



Neighborhood disorder and telomeres: Connecting children's exposure to community level stress and cellular response

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ABSTRACT

Our objective was to explore the utility of salivary telomere length (sTL) as an early indicator of neighborhood-level social environmental risk during child development. We therefore tested the hypothesis that sTL would be associated with markers of social stress exposure in children. Children age 4–14 from 87 neighborhoods were recruited through five urban schools in New Orleans, Louisiana, U.S. Data were collected at the level of the child, family/household, and neighborhood. DNA was obtained from saliva using commercially available kits and sTL was determined for 104 children using quantitative PCR. Analysis was performed on 99 children who had complete data including sTL, social environmental stress, and additional covariates. The mean sTL value was 7.4 T/S (telomere signal/single-copy signal) ratio units (± 2.4 , range = 2.5–18.0), and 4.7% of the variance in sTL was attributed to differences across neighborhoods. Children living in neighborhoods characterized by high disorder had an sTL value 3.2 units lower than children not living in high disordered environments ($p < 0.05$) and their odds of having low relative sTL (defined as < 1 standard deviation below standardized Z-score mean) values was 3.43 times that of children not living in high disorder environments (adjusted OR = 3.43, 95% CI = 1.22, 9.62). Our findings are consistent with previous studies in adults demonstrating a strong link between psychosocial stress and sTL obtained from peripheral blood, consistent with previous studies in youth demonstrating an association between early life stress and sTL obtained from buccal cell DNA and offer increased support for the hypothesis that sTL represents a non-invasive biological indicator of psychosocial stress exposure (i.e., neighborhood disorder) able to reflect differences in stress exposure levels even in young children.

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Introduction

The American Academy of Pediatrics recently emphasized the need to increase the understanding of the early roots of health disparities. They proposed the incorporation of an eco-biodevelopmental (EBD) framework that underscores the need to identify the biological indicators of exposure to early adversity, track these indicators across development, and use these indicators to unravel the underlying mechanisms, improve health outcomes, and minimize health disparities (Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood Adoption and Dependent Care, Section on Developmental and Behavioral Pediatrics, & American Academy of Pediatrics, 2012). This extension of the

allostasis framework, and other more recent models, including the adaptive calibration model, together with the need to define the biological changes associated with potentially “toxic” early life stress requires the development of novel biomarkers that: reflect salient environments (Essex et al., 2011), are sensitive to changes across developmental time points (Buss, Davis, & Kiel, 2011), validated in individuals of all ages including young children, and, ideally, obtainable via non-invasive methods (Bush, Obradovic, Adler, & Boyce, 2011; Buss et al., 2011; Essex et al., 2011).

Telomeres represent one novel biomarker as they are (a) responsive to environmental changes and stressors, (b) have diverse effects in different organ systems, and (c) may be integral in the process by which an individual is able to calibrate their physiologic response to their social and physical environments (Lupien et al., 2006; Skinner, Shirtcliff, Haggerty, Coe, & Catalano, 2011). These are critical criteria for measures of the stress response system

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(Del Giudice, Ellis, & Shirtcliff, 2011) and indices of allostasis (McEwen, 2006). Allostasis is a model of physiologic regulation, whereby the goal of regulation is not constancy but fitness and change under natural selection to ensure regulation as opposed to an alternate model—homeostasis—where preserving constant conditions is the goal. Telomeres are specialized nucleoprotein complexes located at the termini of chromosomes that prevent genomic instability and ensure complete chromosomal replication. Telomere size normally decreases with cellular replication. Once a critically short length is reached cellular senescence is triggered. However, telomeres are dynamic structures and additional processes can result in more rapid changes in both their length and distribution (Li & Lustig, 1996). Accelerated loss of telomere length from DNA extracted from whole blood (leukocyte TL, LTL) has been associated with multiple negative health outcomes across the lifespan, including cardiovascular disease, dementia, diabetes, and cognitive decline (Fitzpatrick et al., 2007; Martin-Ruiz et al., 2006). Environmental factors that have been associated with alterations of LTL include cigarette smoking (Valdes et al., 2005), radiation (Derradji et al., 2008), oxidative stress (Bull & Fenech, 2008; Zglinicki, 2002), and, most recently, psychological stress exposure, including a history of early maltreatment, mood disorders, perceived stress, and stress related to high intensity care-giving (Kananen et al., 2010; Lung, Chen, & Shu, 2007; Sapolsky, 2004; Simon et al., 2006; Tyrka et al., 2009). Hypothalamic–pituitary axis (HPA) dysregulation and oxidative stress have also been associated with damage to telomere DNA and decrease TL (Choi, Fauce, & Effros, 2008; Sapolsky, 2004).

