Title

Place and Biological Aging: Hierarchical Analyses of Neighborhood Changes and Leukocyte Telomere Length Malleability

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Place and Biological Aging: Hierarchical Analyses of Neighborhood Changes and Leukocyte Telomere Length Malleability

by

Rashida Brown

A dissertation submitted in partial satisfaction of the

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of the

University of California, Berkeley

Committee in charge:

Professor Mahasin S. Mujahid, Chair
Professor Nicholas P. Jewell
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Abstract

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Background

Understanding why certain population subgroups age faster than others is a pressing public health concern. Few biomarkers consistently predict morbidity and mortality, which has made it difficult to identify high-risk population subgroups earlier in the disease cascade. Telomeres are the repeat sequence at the ends of DNA that protect the cell from damage during each replicative cycle. Telomeres shorten with age, and individual-level exposures may exacerbate telomere length attrition. There is evidence that telomere length has an inverse association with psychosocial stress, poor health behaviors, and chronic diseases. However, multilevel determinants of telomere length remain understudied despite numerous connections among physical and mental health, lifestyle, and place of residence. The extant literature exhibits that better physical and social contexts have a positive association with telomere length.

Methods

This dissertation examines the associations among specific features of residential built, social, and socioeconomic environments and the 10-year change in telomere length using data from the Multi-Ethnic Study of Atherosclerosis (2000-2010). Chapter 2 presents cross-sectional findings on the relationship between the physical environment and leukocyte telomere length. Chapter 3 investigates the association between changes in physical environment features and the 10-year change in leukocyte telomere length. Chapter 4 explores the interplay among changes in neighborhood socioeconomic status, social context, and leukocyte telomere length. Physical environment features comprise of the physical activity and food environment. The social environment includes measures of aesthetic quality, safety, and social cohesion.

Significance

This dissertation presents the first studies to examine changes in neighborhood features and change in telomere length. The findings suggest that telomere length is a biological marker that is sensitive to changes in built, social, and socioeconomic contexts. Thus, health policy interventions should target specific features of the residential environment to support healthy aging trajectories.

Dedication

To my son, Andrew Brown-Peynado Jr., my husband, Andrew Peynado, my parents, Dotty Brown and Dr. Dean Brown, and my grandmother, Menita Parchment. Thank you for your endless inspiration and support.

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Acknowledgments

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Chapter 1 Introduction

1.1 Background information

As the year-over-year growth of mid- to older-aged adults continues to outpace other age groups, it is becoming increasingly important to understand how to slow the onset of morbidity and premature mortality. Subclinical indicators of premature aging may be the key to identifying those at the highest level of risk. Telomere length is a metric of aging at the cellular level. Telomeres shorten with increasing age, and the rate at which telomere length attrition occurs can indicate underlying biological dysfunction. In particular, leukocyte telomere length provides valuable information about immune cell health. Higher levels of psychosocial stress, poor health behaviors, and chronic diseases have an inverse association with telomere length. Despite the influence of neighborhood exposures on health, multilevel determinants of cell aging remain understudied in the literature. Supportive built, social, and socioeconomic environments can limit exposure to stressful life circumstances, facilitate healthy lifestyle choices, and reduce chronic disease risk. Thus, this dissertation refines the understanding of multilevel predictors of immune cell aging by examining specific neighborhood features and their changes over time. This research uncovers policy-relevant nodes of intervention that could improve the aging experience by slowing telomere length attrition over time.

Immune cell aging dynamics

Cell aging is an inevitable phenomenon in somatic eukaryotic cells (cells other than the sperm and egg). However, differential life exposures or genetic predispositions may cause accelerated cell aging and result in some individuals aging faster than others. The role of chronic psychological stress in mental health disorders, metabolic function, cardiovascular disease, and cognitive decline is well documented (1). Chronic psychological stress, defined as the way in which the mind handles repeated challenges (2, 3), may arise from a myriad of perceived or objective threats (4). Cell aging, which is sensitive to stress, may be accelerated by exposure to adverse contextual factors and poor health behaviors. Telomeres are the repeat sequences at the ends of chromosomes that serve as protective caps; they shorten during each replicative phase, and shorter telomere length is a sign of aging. Short leukocyte telomere length (LTL) is associated with higher psychosocial stress (5, 6), higher body mass index (7), systolic and diastolic blood pressures (8), use of statin drugs for cholesterol or blood pressure (9), LDL and HDL cholesterol (10), inflammatory markers (IL-6 and TNF-α) (11), smoking (12-16), consumption of processed meats and other diets (16-19), low moderate/vigorous physical activity (14, 16, 20-25), and morbidity (e.g., coronary artery calcification, cardiovascular disease, and obesity) (26-28). Telomerase activity and expression of telomerase-regulating genes such as TERT and TERC maintain LTL. Repeated stress exposure is related to accelerated shortening and senescence (5, 6). Concomitantly, these processes are hypothesized to increase susceptibility to apoptosis (i.e., programmed cell death) and age-related diseases.

