The relationship between neighborhood socioeconomic deprivation and telomere length: The 1999–2002 National Health and Nutrition Examination Survey

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ABSTRACT

Socioeconomically disadvantaged neighborhoods have been associated with poor health outcomes. Little is known about the biological mechanism by which deprived neighborhood conditions exert negative influences on health. Data from the 1999–2002 National Health and Nutrition Examination Surveys (NHANES) were used to assess the relationship between neighborhood deprivation index (NDI) and log-transformed leukocyte telomere length (LTL) via multilevel modeling to control for census tract level clustering. Models were constructed using tertiles of NDI (ref = low NDI). NDI was calculated using census tract level socioeconomic indicators from the 2000 U.S. Census. The sample (n = 5,106 adults) was 49.8% female and consisted of 82.9% non-Hispanic whites, 9.4% non-Hispanic blacks, and 7.6% Mexican Americans. Mean age was 45.8 years. Residents of neighborhoods with high NDI were younger, non-white, had lower educational attainment, and had a lower poverty to income ratio (all p < 0.0001). Neighborhood deprivation was inversely associated with LTL among individuals living in neighborhoods with medium NDI (β = −0.043, SE = 0.012, p = 0.0005) and high NDI (β = −0.039, SE = 0.013, p = 0.003). Among men, both medium (β = −0.042, SE = 0.015, p = 0.006) and high (β = −0.047, SE = 0.015, p = 0.001) NDI were associated with shorter LTL. Among women, only medium NDI (β = −0.020, SE = 0.016, p = 0.009) was associated with shorter LTL. After controlling for individual characteristics, including individual-level socioeconomic status, increasing neighborhood socioeconomic deprivation is associated with shorter LTL among a nationally representative sample of US adults. This suggests that telomere shortening may be a mechanism through which neighborhood deprivation results in poor health outcomes.

1. Introduction

Telomeres are protective DNA sequences on the ends of chromosomes that preserve genomic integrity during cellular replication (Starkweather et al., 2014). Shorter leukocyte telomere length (LTL) has been associated with age-related health conditions (Holohan, Wright, & Shay, 2014; Rizvi, Raza, & Mahdi, 2014), including increased morbidity (Holohan et al., 2014; Starkweather et al., 2014) and mortality (Needham, Rehkopf, Adler, Gregorich, & Lin, 2015), and may be useful as a biomarker to assess the cumulative effect of prolonged stressors. High levels of psychological stress, neighborhood disorder, and poor health behaviors have been associated with shortened telomeres (Starkweather et al., 2014). Nationally representative data show an association between exposure to environmental toxins and shortened telomeres (Patel, Manrai, Corona, & Kohane, 2017), as well as between poor cardiovascular health and decreased LTL (Gebreab et al., 2017). Similarly, observational studies show modest associations between telomere length and coronary artery calcification (Mwasongwe et al., 2017) and myocardial infarction (Weischer et al., 2012). A meta-analysis demonstrated an inverse association between LTL and coronary heart disease risk even after controlling for traditional risk factors (Haycock et al., 2014). Causality cannot be derived from observational studies; however, mounting genetic evidence is consistent with a causal association between telomere length and cardiovascular disease. For example, a
Several biochemical pathways have been hypothesized to be involved in the causal pathway between stress/environmental influences and telomere length. Specifically, life stress may chronically activate the autonomic or neuroendocrine systems, thereby promoting the formation of reactive oxygen species (Mason, 2017). Furthermore, fasting insulin may be a mediator between genetic factors and telomere length and cardiovascular disease risk, representing a portion of the causal pathway (Zhan et al., 2017).

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2. Methods

2.1. Study sample

The study population is from NHANES, a survey conducted by the Centers for Disease Control (CDC) that utilizes a complex survey design of stratified, multistage probability sampling to represent the noninstitutionalized U.S. population. In this study, NHANES years 1999–2000 and 2001–2002 were merged for analysis. Of the 9,882 adults between 20 and 85 years old, those who did not have a LTL measurement (n = 2,466) and those who reported “Other” or “Other Hispanic” race/ethnicity (n = 653) were excluded. Other race/ethnicity were excluded to reduce the potential impact of racial heterogeneity on LTL. Of the remaining 6,957 possible participants, 1851 were excluded due to missing ND1 and covariates, such as education (0.1%), marital status (4.8%), nativity (0.06%), poverty-to-income ratio (8.7%), smoking status (0.14%), healthy eating index (10.0%), physical activity (3.4%), BMI (2.5%), C-reactive protein (0.01%), and hypertension status (0.04%). The final analytic sample was 5,106.