Previously, we have shown an association between cumulative exposure to early severe social deprivation as a result of institutional rearing and TL in children derived from buccal epithelial cells (Drury et al., 2011). Additionally, cross-sectional and longitudinal work by others has linked other measures of exposures to altered TL, specifically socioeconomic conditions and violence exposure (Hastings et al., 2011; Needham, Fernandez, Lin, Epel, & Blackburn, 2012; Shalev et al., 2012). While most studies have utilized DNA from whole blood, which contain predominately a mixed cell population of lymphocytes, previous studies in children have also utilized buccal epithelial cells. Saliva contains both lymphocytes and buccal epithelial cells, and thus has similarities, and differences, to both of the previously utilized sources of DNA in telomere studies. Although significant future research remains to be done examining the correlation between TL obtained from peripheral and tissue samples the establishment of TL measured from non-invasive sources as a feasible biological indicator of cumulative stress exposure, applicable even in young children (Drury et al., 2011; Kroenke et al., 2011), would significantly advance the field. Accelerated TL loss, and potentially other alterations in telomere dynamics triggered by cellular stress pathways, may link early adversity to life-long poor health outcomes (Adams & White, 2004; Geronimus, Hicken, & Keene, 2006).

Together these previous studies offer significant evidence supporting the hypothesis that TL reflects exposure at the individual level. However, no previous study has examined whether TL is associated with neighborhood risk above and beyond household and individual exposure risk. Although environmental conditions such as physical and psychosocial stress are believed to play an important role in producing and maintaining health disparities (Lee, 2002; Yen & Syme, 1999), differential exposure to negative environmental conditions among many low socioeconomic and minority populations may accentuate the negative impact (LaVeist & Wallace, 2000; Massey, 2001). Lower neighborhood socioeconomic position in the U.S. has been associated with significantly greater allostatic load (i.e., the cumulative wear-and-tear on physiological processes due to recurrent or chronic stress (McEwen,

1998)), independent of individual-level socioeconomic status (SES) (Bird et al., 2010; King, Morenoff, & House, 2011), with the strongest association observed among African Americans (Merkin et al., 2009). Stemming in part from disparities in neighborhood-level factors (Lupien et al., 2006), African Americans have been found to have more dysregulation in the hypothalamic–pituitary axis (HPA) compared to Whites (Chong, Uhart, McCaul, Johnson, & Wand, 2008; Skinner et al., 2011). Although most studies to date have focused primarily on neighborhood SES and similar constructs like socioeconomic position (SEP), additional distinct neighborhood conditions such as neighborhood social and physical disorder (Sampson & Morenoff, 2004) such as lawlessness, crime, abandoned buildings, would be predicted to further impact an individual's stress response system and may be one pathway through which SEP at the community level “gets under the skin”. Neighborhood disorder is distinct from SEP and may represent indicators of neighborhood disinvestment that are beyond the control of the individual and may be one consequence of lower SEP in a neighborhood (Sampson & Morenoff, 2004). Furthermore, we examine both objective and subjective neighborhood environments and subjective disorder, in particular. Research has demonstrated a discrepancy between observed indicators of neighborhood environments and residents' perceptions or self-reports of those environments (Caughy, O'Campo, & Patterson, 2001; Lin & Moudon, 2010; Sampson & Raudenbush, 2004) and there is evidence to suggest that perceptions of neighborhood environments are shaped by both observed characteristics (e.g., observed neighborhood conditions) as well as subjective experiences associated with race, ethnicity and SEP (Krysan, 2002; Krysan & Farley, 2002; Sampson & Raudenbush, 2004).

We previously have demonstrated the impact of the cumulative neighborhood environmental risk, above and beyond household level exposures, on allostatic load among adolescents in the U.S. (Theall, Drury, & Shirtcliff, *in press*). To provide increased support for sTL as a biological indicator of stress exposure, defined at the level of the individual, household and community, we sought to connect these programs of research by testing the hypothesis that sTL represents a proximate biological indicator of adverse neighborhood conditions in a group of African-American children in the U.S. This would be the first study, to date, associating a cellular marker of stress exposure and aging with community level factors.

Materials and methods

Subjects

Children (one per household) and their families were recruited via active consent from January–May 2010 through five local public elementary and middle schools in an urban community in New Orleans, Louisiana as part of a larger study to examine neighborhood influences on childhood health disparities (Fig. 1, highlighted area). 87 Different residential census tracts were represented. A total of 199 children, ages 4–14 years, were enrolled; sTL was available for 104 African-American children, whose parents consented to saliva sampling, and 99 children were included in final modeling once all covariates were considered. Children without sTL data, or with incomplete data, did not differ significantly ($p > 0.05$) from children included in the final analysis on any measures. Data about the child were collected from parental caregivers about multiple levels of his/her social ecology (i.e., household and neighborhood).

This study was approved by the Tulane and Louisiana State University Institutional Review Boards. Written informed consent was obtained from caregivers and assent for children over age eight.

