi-level models, which account for the clustering of individuals within neighborhoods, to estimate associations between neighborhood variables and telomere length before and after adjusting for sets of covariates. The geocoding match rate was 99.8%. Respondents were from 498 census tracts, with 1–12 respondents per tract. The intraclass correlation coefficient (ICC) for the model with no predictors indicated that 5.3% of the variance in telomere length was between neighborhoods. In all models, the neighborhood variables were scaled by the standard deviation for ease of interpretation. Model 1 adjusted for sociodemographic factors, including age, sex, race/ethnicity, nativity, education, income, home ownership, and marital status, and percent Hispanic in the census tract. Model 2 added controls for biomedical risk factors that have been linked to telomere length in previous research, including body mass index, systolic and diastolic blood pressure, use of cholesterol-lowering drugs, LDL and HDL cholesterol, and interleukin-6. In Model 3, additional adjustments were made for lifestyle factors that have been linked to telomere length in prior studies, including smoking, processed meat consumption, and physical activity. Previous research on telomere length in the MESA study has reported larger race/ethnic differences and smaller gender differences at older ages (Diez Roux et al., 2009). Therefore, we also included interactions of age by race/ethnicity and age by sex as covariates in all models. Missing data on the predictor variables was replaced with the sample mean. The amount of missing data for each variable ranged from 0 to 10.7%. Descriptive statistics for all study variables are shown in Table 1.

Table 1
Descriptive statistics for all study variables (n=978).

Characteristic	Mean (SD)	Proportion
Leukocyte telomere length (T/S ratio)	.85 (.18)	–
Neighborhood socioeconomic disadvantage	.02 (1.40)	–
Neighborhood poor social environment	1.24 (2.39)	–
Age	61.41 (9.93)	–
Sex		
Female	–	.52
Male	–	.48
Race/ethnicity		
White	–	.19
African–American	–	.28
Hispanic	–	.53
Nativity		
Foreign-born	–	.49
US-born	–	.51
Per capita household income (in 10,000 s)	2.07 (1.73)	–
Education		
Less than high school	–	.27
High school	–	.20
Some college	–	.30
College	–	.23
Home ownership		
Owner	–	.41
Renter	–	.59
Marital status		
Married	–	.58
Single, divorced, or widowed	–	.42
Percent Hispanic in census tract	.48 (.30)	–
Body mass index	29.02 (5.53)	–
Systolic blood pressure (mmHg)	125.32 (20.96)	–
Diastolic blood pressure (mmHg)	71.98 (10.21)	–
Cholesterol medication		
Current user	–	.15
Non-user	–	.85
LDL cholesterol (mg/dL)	118.32 (31.77)	–
HDL cholesterol (mg/dL)	50.65 (14.59)	–
Interleukin-6 (pg/L)	1.60 (1.16)	–
Pack-years smoking	8.10 (15.61)	–
Processed meat consumption (servings/day)	.14 (.24)	–
Physical activity (MET-minutes per week, in 1000 s)	5.71 (5.56)	–

Notes: SD=standard deviation.

3. Results

The first hypothesis was that individuals living in socioeconomically disadvantaged neighborhoods would have shorter telomeres than those living in more advantaged neighborhoods. As shown in Table 2, we found no association between neighborhood socioeconomic disadvantage and telomere length before (see Panel A) or after (see Panel C) adjusting for neighborhood social environment.

The second hypothesis was that individuals living in neighborhoods with poorer social environments, as indicated by lower aesthetic quality, safety, and social cohesion, would have shorter telomeres than those living in neighborhoods with more salutary social environments. As shown in Panel B of Table 2, poor social environment was inversely associated with telomere length. Adjusting for individual-level sociodemographic characteristics and percent Hispanic in the neighborhood, a one standard deviation increase in poor social environment was associated with a.02 decrease in T/S ratio (p=.001). The average T/S ratio for respondents residing in more socially advantaged neighborhoods (defined as one standard deviation below the mean on poor social environment) was.86 compared to.81 for respondents residing in more socially disadvantaged neighborhoods (defined as one standard deviation above the mean on poor social environment). This corresponds to a difference of.04 in T/S ratio. A one-year increase

Table 2
Mean differences in leukocyte telomere length (T/S ratio) associated with neighborhood characteristics, before and after adjustment for sets of covariates (n=978).