Access to a restricted-use NHANES variable identifying participant census tract was required to merge NHANES public use files with neighborhood-level data from the U.S. Census Bureau. Therefore, a proposal was submitted to the National Center for Health Statistics (NCHS) and data files were accessed through the Research Data Center (RDC). Analysis of restricted data was approved by the NCHS Ethics Review Board. Data collection for NHANES was approved by the NCHS Research Ethics Review Board and all participants provided written informed consent. This study was exempted from human subjects review by the NIH Office for Human Subjects Research Protection. The conclusions in this paper are those of the authors and do not necessarily represent the views of the NIH, NCHS, RDC, or CDC.

2.2. LTL measurement

Detailed analytical methods for assaying LTL have been published elsewhere (Cawthon, 2002; Needham et al., 2015). The NCHS extracted DNA from whole blood and purified it using a Puregene kit protocol (Gentra Systems, Inc., Minneapolis MN). The DNA was assayed via polymerase chain reaction by the Blackburn lab at the University of California, San Francisco. The protocol measured the ratio of LTL (T) to standard (S) single-copy gene reference to derive a T/S ratio (Cawthon,
2.3. Neighborhood deprivation index

U.S. Census Bureau data was used to create a Neighborhood Deprivation Index (NDI) for each U.S. Census tract, as previously published (Diez Roux et al., 2004). Principal axis factoring was used to identify key variables for the NDI from the following categories: income, wealth, education, employment/occupation, and housing conditions (Diez Roux et al., 2010). Each variable was z-standardized prior to factor analysis and reverse coded as necessary. Oblique rotation was applied (minimum loading score 0.40; minimum eigenvalue 1). Cronbach’s alpha was used to measure the internal consistency of each factor (minimum alpha 0.70). The neighborhood variables that loaded into factors were log-transformed median household income, log-transformed median home value, % receiving welfare, % below the poverty level, % single mothers with children, % households without a telephone, % non-owner occupied units, % households not receiving dividends, interest, or rental income, % adults ≥25 years old without a high school diploma, % adults ≥25 years old without a Bachelor’s degree, and % working adults not in an executive, managerial, or professional occupation. The sum of these z-standardized neighborhood variables was used to calculate a summary NDI score where a higher score represented a more deprived neighborhood. A unique NDI was calculated for each U.S. census tract (n = 66, 143).

2.4. Covariates

Sociodemographic characteristics, health behaviors, and biomedical risk factors were included as they may confound or mediate the association between NDI and LTL. The self-reported sociodemographic characteristics were age (years), sex, race/ethnicity (Mexican American, Non-Hispanic Black, Non-Hispanic White), nativity (foreign born or US born), marital status (married/living with partner or never married/ separated/divorced/widowed), education (less than high school; high school graduate or graduate equivalency diploma (GED); some college/ associate degree; or college graduate or above), residential location (rural/small town or urban), and family poverty to income ratio (as defined by the U.S. Census Bureau (U. S. Census Bureau, 2007)). Smoking status was assessed as current, former, or never smoker. Physical activity was assessed using the U.S. physical activity guidelines (above or below the recommended 500 MET-minutes/week) (U.S. Department of Health and Human Services, 2008). Dietary quality was assessed based on the 2005 Healthy Eating Index (Guenther et al., 2006). Disease states that might affect LTL were also included (diabetes, hypertension, hyperlipidemia, obesity). These were defined by self-reported physician diagnosis, self-reported medical information, or measured clinical indicators (diabetes: HbA1c ≥ 7.0; hypertension: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg; hyperlipidemia: total cholesterol ≥ 240 mg/dL; obesity: BMI ≥ 30 kg/m²). C-reactive protein (mg/dL) was measured by high-sensitivity nephelometry at the University of Washington (Gebreab et al., 2017), and was examined as a log-transformed continuous variable. Leukocyte count (% white blood cells, % neutrophils, % lymphocytes, % monocytes, % eosinophils, and % basophils) was also included. Adjustment for cell composition was performed to account for potential confounding from infection-induced cell proliferation, as well as due to prior findings that changes in telomere length are influenced by naïve T-cell percentages and known correlations between constituents of cell composition relative to LTL (Lin et al., 2015; Rehkopf et al., 2016).

2.5. Statistical analysis

Weighted means and standard errors of continuous variables and weighted percentages of categorical variables were compared across NDI tertile using chi-squared analysis and univariate linear regression. Weighted, age-adjusted log-LTL geometric mean was evaluated across participant characteristics using univariate linear regression.