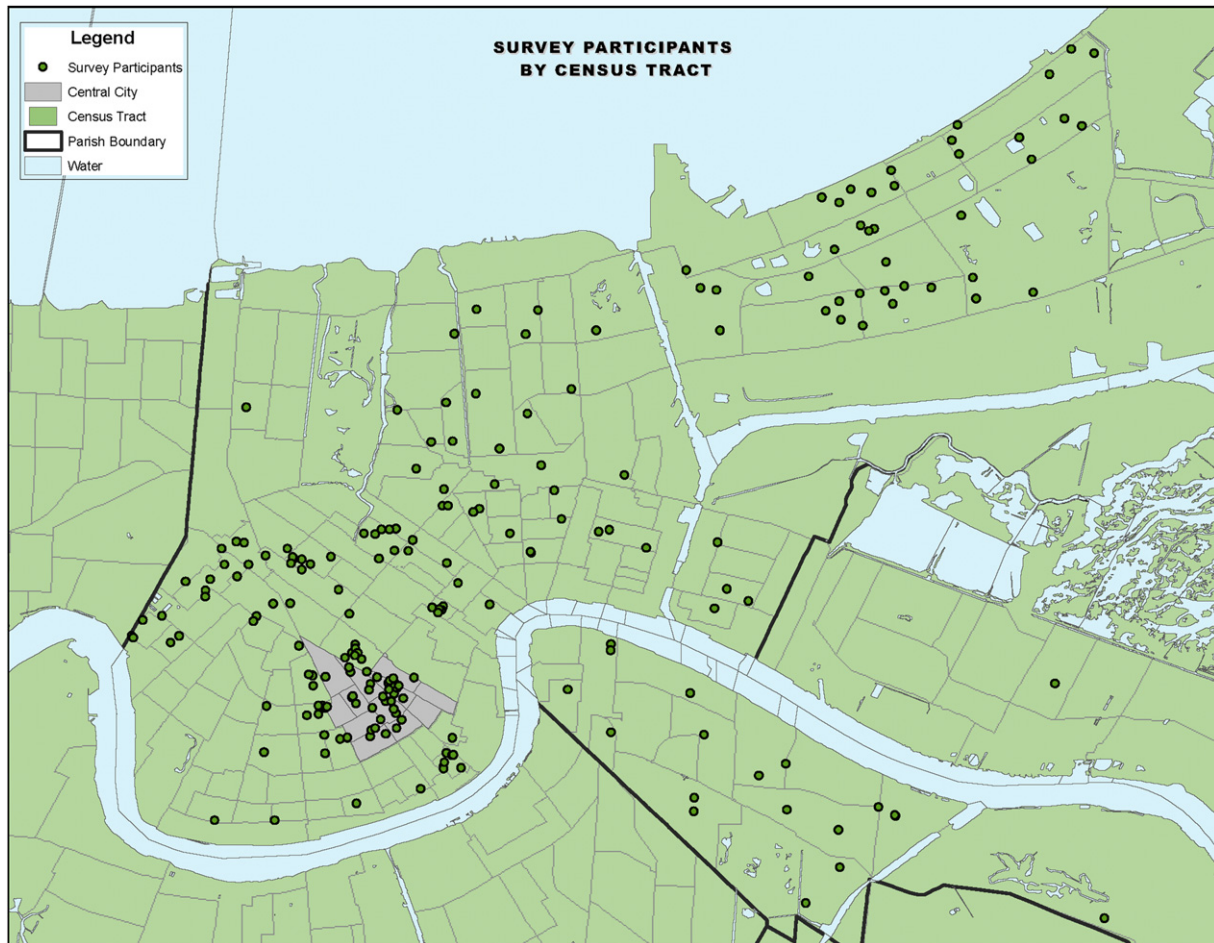


Fig. 1. Complete sample respondents geocoded, City of New Orleans.

Cumulative stress exposure

A caregiver survey assessing numerous factors, including socio-demographics and perception of neighborhood conditions was sent home with the child and returned to the school. The child's residential address was utilized for geocoding.

A multilevel data system of children nested within their neighborhood environments was created. Neighborhood-level data were generated using the geographic identifiers for each child. For all measures, neighborhood was defined as a U.S. census tract—a small, relatively permanent statistical subdivisions of a county, with a typical population size between 2500 and 8000 persons and relatively homogeneous with respect to population characteristics, economic status, and living conditions. Additional sources of neighborhood data included the 2000 U.S. Census, geographic data from ArcGIS and the U.S. Census.

Three well-established standardized indicators of neighborhood adversity were examined as key environmental exposures: (1) economic deprivation, (2) percentage of the population below the U.S. poverty line, and (3) individual-level marker of perceived neighborhood disorder. The first two exposures came from the neighborhood data described above.

Economic deprivation was measured using a Z-score standardized index of concentrated disadvantage (Sampson & Morenoff, 2004) measuring economic disadvantage in racially segregated urban neighborhoods. This value is defined by the percentage of families who are a) below the poverty line,

b) receiving public assistance c) unemployed in the civilian labor force, d) female-headed with children, and e) African-American residents (Cronbach's alpha in this sample = 0.85). These five measures were combined into a *concentrated neighborhood disadvantage* measure by summarizing Z-scores across the variables.

Perceived neighborhood disorder (Sampson & Morenoff, 2004) was calculated as a summary score of caregiver report of the presence or absence of seven items surrounding the child's home, 1) garbage, litter, or broken glass, 2) graffiti, 3) vacant, abandoned, or boarded-up buildings, 4) abandoned vehicles, 5) broken steps, 6) broken glass or broken toys, and 7) the presence of strewn garbage/litter immediately outside the child's home. The number of high-risk markers was summed to create a cumulative neighborhood disorder value, which ranged from 0 to 5 in this sample. High disorder in the external environment around the home was defined based on the distribution as having four or more of these indicators.