The theories of allostatic load and allostasis describe the damage induced by repeated activation of hormonal responses to stressors and a subsequent blunted response that inhibits an individual's ability to maintain homeostasis adequately (2-4). Many indices of allostatic load exist. In general, the summary measure combines various biological markers that cover physiological systems such as neuroendocrine, immune, cardiovascular, anthropometric, and metabolic. This measure of multisystem dysregulation, resulting from inadequate hormonal dynamics, is also associated with immune cell function. Using a laboratory stress test, one study of older adults found that men with short telomeres and high telomerase activity exhibited a blunted physiological responses; however, there were no differences among women (29). Another study of female caregivers for partners with dementia and matched controls found that a heightened cortisol response to an acute laboratory stressor had an association with shorter telomeres (30). Overall, the process of allostasis exhibits the transduction of acute stressful circumstances to cell aging mechanisms.

This dissertation examines how the socioeconomic, social, and physical features of neighborhoods are related to leukocyte telomere length using both cross-sectional and longitudinal analyses. The overarching hypothesis is that those who experience positive changes in access to built and social environment resources have less telomere shortening over 10 years. Conversely, accelerated telomere shortening would be the consequence of living in adverse neighborhood circumstances. Access to resources for physical activity and healthy food outlets were examined in detail to assess alternative mechanisms that may influence immune cell aging.

Neighborhoods and telomere length

Several studies demonstrated that features of the residential areas in which people live, commonly referred to as neighborhoods, are associated with mental health outcomes (31-33), health behaviors (34-36), the risk of chronic conditions (37-41), and mortality (42-44). In the United States, some urban neighborhoods have extensive and systematic racial/ ethnic and socioeconomic segregation. Over time, shifting macroeconomic forces and systematic disinvestment have compromised the viability of certain metropolitan areas, leading to challenging physical and social circumstances. Coping with crime, disorder, lack of natural spaces, and poor aesthetic quality within one's neighborhood environment may serve as a source of chronic life stressors with biological consequences for those who are less resilient and unable to adapt effectively. There is growing cross-sectional evidence indicating that chronic exposure to unfavorable neighborhood circumstances has an association with short telomere length. However, insights on the change in exposure to neighborhood context may provide a more meaningful assessment of the relationship between residential areas and biological aging.

Empirical evidence to support the role of neighborhood-level influences on LTL is nascent. In one cross-sectional study, poor neighborhood social environment (as measured by a composite of aesthetic quality, safety, and social cohesion), but not neighborhood socioeconomic status had a negative association with telomere length (45). Theall *et al*. were also unable to find a statistically significant association between neighborhood socioeconomic disadvantage and telomere length (46). In another cross-sectional study that used a convenience sample of African American children, residents of highly disordered areas were three times as likely to have lower salivary TL, but there was no statistically significant association between neighborhood disadvantage and lower salivary TL levels (46). General measures of the social environment had an association with telomere length. Park *et al*. conducted a study in the Netherlands and found that poor perceived neighborhood quality (measured by fear of crime and vandalism, and noise) had an association with short telomere length (47). Similarly, Gebreab, *et al*. reported that an unfavorable neighborhood perception had an association with shorter telomeres (48). However, there was no association between perceived physical environment and telomere length (49). In a cross-sectional study, Geronimous and colleagues found that a lack of neighborhood satisfaction ("I would move out of this neighborhood if I could") had an inverse relationship with shorter telomere length (49). Physical environment characteristics, such as a higher density of liquor stores (50), higher population density (51), and more urban crowding (51) are independently associated with short telomere length. Higher levels of neighborhood disorder (46), violent crime (50), and perceived problems (48) exhibited consistent, inverse associations with telomere length. Overall, the extant literature suggests that living in adverse neighborhood physical and social circumstances is related to shorter telomere length.