An intraclass correlation coefficient (ICC) was calculated from the intercept only model to evaluate the need for multilevel modeling due to the nested data structure (individuals within census tracts). The ICC was 29.6%, therefore sequential multilevel modeling was used to assess the relationship between NDI and log-LTL (Diez Roux et al., 2010). Modeling was performed sequentially in order to appreciate changes in the relationship between neighborhood deprivation and LTL after the addition of categories of covariates (i.e. socioeconomic status, cardiovascular risk factors, etc.) (Gebreab et al., 2017; Geronimus et al., 2015). Tertiles of NDI were used in the primary models to identify group-level effects that may not be seen with small changes in a continuous variable. Models were weighted using sample weights rescaled to the census tract level. Model 1 was unadjusted. Model 2 adjusted for demographic characteristics (age, age-squared, sex, race/ethnicity, marital status, nativity). Both continuous linear age and an age-squared term were used to account for potential non-linearity in the association between age and LTL (Needham et al., 2015; Rehkopf et al., 2016). Model 3 further adjusted for socioeconomic status (education, poverty to income ratio), and urban/rural classification. Model 4 further adjusted for traditional risk factors (smoking, diet, physical activity) and leukocyte count (white cell count, % neutrophils, % lymphocytes, % monocytes, % eosinophils, % basophils). Model 5 further adjusted for cardiovascular risk factors (BMI, hypertension, diabetes, hyperlipidemia). Model 6 further adjusted for c-reactive protein.

Some of the covariates are included in the models as confounders, as they are associated with both neighborhood deprivation and LTL (age, sex, race/ethnicity, education, nativity, marital status, residential location, income, smoking status, cardiovascular risk factors, C-reactive protein). Although other covariates may be better characterized as mediators (i.e. physical activity, diet) or moderators (i.e. sex, race/ethnicity), due to the limitations of cross-sectional data in mediation analysis, they were included in the models to reduce the number of potential unmeasured confounders. Sex and race interactions were also assessed. Sensitivity analyses were conducted using standard deviation units of continuous NDI and excluding those with a self-reported history of cardiovascular disease (stroke, myocardial infarction, heart failure, coronary artery disease, angina). A conversion from T/S ratio to base pairs was calculated using the formula 3,274 + 2,413*(T/S) to illustrate absolute change in LTL (Needham et al., 2015). Analyses were conducted using SAS survey procedures (SAS 9.4; SAS Institute Inc., Cary, NC) to account for complex sampling design.

3. Results

3.1. Descriptive statistics

Weighted descriptive statistics demonstrated that the study population (n = 5,106) was 49.8% female and consisted of 82.9% non-Hispanic whites, 9.4% non-Hispanic blacks, and 7.6% Mexican Americans. Mean age of the sample was 45.8 years. The NDI distribution ranged from 25 years old without a high school diploma, % adults ≥25 years old without a Bachelor’s degree, and % working adults not in an executive, managerial, or professional occupation. The sum of these z-standardized neighborhood variables was used to calculate a summary NDI score where a higher score represented a more deprived neighborhood. A unique NDI was calculated for each U.S. census tract (n = 66, 143).

Differences in age-adjusted geometric mean of LTL were observed across demographic characteristics (Table 2). Shorter age-adjusted LTL
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Table 1
Weighted baseline characteristics by tertile of neighborhood deprivation index, NHANES, 1999–2002.