Covariates included sociodemographic characteristics including, sex, age, the number of children in the household, household receipt of public assistance, years living in the neighborhood, and a marker of the socioeconomic position (SEP) of the household. SEP was based on a modified Four Factor Hollingshead Index of Social Status (Hollingshead, 1975) taking into account maternal and paternal education, employment, and household income. SEP score ranged from 11 to 49 in this sample, with higher values indicating higher socioeconomic position.

Telomere length

Saliva was collected from children by the study staff at the school using Oragene[®] Salivary kits. Subjects spit approximately 2 ml of saliva into a plastic container. Once saliva collection was complete, the containers were sealed, releasing the Oragene[®] DNA stabilizing agent that limits DNA degradation and bacterial growth. Saliva samples were then frozen until DNA was extracted following the manufacturer's recommendations. DNA was then ethanol precipitated and resuspended in water. A portion of the DNA was visualized on a 0.8% agarose gel to ensure intact DNA for PCR analysis. sTL values were determined using repeat copy number to single gene copy number (T/S) ratio after quantitative real-time polymerase chain reaction (qPCR) (Cawthon, 2002). Briefly, 5 ng of genomic DNA was dried down in a 384-well plate and resuspended in 10 μ L of either the telomere or 36B4 PCR reaction mixture. The telomere reaction mixture consisted of 1x Qiagen Quantitect Sybr Green Master Mix, 2.5 mM of DTT, 270 nM of Tel-1 primer (GGTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT), and 900 nM of Tel-2 primer (TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA). The reaction proceeded for 1 cycle at 95 °C for 5 min, followed by 40 cycles at 95 °C for 15 s, and incubation at 54 °C for 2 min. The 36B4, single-copy gene, reaction consisted of 1x Qiagen Quantitect Sybr Green Master Mix, 300 nM of 36B4U primer (CAGCAAGTGGGAAGGTGTAATCC), and 500 nM of 36B4D primer (CCCATTCTATCATCAACGGGTACAA). The 36B4 reaction proceeded for 1 cycle at 95 °C for 5 min, followed by 40 cycles at 95 °C for 15 s, and the mix incubated at 58 °C for 70 s. All samples for both the telomere and single-copy gene reactions were performed in triplicate on different plates in the same well positions. Inter-plate coefficients of variations for the Ct (cycle threshold) values were below 1% for both the telomere and single-copy gene reactions, indicating consistent amplification between replicate plates. In addition to the samples, each 384-well plate contained a six-point standard curve from 0.625 ng to 20 ng of genomic DNA. The exponentiated T/S ratio ($-dCt$) for each sample was calculated by subtracting the average 36B4 Ct value from the average telomere Ct value and expressed as $2^{-(-dCt)}$. sTL values were calculated as the ratio of telomere repeats to single-copy gene values (T/S ratio). sTL values were examined as both a continuous variable (the T/S ratio) and a standardized Z-score of the T/S ratio to account for the wide variance of T/S ratios. Different classifications of sTL were utilized given the lack of a standard definition of low or high telomere length. As a consequence, the sTL of each child was measured relative to the average of the sTL values of all children within the complete sample using a Z-score. Additionally, sTL values were classified as a dichotomous variable where low sTL values were defined at ≤ 1 standard deviation below the standardized mean score (≤ -1) compared to those who were equivalent or above the mean sTL score (> -1).

Statistical analysis

Multivariate analyses were based on a sample of 99 children with data on sTL and all covariates, from 52 census tracts, with a range of 1–8 children per tract. Univariate, bivariate, and multivariate analyses were performed using SAS version 9.2, including PROC MIXED and GLIMMIX for two-level hierarchical models with children nested within census tract. Such models allow for partitioning variance estimates at all levels (Merlo et al., 2006; Snijders & Boskers, 1999), expressed as the intraclass correlation coefficient (ICC), thereby accounting for variance in individual-level outcomes that can be attributed to differences between neighborhoods. To examine clustering in sTL based on unconditional means models, we utilized the traditional ICC calculation. When

sTL was examined as a dichotomous outcome (low vs. standardized mean or higher), the pseudo-ICC was calculated following Snijders formula based on an underlying continuous variable with $V_{\text{individual}} = I^2/3$ (Snijders & Boskers, 1999). Because the pseudo-ICC for non-linear models may not be appropriate in all analyses, we also calculated the median odds ratio (MOR); this parameter is interpreted as the median value of the odds ratio between a neighborhood at high versus low risk, thus indicating the increased or decreased risk associated with a high-risk area (Merlo et al., 2006). Modeling was performed in the following steps: (1) examination of empty models, in which there were no predictors, to determine the extent of clustering of sTL values by neighborhood (Model A), (2) testing the unadjusted associations between each of the three neighborhood risk exposures and sTL (not shown), and (3) testing the adjusted association, after accounting for covariates, between those neighborhood characteristics significantly associated with sTL in bivariate analyses (Models B, C and D).