The analyses of this dissertation extend prior research by exploring whether moving modified the associations among changes in neighborhood indicators and change in telomere length. This assessment of effect modification by moving status helps to elucidate issues related to the chronicity of residential exposures and reversibility of aging trajectories. In addition, tests of specific features of the built (walking environment, physical activity resources, access to healthy foods) and social (aesthetic quality, safety, and social cohesion) account for individual-level characteristics and neighborhood socioeconomic status. Finally, empirical models that additionally adjust for diet and exercise elucidate competing hypotheses that suggest the areas in which people live shape healthy lifestyle choices.

Gaps in the literature

Neighborhood exposures are important upstream indicators of life experiences that have significant implications for aging trajectories. The body of literature on place and telomere length only includes cross-sectional designs and general measures of physical and social contexts. As a result, it remains unclear how a change in a particular neighborhood features impact telomere length dynamics. Furthermore, a single observation cannot provide information about how the acute change in context due to moving could benefit telomere length maintenance. Residential areas are not homogeneous; thus, accounting for structural confounding from disparities in neighborhood socioeconomic status could help to estimate unbiased measures of association. Finally, no study directly examined how the availability or perceptions of physical activity resources or food environments, important features that shape positive health behaviors, are related to telomere length. This dissertation helps to quell some of the pain points in this area of research by using two time points of data and exploring competing hypotheses related to lifestyle choices and socioeconomic heterogeneity in built and social contexts.

1.2 Specific aims

The overall objective of this dissertation is to investigate whether features of the neighborhood built, social, and socioeconomic environments are associated with leukocyte telomere length, using both cross-sectional and change-versus-change analyses. The central hypothesis is that exposure to better neighborhood environments or improvement in neighborhood conditions is related to longer telomere length at baseline and less telomere shortening over 10 years. The specific aims that each chapter addresses are:

> ***Chapter 2*** Unexpected trends in leukocyte telomere length by physical activity and food environments
> To examine (1) if independent measures of neighborhood physical activity and food environments are associated with telomere length, independent of sociodemographic confounders; and (2) if accounting for neighborhood socioeconomic status, diet, and exercise attenuate these associations.
>
> > *Hypothesis*: Subjects who live in neighborhoods with better physical environment features will have longer telomeres than those in adverse circumstances. Adjusting for neighborhood socioeconomic status, diet, or exercise will not attenuate the measures of association.
>
> ***Chapter 3*** Changes in availability and perceptions of physical activity and healthy food resources may slow leukocyte telomere length attrition
> To evaluate (1) if changes in GIS- and survey-based measures of the walking environment, availability of physical activity resources, and food environment are associated with the change in telomere length after 10 years, independent of sociodemographic confounders; (2) if accounting for change in neighborhood socioeconomic status, diet, and exercise will attenuate these associations; and (3) if the associations among changes in physical activity resources, food environments, and telomere length differ by moving status.
>
> > *Hypothesis*: Persons who live in neighborhoods with positive built environment changes experience less telomere length shortening after ten years compared to those who live in neighborhoods with unfavorable built environment changes. Adjusting for neighborhood socioeconomic status, diet, or exercise will not attenuate the measures of association. These associations will differ by moving status and movers experience even less telomere shortening than those who remain in the same neighborhood context.
>
> ***Chapter 4*** Change in leukocyte telomere length is related to changes in neighborhood safety and socioeconomic status
> To investigate (1) if changes in neighborhood socioeconomic status are associated with the change in leukocyte telomere length, independent of sociodemographic confounders; (2) if changes in survey-based reports of neighborhood aesthetic quality, safety, and social cohesion are related to the 10-year change in leukocyte telomere length, independent of sociodemographic confounders and change in neighborhood socioeconomic status; and (3) if these associations differ by moving status.
>
> > *Hypothesis*: Individuals who live in neighborhoods that experience improvements in socioeconomic composition, safety, aesthetic quality, and social cohesion

should have a smaller 10-year decline in leukocyte telomere length compared to those who live in neighborhoods that decline in socioeconomic status and perceptions of the social environment. Adjusting for change in neighborhood socioeconomic status will not attenuate the measures of association. These associations will differ by moving status and movers experience even less telomere shortening than those who remain in the same neighborhood context.