| Baseline Characteristics | Low NDI | Medium NDI | High NDI | P-value |
|-------------------------|---------|------------|----------|---------|
| N (%)                   | 1596 (31.3) | 1714 (33.6) | 1796 (35.2) |        |
| NDI Range               | ~10.8 to 2.5 | 2.1 to 22.2 |        |        |
| Age (years), mean (SE)  | 47.2 (0.6) | 46.1 (0.5) | 42.6 (0.6) | <0.0001 |
| Sex, % (SE)             | 50.7 (0.7) | 49.5 (0.8) | 50.5 (0.8) | 0.70    |
| Race/ethnicity, % (SE)  |         |            |          | <0.0001 |
| Non-Hispanic blacks     | 3.4 (0.3) | 7.8 (0.4)  | 23.0 (0.8) |        |
| Non-Hispanic whites     | 93.9 (0.3) | 86.8 (0.5) | 56.6 (1.0) |        |
| Mexican Americans       | 2.7 (0.2) | 5.4 (0.3)  | 20.3 (0.8) |        |
| Education, % (SE)       | 8.5 (0.4) | 18.3 (0.6) | 35.7 (0.9) | <0.0001 |
| Less than high school   |         |            |          |        |
| High school/GED         | 1.1 (0.3) | 3.1 (0.7)  | 25.5 (0.9) |        |
| Some college/associate degree | 29.3 (0.7) | 30.2 (0.7) | 27.8 (0.9) |        |
| College degree or above | 40.8 (0.7) | 17.1 (0.6) | 10.9 (0.6) |        |
| Urban/Rural Classification, % (SE) | 97.4 (0.2) | 87.4 (0.5) | 88.7 (0.6) | 0.16    |
| Urban                   |         |            |          |        |
| Rural/Small Town        | 2.6 (0.2) | 12.6 (0.5) | 11.3 (0.6) |        |
| Poverty to Income Ratio, mean (SE) | 3.85 (0.06) | 2.96 (0.08) | 2.27 (0.08) | <0.0001 |
| Nativity, % (SE)        | 93.6 (0.4) | 93.0 (0.4) | 83.0 (0.7) | <0.0001 |
| US born                 | 6.4 (0.4) | 7.0 (0.4)  | 17.0 (0.7) |        |
| Marital status, % (SE)  |         |            |          | <0.0001 |
| Never married, separated, divorced, or widowed | 27.7 (0.7) | 30.5 (0.7) | 42.1 (1.0) |        |
| Married/Living with partner | 72.3 (0.7) | 69.5 (0.7) | 57.9 (1.0) |        |
| C-reactive Protein (mg/dL), mean (SE) | 0.27 (0.009) | 0.28 (0.008) | 0.30 (0.01) | <0.0001 |
| Physical Activity, % (SE) |         |            |          | <0.0001 |
| Below Recommendations <500 MET-mins/week | 44.5 (0.7) | 58.2 (0.8) | 62.9 (0.9) |        |
| Meeting Recommendations ≥500 MET-mins/week | 55.5 (0.7) | 41.8 (0.8) | 37.1 (0.9) |        |
| Dietary Intake, % (SE)  |         |            |          | <0.0001 |
| Poor (<50 HEI-2005)     | 44.1 (0.7) | 54.7 (0.8) | 58.5 (1.0) |        |
| Intermediate (50–80 HEI-2005) | 54.0 (0.7) | 44.0 (0.8) | 29.9 (1.0) |        |
| Ideal (≥81 HEI-2005)    | 1.9 (0.2) | 1.4 (0.2)  | 1.6 (0.2)  |        |
| Alcohol Consumption, % (SE) |         |            |          | <0.0001 |
| Never drinker           | 87.1 (0.5) | 78.9 (0.7) | 77.4 (1.0) |        |
| Current drinker         | 12.9 (0.5) | 21.1 (0.7) | 22.6 (1.0) |        |
| Tobacco Use, % (SE)     |         |            |          | <0.0001 |
| Never smoker            | 53.3 (0.7) | 49.5 (0.8) | 50.5 (1.0) |        |
| Former smoker           | 28.7 (0.6) | 25.0 (0.7) | 21.5 (0.8) |        |
| Current smoker          | 18.0 (0.6) | 25.5 (0.7) | 28.0 (0.9) |        |

Abbreviations: GED, General Education Development; GM, Geometric Mean; HEI, Healthy Eating Index; NHANES, National Health and Nutrition Examination Survey; SE, Standard Error.

was seen in individuals with older age (p < 0.0001), male sex (p = 0.04), Mexican origin (p = 0.01), lower educational attainment (p = 0.002), and those living in rural/small town areas (p = 0.02). Additionally, shorter age-adjusted LTL was found in individuals with lower levels of physical activity (p = 0.003), poor diet (p = 0.003), and alcohol consumption (p = 0.005). Finally, shorter age-adjusted LTL was also observed in those living in neighborhoods with higher NDI (p = 0.03).

3.2. Evaluating the relationship between NDI and Log-LTL.

Neighborhood deprivation was inversely associated with log-LTL among individuals living in neighborhoods with medium NDI (β = −0.040, SE = 0.013, p = 0.003) and high NDI (β = −0.030, SE = 0.013, p = 0.021) in the unadjusted model and across subsequent models (all p < 0.005) (Table 3). The association remained significant for both medium deprivation (β = −0.050, SE = 0.012, p < 0.0001) and high deprivation (β = −0.049, SE = 0.013, p < 0.0001) neighborhoods following adjustment for demographic characteristics. Slight attenuation in the effect was seen with adjustment for socioeconomic status and urban/rural classification, but the inverse relationship between NDI and log-LTL remained significant for both medium NDI (β = −0.045, SE = 0.012, p = 0.0003) and high NDI (β = −0.040, SE = 0.013, p = 0.002) neighborhoods. This persisted in the fully adjusted model (medium NDI: β = −0.043, SE = 0.012, p = 0.0005; high NDI: β = −0.039, SE = 0.013, p = 0.003). Holding the covariates constant, the differences in LTL for individuals living in a medium and a high deprivation neighborhood compared to those living in a low deprivation neighborhood correspond to 104 and 95 base pairs, respectively. Given that a one-year increase in age was associated with a 0.0052 decrease in T/S ratio (12.6 base pair) in our model, these differences are roughly equivalent to 8.3 and 7.5 additional years of aging for individuals living in a medium or high deprivation neighborhood, respectively, compared with those living in a low deprivation neighborhood of the same chronological age.