Results

Respondent characteristics are presented in Table 1. Most children in this sample (70.2%) were under the age of 10 and 52.9% were female. Most of the children's mothers (80.0%) were not married or cohabitating and 26.5% had more than high school education. Someone in the household was on public assistance for 56.8% of families. SEP score was low (18.8, range 11–49). Children lived at their current address for an average of 2.9 years (SD = 2.7); thus, most had ongoing or cumulative exposure to their neighborhood environments. The relative sTL value was 7.4 (± 2.4 , range = 2.5–18.0), with 62% classified as having low sTL.

Study children resided in disadvantaged neighborhoods. Across all neighborhoods where children resided, the average percent of residents living below the poverty line was 33% and the average percent of female as head of household was 43%. The average percent of residents with more than a high school education was 26.5%. The mean level of neighborhood concentrated disadvantage was 2.1 (range = -5.0 to 15.0). With respect to caregiver perceptions, 36.1% of caregivers reported four or more markers of perceived disorder in the neighborhood environment immediately surrounding the child's home.

Table 2 presents the results of models estimating the effect of neighborhood adversity on the dichotomous measure of sTL (low vs. standardized mean or higher). Results of Model A (the empty model without any predictors) demonstrated that 7.61% of the variance in low sTL could be attributed to differences across neighborhoods. The MOR of 1.69 suggests that residing in a low (compared to high) concentrated adversity neighborhood was associated with almost a doubling of risk for low sTL values. These ICC findings suggest that a large amount of variance in sTL that may be explained by neighborhood-level factors.

To examine neighborhood-level factors associated with low sTL values we examined the separate impact of key neighborhood adversity measures that demonstrated a significant association with sTL in the unadjusted models. These results are presented in Models B–D of Table 2. After accounting for child sex, and age, household SEP, and years living in the neighborhood, children living in neighborhoods characterized by high perceived disorder were more than three times as likely to have low sTL values compared to children not living in high disordered neighborhoods (adjusted OR = 3.43, 95% CI = 1.22, 9.62). When treating sTL as a standardized Z-score, we observed a similar effect of perceived disorder ($\beta = -0.478$, s.d. = 0.184, $p < 0.05$). A similar finding was also observed for the continuous measure of sTL ($\beta = -1.280$, s.d. = 0.492, $p < 0.05$).

Table 1
Sample characteristics ($N = 104$).

Children's characteristics	
Age	
4–6	48.1%
7–9	22.1%
10–14	29.8%
Gender	
Male	47.1%
Female	52.9%
Salivary telomere length structure (\pm s.d.), range = 2.5–18.0	7.4 (2.4)
Low telomere length (<0 on Z-score)	62.0%
Household characteristics	
Mother's marital status	
Not married or not cohabiting	80.0%
Married or cohabiting	20.0%
Mother's education	
Less than high school	24.5%
High school (or GED)	49.0%
More than high school (e.g., vocational school, some college, college degree)	26.5%
Number of children in the household	
1–2	71.3%
3+	28.7%
Anyone in household on public assistance	
No	43.2%
Yes	56.8%
Average years living in neighborhood (\pm s.d.), range = 0–11	2.9 (2.7)
Average socioeconomic position (SEP) score (\pm s.d.), range = 11–49	18.8 (6.3)
Neighborhood characteristics	
Average perceived neighborhood disorder (\pm s.d.), range = 0–5	3.1 (1.3)
High disorder (4 or more markers of disorder)	36.1%
Average concentrated disadvantage (\pm s.d.), range = –5.0 to 15.0	2.1 (3.3)
Average percent of population with female as head of household (\pm s.d.), range = 5.4–88.6	43.2 (23.6)
Average percent of population with at least a college education (\pm s.d.), range = 0–55.5	14.2 (12.0)
Average percent of population below U.S. federal poverty line (\pm s.d.), range = 3.9–85.2	33.6 (21.7)

Note. Values based on non-missing data.

As shown in Model C of Table 2, after controlling for age, sex, household SEP, and years living in the neighborhood, concentrated neighborhood disadvantage was no longer significantly associated with low sTL values (unadjusted OR = 1.13; adjusted OR = 1.10, 95% CI = 0.95, 1.28). The association between percentage of the population in the neighborhood below poverty and low sTL remained even after accounting for SEP and other covariates (Model D, Table 2), with each one-unit increase in the percentage of residents in a neighborhood living below the U.S. poverty line being associated with a 2% increased odds of having low sTL values (adjusted OR = 1.02, 95% CI = 1.01, 1.04). When treating sTL as a standardized Z-score, we observed a similar effect of percent below poverty ($\beta = -0.010$, s.d. = 0.004, $p < 0.05$), as well as for the continuous measure of sTL ($\beta = -0.020$, s.d. = 0.012, $p < 0.10$), where increased poverty was associated with lower sTL.