	Panel A			Panel B			Panel C		
	Estimate[a]	SE	p Value	Estimate[a]	SE	p Value	Estimate[a]	SE	p Value
Model 1[b]									
Socioeconomic disadvantage	.00	.01	.80	–	–	–	.01	.01	.32
Poor social environment	–	–	–	−.02	.01	.001	−.02	.01	.001
Model 2[c]									
Socioeconomic disadvantage	.00	.01	.90	–	–	–	.01	.01	.40
Poor social environment	–	–	–	−.02	.01	.002	−.02	.01	.001
Model 3[d]									
Socioeconomic disadvantage	−.00	.01	.91	–	–	–	.01	.01	.55
Poor social environment	–	–	–	−.02	.01	.002	−.02	.01	.002

[a] All effect estimates are scaled to a one standard deviation increase in the neighborhood variables.
[b] Model 1 adjusted for age, sex, age × sex, race/ethnicity, age × race/ethnicity, nativity, per capita household income, education, home ownership, marital status, and percent Hispanic in census tract.
[c] Model 2 adjusted for age, sex, age × sex, race/ethnicity, age × race/ethnicity, nativity, per capita household income, education, home ownership, marital status, percent Hispanic in census tract, body mass index, systolic and diastolic blood pressure, use of cholesterol medication, LDL and HDL cholesterol, and interleukin-6.
[d] Model 3 adjusted for age, sex, age × sex, race/ethnicity, age × race/ethnicity, nativity, per capita household income, education, home ownership, marital status, percent Hispanic in census tract, body mass index, systolic and diastolic blood pressure, use of cholesterol medication, LDL and HDL cholesterol, interleukin-6, pack years smoking, processed meat consumption, and physical activity.

in age was associated with a.005 decline in T/S ratio. Using this estimate, the difference in telomere length between respondents living in more socially disadvantaged neighborhoods compared to less socially disadvantaged neighborhoods was roughly equivalent to eight additional years of aging. The association between neighborhood social environment and telomere length persisted after additional adjustment for biomedical and lifestyle factors that have been linked to telomere length in prior studies (see Models 2 and 3 in Panel B of Table 2) and after adjustment for neighborhood socioeconomic disadvantage (see Panel C of Table 2).

4. Discussion

Although a growing body of evidence suggests that the neighborhood context is an important determinant of health (Diez Roux and Mair, 2010; Meijer et al., 2012), the biological mechanisms by which neighborhood characteristics influence an individual's risk of disease and death are not well-understood. The purpose of this study was to examine the association between neighborhood characteristics and leukocyte telomere length, a biomarker of cell aging that has been linked to psychosocial stress exposure (Damjanovic et al., 2007; Drury et al., 2011; Epel et al., 2004; Kananen et al., 2010; Tyrka et al., 2010). Using data from a population-based sample of adults aged 45–84, we found that neighborhood social environment (but not neighborhood socioeconomic disadvantage) was associated with telomere length. Respondents who lived in neighborhoods characterized by lower aesthetic quality, safety, and social cohesion had shorter telomeres than those who lived in neighborhoods with a more salutary social environment, even after controlling for individual-level socioeconomic status, neighborhood socioeconomic disadvantage, and biomedical and lifestyle risk factors.

Only one prior study has examined the association between neighborhood characteristics and telomere length. Theall et al. (2013) found that neighborhood socioeconomic disadvantage (as indicated by the percentage of residents living below the poverty line) and parental perceptions of neighborhood disorder (as indicated by responses to several questions about aesthetic quality in the area surrounding the home) were associated with salivary telomere length in a sample of 99 African–American children in New Orleans, LA. Consistent with the results presented here, Theall et al. (2013) did not find an association between neighborhood socioeconomic disadvantage and telomere length when examining an economic deprivation index that combined multiple indicators of disadvantage. Despite significant differences between the two studies, including differences in age (children vs. older adults), region (Southeast vs. Northeast and West), and measurement of telomere length (in saliva vs. white blood cells), the results were very similar.