A significant sex interaction was observed, therefore the results were sex-stratified to further clarify the relationship (p-interaction = 0.054). The inverse association between NDI and log-LTL was not consistently observed (Table 4). Among men, in the fully adjusted model, neighborhood deprivation was associated with decreased log-LTL among residents of both medium deprivation (β = −0.045, SE = 0.014, p = 0.002) and high deprivation tertiles (β = −0.049, SE = 0.015, p = 0.001). These differences are roughly equivalent to 8.6 and 9.4 additional years of aging for men living in a medium or high deprivation neighborhood compared to those living in a low deprivation neighborhood, respectively. Among women, in the fully adjusted model, medium deprivation (β = −0.020, SE = 0.016, p = 0.009) and not high deprivation (β = −0.039, SE = 0.015, p = 0.212) was associated with decreased log-LTL. This represents approximately 7.5 additional years of aging for women living in a medium deprivation neighborhood.

Sensitivity analyses demonstrated consistent findings after excluding participants with self-reported cardiovascular disease (medium NDI: β = −0.038, SE = 0.013, p = 0.001; high NDI: β = −0.041, SE = 0.013, p = 0.004) (Supplemental Table 1). We repeated the analyses with NDI as a continuous measure and found that neighborhood deprivation was associated with decreased log-LTL in the fully-adjusted model using a continuous NDI (β = −0.006, SE = 0.002, p = 0.008) (Supplemental Table 1). No effect modification was observed by race (p-interaction = 0.310).
Table 2
Weighted age-adjusted geometric mean of leukocyte telomere length by participant characteristics, NHANES, 1999–2002.

| Characteristic                          | Geometric Mean | 95% CI          | P-value<sup>a</sup> |
|-----------------------------------------|----------------|-----------------|---------------------|
| Age (years)                             |                |                 |                     |
| 20 to 39                                | 1.13           | 1.09, 1.16      | <0.0001             |
| 30 to 59                                | 1.01           | 0.98, 1.05      | 0.04                |
| 60 or older                             | 0.88           | 0.86, 0.92      | 0.002               |
| Sex                                     |                |                 |                     |
| Men                                     | 0.99           | 0.96, 1.02      | 0.01                |
| Women                                   | 1.00           | 0.97, 1.03      |                     |
| Race/ethnicity                          |                |                 |                     |
| Non-Hispanic blacks                     | 1.04           | 1.00, 1.07      |                     |
| Non-Hispanic whites                     | 0.99           | 0.96, 1.03      | 0.02                |
| Mexican Americans                       | 0.96           | 0.92, 1.00      |                     |
| Education                               |                |                 |                     |
| Less than high school                   | 0.96           | 0.93, 0.99      |                     |
| High school/GED                         | 1.00           | 0.96, 1.04      |                     |
| Some college/associate degree           | 1.00           | 0.97, 1.03      |                     |
| College degree or above                 | 1.00           | 0.98, 1.03      |                     |
| Urban/Rural Classification              |                |                 |                     |
| Urban                                   | 1.00           | 0.97, 1.03      | 0.08                |
| Rural/Small Town                        | 0.94           | 0.89, 0.99      |                     |
| Poverty to Income Ratio                 |                |                 |                     |
| <1                                      | 0.99           | 0.96, 1.03      | 0.09                |
| 1 to 3                                  | 0.98           | 0.95, 1.01      |                     |
| >3                                      | 1.00           | 0.98, 1.04      |                     |
| Nativity                                |                |                 | 0.86                |
| United States born                      | 1.00           | 0.97, 1.03      |                     |
| Foreign born                            | 1.00           | 0.97, 1.03      |                     |
| Marital status                          |                |                 |                     |
| Married/living with partner             | 0.99           | 0.96, 1.02      | 0.03                |
| Never married, separated, divorced, or widowed | 1.00 | 0.98, 1.03 |                     |
| C-reactive Protein (mg/dL)<sup>b</sup>  |                |                 |                     |
| <0.1                                    | 1.02           | 0.99, 1.05      | 0.02                |
| 0.1 to 0.3                              | 1.00           | 0.97, 1.03      |                     |
| >0.3                                    | 0.98           | 0.95, 1.01      |                     |
| Physical Activity                       |                |                 |                     |
| Below Recommendations (<500 MET-mins/week) | 0.98 | 0.95, 1.01 | 0.003               |
| Meeting Recommendations (>500 MET-mins/week) | 1.01 | 0.98, 1.04 |                     |
| Dietary Intake                          |                |                 |                     |
| Poor (<50 HEI-2005)                     | 0.98           | 0.95, 1.01      | 0.003               |
| Intermediate (50–80 HEI-2005)           | 1.01           | 0.98, 1.03      |                     |
| Ideal (>81 HEI-2005)                    | 0.99           | 0.95, 1.04      |                     |
| Alcohol Consumption                     |                |                 |                     |
| Never drinker                           | 1.00           | 0.97, 1.03      | 0.005               |

Abbreviations: CI, Confidence Interval; GED, General Education Development; HEI, Healthy Eating Index; NHANES, National Health and Nutrition Examination Survey.