While a proportion of the neighborhood-level variance in sTL was explained by the addition of both individual household and neighborhood factors, as indicated by a change in ICC and MOR estimates, the fact that a substantial amount of the neighborhood-level variance in sTL remained unexplained suggests that additional factors or the non-binomial distribution of telomere sizes (affecting sTL values) may be contributing to the variation.

Discussion

This study is the first to demonstrate that neighborhood-level disorder and poverty are associated with lower sTL values in children. Specifically high rates of community level disorder, poverty, and disadvantage were significantly associated with lower sTL in children. Although previous studies have linked lower sTL with individual stress exposures, our results are the first to demonstrate this association with factors at the community level. These results suggest that future studies exploring the impact of stress on the developing child ought to assess exposure at multiple levels and include a broader range of indicators that extend beyond exposure to individual events or household level factors. These results are also consistent with our previous study of TL in children exposed to institutional care where greater exposure to institutionalization at two earlier time points was significantly associated with lower TL in middle childhood (Drury et al., 2011) as well as our previous study of the association between sTL and exposure to prenatal smoking (Theall, McKasson, Mabile, Dunaway, & Drury, in press).

Table 2
Neighborhood adversity's impact on lower telomere length^a: results of hierarchical logistic regression models ($N = 52$ tracts, $N = 99$ children).

Variables	Model A	Model B	Model C	Model D
	Empty model	High disorder	Concentrated disadvantage	Percent below poverty
Adjusted odds ratio (95% confidence interval)				
Individual-level variables				
Female		1.22 (0.46, 3.20)	1.09 (0.44, 2.67)	1.12 (0.47, 2.69)
Age (years)		1.00 (0.83, 1.22)	1.03 (0.86, 1.23)	1.02 (0.85, 1.21)
Household SEP score (range = 11–49)		0.91 (0.82, 1.01)	0.91 (0.82, 1.01)	0.88 (0.77, 0.99)*
Years lived in neighborhood		1.09 (0.89, 1.32)	1.11 (0.90, 1.36)	1.11 (0.90, 1.36)
Neighborhood-level variables				
High perceived disorder		3.43 (1.22, 9.62)*	–	–
Concentrated disadvantage		–	1.10 (0.95, 1.28)	–
Percent below poverty		–	–	1.02 (1.01, 1.04)*
Random effects				
Neighborhood ICC ^b	7.61%	5.51%	7.57%	5.79%
Neighborhood median odds ratio (MOR) ^b	1.69	1.52	1.64	1.53

*Note. p -Value < 0.05.

^a Low telomere structure defined as 1 standard deviation below the mean of standardized Z-score. Results similar with linear models and telomere structure as continuous average score.

^b ICC = intraclass correlation coefficient (with individual-level variance calculated using the formula of Snijders based on an underlying continuous variable with $V_{\text{student}} = \Pi^2/3$ (Snijders & Boskers, 1999)). Because of limitations of the ICC for non-linear outcomes, the median odds ratio (MOR) (Merlo et al., 2006) was also calculated.

Our results compliment a series of studies in youth which link parental SEP (Needham et al., 2012), violence exposure in early childhood (Shalev et al., 2012) and obesity (Buxton et al., 2011) with alterations in telomere structure and extend the growing literature that links early adversity and stress to accelerated TL decline in adulthood (Kananen et al., 2010; Lung et al., 2007; Simon et al., 2006; Tyrka et al., 2009). Kroenke et al. (2011) found in a cross-sectional analysis high physiologic stress reactivity and elevated internalizing symptoms were associated with decreased TL values in community recruited children age 5–6. In the most recent longitudinal study, Shalev and colleagues demonstrated that violence exposure was associated with a rapid decrease in TL values, between 5 and 10 years of age (Shalev et al., 2012). In these two studies, TL values were derived from DNA extracted from buccal swabs. Additional studies, using DNA from whole blood, demonstrated altered LTL in youth in association with obesity in a case-control study (Buxton et al., 2011), physical activity in a cross-sectional study (Zhu et al., 2011), and parental education in a cross-sectional study (Needham et al., 2012). Thus our results are consistent with TL measured from alternative peripheral sources of DNA in youths and adults.

Of the adverse neighborhood conditions evaluated in this study, perceived neighborhood disorder immediately surrounding the child's home had the strongest association with sTL. Similar measures of physical and social neighborhood disorder, commonly referred to as “broken windows”, have previously been associated with negative health outcomes, including physical activity and dysregulated cortisol levels among children (Dulin-Keita, Casazza, Fernandez, Goran, & Gower, 2012; Molnar, Gortmaker, Bull, & Buka, 2004). SEP in childhood has been shown to have a greater impact on whole genome methylation compared to adult SEP, thus suggesting that that earlier experiences may have a greater lasting impact than exposure in adulthood (Borghol et al., 2011). Our SEP association, however, was positive so that higher family SEP was associated with lower telomere length. The evidence for the relationship between adult SEP and telomere length is mixed, with some studies have reported a positive association between low SEP and shorter telomeres (Cherkas et al., 2008; Needham et al., 2012), others a negative effect (Parks et al., 2011; Woo, Suen, Leung, Tang, & Ebrahim, 2009), while others null associations (Adams et al., 2007; Epel et al., 2004; Geronimus et al., 2010). Additionally, many studies find a hybrid of both positive and null associations depending on the SEP marker utilized (Batty et al., 2009; Cherkas et al., 2006; Shiels et al., 2011; Steptoe et al., 2011). There are various potential reasons for the observed associations.