We hypothesized that neighborhood socioeconomic disadvantage would be inversely associated with telomere length because neighborhood disadvantage may be a proxy for a number of neighborhood level stressors that could be related to aging. The use of summary measures of neighborhood SES to characterize neighborhood environments has been criticized because of its lack of specificity and because it introduces difficulties in isolating context from composition. Interestingly, we found that a more specific measure of neighborhood stressors was related to telomere length while the summary disadvantage measure was not. This argues for the need to measure specific aspects of neighborhood environments when investigating the effects of neighborhoods on health.

4.1. Strengths, limitations, and directions for future research

A key strength of this study was the use of a large, multi-ethnic, population-based sample. Most prior research on telomere length has been conducted in small, homogeneous samples, which limits statistical power and generalizability (Aviv, 2008). Another strength of this study was the neighborhood measurement. We used previously tested scales to characterize specific neighborhood features that we hypothesized could be linked to stress and telomere length. The scales we used have shown good test-retest and neighborhood-level reliability (Mujahid et al., 2007). In addition, the use of conditional empirical Bayes estimation allowed us to improve the validity of the estimates by averaging across multiple respondents and borrowing information across neighborhoods. In addition, we were also able to account for individual-level factors such as sex and age that may be related to reporting.

This study had several limitations. Although MESA is a population-based study, it is not nationally representative. In general, MESA participants are healthier and have higher income and education than a random sample of same-age adults in the US. Thus, the extent to which our results are generalizable to the entire population of US adults aged 45–84 is unknown. Replication studies in more representative samples are needed to confirm or refute the results of this study.

Another limitation was the use of cross-sectional data. The availability of longitudinal data would allow us to determine whether change in the neighborhood environment is associated with change in telomere length. This type of analysis could provide a stronger test of the hypothesis that neighborhood conditions are causally related to cell aging.

Finally, additional research is needed to identify the causal pathway that links neighborhood characteristics to cell aging. In this study, we found that the association between neighborhood social environment and telomere length persisted after adjustment for biomedical and lifestyle factors that have been linked to telomere length in previous research. Thus, neighborhoods do not appear to affect telomere length through BMI, blood pressure, cholesterol, inflammation, smoking, processed meat consumption, or physical activity. Future research should consider whether perceived stress, stress biomarkers, symptoms of depression, social isolation, or other individual-level factors help explain why the neighborhood social environment is associated with telomere length. In prior MESA analyses, we documented that selected features of neighborhoods, including poverty, violence, disorder, and social cohesion, were associated with alterations of daily cortisol rhythms (Do et al., 2011). The results of the current study add to prior work documenting associations of neighborhood factors with biomarkers of stress (Do et al., 2011) and inflammation (Nazmi et al., 2010), as well as changes in regional cortical morphology associated with language and executive function (Krishnadas et al., 2013).

5. Conclusions

Although neighborhood socioeconomic disadvantage was not associated with telomere length, individuals living in neighborhoods with poorer social environments, as indicated by lower aesthetic quality, safety, and social cohesion, had shorter telomeres than those living in neighborhoods with more salutary social environments. Importantly, these findings were independent of individual-level socioeconomic status, neighborhood socioeconomic disadvantage, and biomedical and lifestyle risk factors. Prior work has shown that neighborhood characteristics are linked to poorer physical health (Diez Roux and Mair, 2010) and higher rates of mortality (Meijer et al., 2012). The present findings extend this work by documenting differences in cellular aging prior to morbidity and mortality, and suggest a possible mechanism through which neighborhood characteristics could impact disease risk. This was the first study to examine the association between neighborhood conditions and telomere length in US adults. More work is needed to determine whether neighborhood context is causally related to cell aging.

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