<sup>a</sup> P values from univariate linear regression. Boldface indicates statistical significance (p < 0.05).

<sup>b</sup> Data were natural log-transformed.

4. Discussion

The exact biologic mechanism by which social and physical environments impact human health is not known. Here we provide evidence that increased neighborhood deprivation is associated with shorter LTL, which is an important first finding to assess the role of telomere shortening in the mechanistic pathway between neighborhoods and health. Importantly, we demonstrate this relationship in a large, nationally representative sample after comprehensive adjustment for potential confounders.

The main study finding presented here is the inverse association between neighborhood deprivation and LTL. We found no changes in our model following adjustment for lifestyle factors, individual socioeconomic status, cardiovascular risk factors, and inflammation. This suggests that neighborhood deprivation may not act on LTL through pathways that have been previously implicated in telomere research. For example, inflammation has been heavily studied in the context of telomere dynamics (Park et al., 2015), but we saw no change after adjustment for c-reactive protein. Future analyses should consider investigating additional inflammatory pathways via biomarkers such as interleukin-6 and tissue necrosis factor alpha (Farzaneh-Far et al., 2010; Lopizzo et al., 2017; Zhang et al., 2016). The literature also highlights differences in telomere dynamics between men and women (Gardner et al., 2014). We observed a similar magnitude of effect for the relationship between neighborhood deprivation and LTL among men and women, with the exception of women in high NDI neighborhoods where the relationship became non-significant after adjustment for individual-level socioeconomic status. This may indicate a stress-resilience mechanism among women living in extreme socioeconomic disadvantage. Recent exploratory findings from a longitudinal study of chronic stress suggest that individual-level stressors may be more significant to telomere shortening among women, whereas neighborhood-level stressors may have a greater impact on telomere dynamics among men (Meier et al., 2019). The neuro-endocrine pathways that comprise the stress response are complex (Charney, 2004), but there is evidence for gender-specific stress responses (Bekhbat & Neigh, 2018), possibly due to a combination of the effects of estrogen (Bale & Epperson, 2015; Charney, 2004), differential recruitment of neural networks (Goldfarb, Seo, & Sinha, 2019), and social support (Ozbay et al., 2007). Women tend to report larger social networks with greater network ties for social support (Turner, 1994), which may have been marginally associated with improved self-rated health (Caetano, Silva, &
attributable to the larger, more nationally representative sample.Unless otherwise noted, all models were adjusted for demographic characteristics, socioeconomic status, urban/rural classification, and neighborhood quality in our study, as the data were not collected by NHANES. In

Unfortunately, we were unable to assess the effect of perceived neighbor
dehavioral resources such as education and employment. In our analysis, adjusting for both health behaviors and individual socioeconomic status

did not attenuate the relationship between NDI and LTL. Chronic stress, such as from a deprived neighborhood environment, has been hypoth

described vandalism and fear of crime as being significantly, indepen
dently associated with LTL, but not noise or objectively measured neighborhood population density. These findings suggest that specific elements within the neighborhood, such as perceived neighborhood social environment, may be additionally contributing to the relationship between neighborhoods and LTL. The hypothesis that perception may moderate the relationship between neighborhood socioeconomic deprivation and LTL is supported by prior literature on chronic stress (Diez Roux et al., 2004).

Vettore, 2013) and health outcomes (Freeborne et al., 2019; Uchino, Cacioppo, & Kiecolt-Glaser, 1996; Uphoff, Pickett, Cabieses, Small, & Wright, 2013). Recent findings have demonstrated that social support can buffer against negative mental health effects of neighborhood deprivation (Klijs, Mendes de Leon, Kibele, & Smidt, 2017) and that the buffering hypothesis is strongest for those experiencing the heaviest burden of stress exposure, including neighborhood disorder (Moskowitz, Vittinghoff, & Schmidt, 2013). However, the evidence on social support as a buffer against stress is mixed and may only be valid for acute, rather than chronic, stressors (Cropley & Steptoe, 2005; Gunnar & Hostinar, 2015). Further work is needed to fully elucidate the interaction between stress, gender, and social support in the context of neighborhood deprivation and health.

The present study examines the relationship between neighborhood deprivation and LTL in a nationally representative sample, which may provide insights not seen in typical community-based studies. For example, in a sample of participants from the Multi-Ethnic Study of Atherosclerosis, there was an association between poor neighborhood social environment and decreased LTL, but not overall neighborhood socioeconomic deprivation (Needham et al., 2014). In this study, Needham and colleagues estimated that one year of aging corresponds to a 0.005 decrease in $T/S$ ratio. Applying this to the difference in $T/S$ ratio between socially advantaged and disadvantaged participants, the authors reported 8 years of accelerated cellular aging attributable to poor neighborhood social environment. In contrast, our analysis of objective neighborhood deprivation did yield significant findings, which may be attributable to the larger, more nationally representative sample. Unfortunately, we were unable to assess the effect of perceived neighbor

dehavioral deprivation index and leukocyte telomere length, NHANES, 1999–2002 (n = 5106)\textsuperscript{a}.