First, socio-cultural contexts influence the varying meanings of SES or SEP measures for different populations (Robertson et al., 2012) so that, even if well measured, the use of general SES or SEP indicators, such as household income and education, could mask particular dimensions of SEP that are most related to stress and the health impacts of stress (Dowd, Simanek, & Aiello, 2009). Previous research has indicated that SES measures of income and education may be stronger among whites compared to African Americans (Karlman et al., 2005; Kraus, Borhani, & Franti, 1980; Seeman et al., 2008; Watkins, Neaton, & Kuller, 1986). Therefore, measures that reflect minority status and its associations with discrimination and disadvantage may provide a more appropriate reflection of the SEP-telomere relationship in children compared to general markers of SEP. Responses to racial discrimination may vary by SEP in the degree of socialization parents impart on the child and may be protective in neighborhoods characterized by high levels of disorder (Caughy, O'Campo, & Muntaner, 2004). Additionally, the SEP measures utilized in this study may have resulted in a ‘cohort effect’, in which parental SEP measures may not have accurately reflected SEP stress for children. Utilizing measures that captures

SES at specific points of the life course will provide a better metric in understanding the relationship between physiological functioning and socioeconomic status in children.

Nonetheless, our results also dovetail an emerging literature that links early adversity or psychosocial stress with shortened TL in adults (Entringer et al., 2011; Kananen et al., 2010; Simon et al., 2006; Theall, Drury, et al., in press; Tyrka et al., 2009). We illustrate that the process of cellular aging, and putatively the impact of early adversity on underlying biological processes, may not be limited to adulthood. Instead our findings suggest that these changes may begin much earlier in development. These results indicate that sTL may represent a biological indicator of stress exposure able to reflect exposure earlier in development than traditional markers of allostatic load (Danese & McEwen, 2012; Lupien et al., 2006). While allostatic load is measurable in young adult populations (Bahreinian et al., 2012; Theall, Drury, & Shirtcliff, 2012) these measures have decreased reliability in childhood given that many of the traditional biomarkers and cut-points used to defined ‘risk’ or ‘biological risk’ are not validated for children (Lupien et al., 2006). Recent work on allostatic load in children has begun to focus instead on primary allostatic mediators of the stress response system (Blair, Raver, Granger, Mills-Koonce, & Hibel, 2011; Bush et al., 2011; El-Sheikh & Hinnant, 2011; Hastings et al., 2011; Johnson, Bruce, Tarullo, & Gunnar, 2011) or uniquely constructed risk indices with putatively more applicability for younger populations (Buss et al., 2011; Evans, 2003; Evans, Kim, Ting, Teshler, & Shannis, 2007; Rogosch, Dackis, & Cicchetti, 2011; Worthman & Panter-Brick, 2008). These measures focus on the process whereby environmental stressors “get under the skin” but are not necessarily direct health and disease conditions apparent in childhood.

Allostatic load and its associated biomarkers are promising as measures of the wear-and-tear of environmental stressors on child development. A potentially more parsimonious theoretical perspective, however, the Adaptive Calibration Model (ACM) emphasizes that even seemingly detrimental outcomes, i.e. shortened sTL or heightened reactivity of the HPA axis, may have both costs and benefits (Del Giudice et al., 2011). Similar to allostatic load, the ACM postulates that environmental forces affect stress responsive systems; it diverges in its emphasis that these changes which prepare the individual for the environment that they're in, for better and for worse (Ellis, Del Giudice, & Shirtcliff, 2012). When an environment is difficult or challenging, physiological adjustments allow the individual adapt to this context even if those adjustments are not desirable to society, the family, or the individual. These necessary tradeoffs of adaptation may be present with sTL insofar as telomere shortening is not desirable for long-term health and aging. Nonetheless accelerated telomere shortening may be adaptive in that accelerating cellular senescence, increased apoptosis, and cellular differentiation, particularly oligodendrocyte differentiation, may speed up particular aspects of development and perhaps establishing a phenotype appropriate to the current environment.

Although most interventions to decrease health disparities and the lasting biological impact of early stress exposure focus on individual factors, our findings suggest that modifiable factors at the neighborhood level, specifically neighborhood disorder and neighborhood poverty, are viable targets for prevention effort focused on reducing the lasting impact of stress exposure in children's health outcomes (Committee on Psychosocial Aspects of Child and Family Health et al., 2012; Goodman, McEwen, Huang, Dolan, & Adler, 2005). As current efforts have failed to achieve the desired reduction in the impact of these stressors, consideration of novel approaches targeting neighborhood-level disorder are warranted.