Table 3
Association between neighborhood deprivation index and leukocyte telomere length, NHANES, 1999–2002 (n = 5106)\textsuperscript{a}.

| Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---------|---------|---------|---------|---------|---------|
| $\beta$ (SE) | $\beta$ (SE) | $\beta$ (SE) | $\beta$ (SE) | $\beta$ (SE) | $\beta$ (SE) |
| Low NDI (Ref) | -0.040 | -0.050 | -0.050 | -0.050 | -0.049 | -0.049 | -0.049 | -0.049 | -0.049 | -0.049 | -0.049 |
| NDI (0.013) | (0.012) | (0.012) | (0.012) | (0.012) | (0.012) | (0.012) | (0.012) | (0.012) | (0.012) | (0.012) | (0.012) |
| High NDI | -0.030 | -0.049 | -0.049 | -0.049 | -0.039 | -0.039 | -0.039 | -0.039 | -0.039 | -0.039 | -0.039 |
| (0.013) | (0.013) | (0.013) | (0.013) | (0.013) | (0.013) | (0.013) | (0.013) | (0.013) | (0.013) | (0.013) |

Abbreviations: NDI, Neighborhood Deprivation Index; NHANES, National Health and Nutrition Examination Survey; Ref, Referent; SE, Standard Error. Boldface indicates statistical significance ($p < 0.05$).

Note: Model 1 is unadjusted. Model 2 adjusts for demographic characteristics. Model 3 further adjusts for socioeconomic status and urban/rural classification. Model 4 further adjusts for leukocyte count and lifestyle factors. Model 5 further adjusts for cardiovascular risk factors. Finally, Model 6 further adjusts for C-reactive protein.

\textsuperscript{a} The estimates were adjusted for the complex survey MEC weights.

Table 4
Sex-stratified association between neighborhood deprivation index and leukocyte telomere length, NHANES, 1999–2002\textsuperscript{b}.

| Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|---------|---------|---------|---------|---------|---------|
| $\beta$ (SE) | $\beta$ (SE) | $\beta$ (SE) | $\beta$ (SE) | $\beta$ (SE) | $\beta$ (SE) |
| Women (N = 2421) | | | | | |
| Low NDI (Ref) | -0.036 | -0.047 | -0.047 | -0.047 | -0.033 | -0.033 | -0.033 | -0.033 | -0.033 | -0.033 | -0.033 |
| NDI (0.015) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) |
| High NDI | -0.013 | -0.034 | -0.034 | -0.034 | -0.025 | -0.025 | -0.025 | -0.025 | -0.025 | -0.025 | -0.025 |
| (0.015) | (0.015) | (0.015) | (0.015) | (0.015) | (0.015) | (0.015) | (0.015) | (0.015) | (0.015) | (0.015) | (0.015) |
| Men (N = 2671) | | | | | |
| Low NDI (Ref) | -0.042 | -0.052 | -0.052 | -0.052 | -0.046 | -0.046 | -0.046 | -0.046 | -0.046 | -0.046 | -0.046 |
| NDI (0.015) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) |
| High NDI | -0.047 | -0.058 | -0.058 | -0.058 | -0.048 | -0.048 | -0.048 | -0.048 | -0.048 | -0.048 | -0.048 |
| (0.015) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) | (0.014) |

Abbreviations: NDI, Neighborhood Deprivation Index; NHANES, National Health and Nutrition Examination Survey; Ref, Referent; SE, Standard Error. Boldface indicates statistical significance ($p < 0.05$).

Note: Model 1 is unadjusted. Model 2 adjusts for demographic characteristics. Model 3 further adjusts for socioeconomic status and urban/rural classification. Model 4 further adjusts for leukocyte count and lifestyle factors. Model 5 further adjusts for cardiovascular risk factors. Finally, Model 6 further adjusts for C-reactive protein.

\textsuperscript{b} The estimates were adjusted for the complex survey MEC weights.

a similar study of neighborhood perception and LTL, Park and col

leagues found that telomeres were 69 and 174 base pairs shorter in those who perceived living in moderate and poor quality neighborhoods, respectively, than those perceiving good quality neighborhoods (Park et al., 2015). This absolute difference was estimated to represent be
tween 8.7 and 11.9 years of accelerated cellular aging. The authors also described vandalism and fear of crime as being significantly, indepen
dently associated with LTL, but not noise or objectively measured neighborhood population density. These findings suggest that specific elements within the neighborhood, such as perceived neighborhood social environment, may be additionally contributing to the relationship between neighborhoods and LTL. The hypothesis that perception may moderate the relationship between neighborhood socioeconomic deprivation and LTL is supported by prior literature on chronic stress (Diez Roux et al., 2004).

Neighborhood socioeconomic deprivation may affect LTL through shaping health behaviors, access to social services, and broader envi
rornental resources such as education and employment. In our analysis, adjusting for both health behaviors and individual socioeconomic status did not attenuate the relationship between NDI and LTL. Chronic stress, such as from a deprived neighborhood environment, has been hypothe
sized to affect multiple physiologic systems via the hypothalamic-pituitary-adrenal axis and may in turn accelerate cellular degradation and telomere shortening (McEwen, 2017). For example, high levels of perceived stress and the chronicity of the stressor have been previously associated with decreased LTL in women (Epel et al., 2004). Epel and colleagues tentatively suggest a causal pathway between chronic stress and LTL, as high perceived stress was associated with telomere shortening and decreased telomerase activity. Poor neighborhood perception
represents one such chronic stressor and therefore may mediate the relationship between neighborhood environment and LTL (Ross & Mirowsky, 2009). This is supported by recent work demonstrating an association between chronic stress and telomere attrition over a 10-year period (Meier et al., 2019).

Prior population cohorts investigating the relationship between neighborhood deprivation and LTL have not specifically addressed the role of race/ethnicity as a modifier (Gebreab et al., 2016; Needham et al., 2014; Park et al., 2015) and thus cannot be directly compared to the findings found here. Racial discrimination and racial residential discrimination represent chronic stressors that may influence cellular aging. Recent evidence suggests an inverse relationship between discrimination and telomere length, depending on the definition and scope of discrimination employed (Chae et al., 2014, 2016; Lee, Kim, & Neblett, 2017; Liu & Kawachi, 2017). However, this effect may not hold constant across all urban environments. For example, within a Detroit-based sample, Geronimus and colleagues found that perceptions of neighborhood physical environment and neighborhood satisfaction were more strongly associated with LTL in African Americans than for other racial/ethnic groups (Geronimus et al., 2015). Overall, however, the results regarding discrimination and LTL were null in this study (Geronimus et al., 2015). Further work is needed to fully assess the role of discrimination as a form of chronic stress impacting the relationship between neighborhood deprivation and telomere length.

4.1. Strengths and limitations

The large, racial/ethnically diverse, nationally representative cohort improves the internal validity of our findings and may provide more generalizability than previous literature (Epel et al., 2004; Park et al., 2015). Despite this strength, the findings may not be generalizable to all populations (i.e. those under 20 years of age). Our models were strengthened by the adjustment for a more comprehensive list of potential confounders than prior studies. Our use of objective neighborhood socioeconomic status derived from Census data is comparable across future studies. For additional consistency, we used the same technique as Needham and colleagues (Needham et al., 2014) to estimate mean LTL shortening per year, despite variability in the literature (Lustig et al., 2017; Müeazzinler, Zaineddin, & Brenner, 2013).

However, we acknowledge several limitations. We elected to exclude participants who were missing data for key covariates, which may have introduced bias in the sample if they were not missing at random. Although multiple imputation may address some of the concerns with missing data, a recent study on cardiovascular biomarkers and LTL using NHANES data found a stable sample after conducting extensive imputation for missing covariates (Rehkopf et al., 2016). Additionally, the study was cross-sectional and not able to make causal inferences or evaluate the impact on health outcomes or mortality. Future studies linking NHANES data to the National Death Index would address this limitation. Although we adjust for c-reactive protein, we recognize that this alone is not sufficient as a biomarker of oxidative stress. Additional biomarkers are likely needed to fully capture the effect of inflammation. Unmeasured confounders, such as early childhood experiences or the demands of caregiving, may have influenced the results, as these forms of stress have been shown to be associated with shortened telomeres and impaired immune function (Damjanovic et al., 2007; Kiecolt-Glaser et al., 2011). Further work is needed to understand the relationship between these stressors and telomere length in the context of neighborhood environment. Finally, knowing the length of time a participant had resided in their neighborhood would have enabled evaluation of a dose-response of environmental exposure on LTL.

5. Conclusions

After controlling for individual characteristics, increasing neighborhood socioeconomic deprivation is associated with shorter LTL, among a nationally representative sample of U.S. adults. Compared to individuals living in areas with lower NDI, the mean LTL of those living in high deprivation neighborhoods is approximately 95 base pairs shorter. This degree of shortening is commensurate with 7.5 years of accelerated cellular aging and suggests that telomere shortening may be a biomarker for neighborhood deprivation and mediator of poor health outcomes and increased mortality.

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Ethics statement

Analysis of restricted data was approved by the NCHS Ethics Review Board. Data collection for NHANES was approved by the NCHS Research Ethics Review Board and all participants provided written informed consent. This study was exempted from human subjects review by the NIH Office for Human Subjects Research Protection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2019.100517.

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