Despite important findings, there are several limitations to the current study. First, this is a cross-sectional study of disadvantaged African-American children and thus the relevance to other demographics needs to be explored. Second, the absence of parental DNA precludes the examination of the independent impact of genetic factors on sTL. Third, we only have limited retrospective prenatal and perinatal data limiting our ability to disentangle current and past stress exposure. Fourth we did not detect a significant relation between telomere length and child age at the time of DNA collection in this sample. The exclusion of children in our study under four years, when rapid telomere length shortening may occur, could limit our ability to detect age-related differences (Rufert et al., 1999). Only one study to date, with a somewhat larger sample size, has examined telomere length longitudinally in this age range (Shalev et al., 2012) and detected age-related differences between age 5 and 10. Interestingly, in their sample a proportion of children demonstrated telomere length *lengthening* between the two time points. Studies have hypothesized that there is a stabilization of telomere length decline in late childhood that is maintained until the 3rd or 4th decade of life, after which the expected aging related decline is observed across studies. Failing to observe an association between telomere length and age in the present study could be due to this stabilization of telomere length in middle childhood, lack of very young children in our sample, inadequate sample size, or ethnic differences in STL change. Fifth, the observed effects could be due to endogenous or structural factors associated with a non-random selection of neighborhoods. Our neighborhood definition is based on administrative census tract boundaries, but may not truly represent a child's neighborhood with respect to opportunities for social interaction, developing meaningful relationships, and experiencing both stressors and stress buffers throughout the many neighborhoods and contexts in which the child exists. Furthermore, our choice of neighborhood economic indicators may be weak markers of the neighborhood environment, dependent on the SEP of individuals living the neighborhood and a potential proxy for other environmental exposures (Diez Roux, 2004; Oakes & Rossi, 2003).

Finally, there are limitations to our measure of telomere length structure. Our current study is the first study, to our knowledge, that utilizes DNA extracted from saliva samples. Bacterial contamination and DNA degradation are potential confounders in any studies of telomere length structure, and may pose a particular problem for saliva samples. Oragene saliva kits contain a DNA stabilizing agent expected to decrease bacterial growth and stabilize DNA and further evaluation of DNA integrity by gel electrophoresis did not indicate significant degradation. However, future studies should pay careful attention to DNA extraction, storage and the level of bacterial contamination that may be present in samples collected non-invasively. As we did not have a biological marker of bacterial content in saliva we examined whether a proximal marker of oral bacterial content, oral health, would influence our results. Controlling for measures of oral health in this sample did not alter the significance our results. PCR-based methodologies measure the telomere structure across all cell types present in the original sample. Replication of our findings in other studies using saliva as the source of DNA is needed as well as comparative studies of telomere length measured in buccal epithelial cells, saliva and peripheral blood. Future studies examining longitudinal differences in TL across sample types, and using multiple measurements of telomere structure, such as Southern blotting, Quantitative fluorescence *in situ* hybridization (Q-FISH), and single telomere length analysis (STELA) are needed to clarify the relation between TL from different peripheral DNA sources and determine the optimal peripheral source of DNA for TL analysis (Lukens, Van Deerlin, Clark, Xie, & Johnson, 2009).

We are currently correlating measures of salivary and buccal telomere length in two additional studies, including one that is a follow-up of the children included in the present study. The paired correlation between buccal and saliva telomere length in this follow-up sample is 0.997 ($p < 0.001$) and between saliva and peripheral blood in another cohort of children is 0.96 ($p < 0.001$). Approximately 80% of the cells in saliva are lymphocytes and 20% of the cells are buccal epithelial cells. While the correlation between salivary TL and future disease and mortality has not previously been demonstrated, both leukocyte and buccal cell TL have been associated with aging and age-related diseases, inflammatory processes, regeneration, diabetes mellitus, coronary artery disease, and ulcerative colitis (Aubert & Lansdorp, 2008; Wong & Collins, 2003). Our initial findings regarding correlation between buccal TL and salivary TL and between blood and salivary TL provide the basis for the potential links but without the evidence that salivary TL is associated with future disease and mortality, this remains an assumption.

Our results support the hypothesis that neighborhoods are critical arenas in which a child's stress response system develops and that neighborhood risks may culminate in a range of biologically-mediated negative health outcomes. Results indicate that the impact of adverse community level factors is measurable at the cellular level, even in young children. Studies should incorporate prenatal exposures and ideally measure TL at birth and longitudinally. The failure to meet the goals of Healthy People 2010 indicates that novel approaches and efforts are needed to enhance the long-term health outcomes of our youth. Our findings suggest interventions and preventions should be targeted as early as possible in development if we expect to alter the lasting impact of early adversity and eliminate health disparities.

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List of abbreviations

AL	allostatic load
sTL	salivary telomere length
Ct	cycle threshold
DNA	deoxyribonucleic acid
DTT	dithiothreitol
EBD	eco-biodevelopmental
HPA	hypothalamic–pituitary axis
ICC	intra-class correlation coefficient
PCR	polymerase chain reaction
T/S	relative telomere to single-copy gene ratio
TIGER	Topologically Integrated Geographic Encoding and Referencing (database)
MOR	Median odds ratio
NCAIS	North American Industry Classification System
SAS	Statistical Analysis System (software)
SEP	socioeconomic position
SIC	standard industrial classification

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