Chapter 2 Unexpected trends in leukocyte telomere length by physical activity and food environments

2.1 Background

It has become increasingly important to understand why certain people age faster than others. According to the 2015 American Community Survey 5-Year Estimates, the proportion of the United States' population 65 years and over was 14.1%, and this age group has grown more rapidly than others. More research is needed to identify reliable indicators of aging to reduce the burden of disease and premature mortality successfully. Unfortunately, there are numerous challenges in identifying biomarkers of aging, but studies of telomere length continue to gain attention. Telomeres are the repeat sequences at the ends of DNA that serve as a protective cap. Telomeres shorten with each replicative cycle, and the cell enters a state of senescence or apoptosis once it reaches a critically short phase. The cell type and site where telomeres are measured also provide information about underlying biological perturbations and vulnerability to age-related diseases (52, 53). When measured in leukocytes, telomere length provides insight on immune system health. Furthermore, leukocyte telomere length (LTL) is a biomarker that is relevant to public health because sample collection is easy, the measurement technique is scalable, and the measure is associated with numerous risk factors for morbidity. A number of lifestyle factors and health conditions exhibit an association with short telomere length, such as increased stress (5, 6), higher body mass index (7), systolic and diastolic blood pressures (8), use of statin drugs for cholesterol or blood pressure (9), LDL and HDL cholesterol (10), inflammatory markers (IL-6 and TNF-α) (11), smoking (12-16), consumption of processed meats and other diets (16-19), low moderate/vigorous physical activity (14, 16, 20-25), and morbidity (e.g., coronary artery calcification, cardiovascular disease, and obesity) (26-28). However, it is unclear how multi-level determinants of health predict biological aging.

Exposure to certain neighborhood features may accelerate or slow telomere shortening. Features of the built infrastructure such as walking environment, resources for active living, and favorable food stores may promote or discourage positive health behaviors such as physical activity and healthy dietary choices. In addition, living in a neighborhood with inadequate physical environment resources may serve as a source of chronic life stress. Thus, access to physical activity resources and healthy food stores are indicators that provide a tangible and relatable point of reference to the neighborhoods and telomere length debate. Only a few studies were available to support the connection between residential areas and telomere length, and many focused on social environment features and neighborhood socioeconomic status (see Table 2.1) (45-51). In one study, living in a community with a higher density of liquor stores (50) was associated with shorter telomere length, an indicator of increased biological age. In another study, population density (51) and more urban crowding (51) were also associated with shorter telomeres. However, Geronimous and colleagues did not find a statistically significant association between perceived neighborhood physical environment attributes and telomere length (49). These studies highlighted that the mechanisms through which neighborhood circumstances impact biological aging are complex and require further investigation.

This study sought to determine whether neighborhood physical activity and food environments were associated with telomere length, independent of individual-level sociodemographic factors. Additional models also included neighborhood socioeconomic status and lifestyle factors (diet and exercise) to evaluate competing hypotheses. The primary hypothesis was that persons who were exposed to more physical activity resources and had more opportunities to procure healthy food would have longer leukocyte telomere length compared to those living in adverse physical environments. These analyses leveraged multiple measurement strategies such as densities derived from GIS estimates and survey-based respondent reports to validate the research findings.

2.2 Methods

Study Sample

The Multi-Ethnic Study of Atherosclerosis (MESA) (N=6,814) is a cohort of adults aged 45-84 who were followed for 10 years using five exams, spaced two years apart (54). The study's objective was to examine the risk factors of subclinical cardiovascular disease among subjects who were asymptomatic at baseline. The sample comprised of Asian, non-Hispanic Black, Hispanic, and non-Hispanic White participants recruited from New York, New York; Los Angeles, California; and Baltimore, Maryland. A random subsample of non-Hispanic White, non-Hispanic Black, and Hispanic MESA participants from the New York, Los Angeles, and Baltimore sites were selected to participate in the MESA Stress Study. Stored blood samples from MESA Exam 1 (July 2000-August 2002) of the ancillary study were used to assess telomere length. Non-Hispanic Asian participants were not selected to participate due to small sample size. This cross-sectional study included data from 1,295 respondents who also participated in the MESA Neighborhood ancillary study. However, only 1,095 of these subjects had diet information. Twenty-four percent of the eligible sample was missing data from at least one study variable (see Figure 2.1). The final analytic sample used complete case analysis and included 835 individuals. Missing data were not imputed.

Study Outcome: Leukocyte Telomere Length

Quantitative polymerase chain reaction (PCR) was used to assay telomere length in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco, as described in detail elsewhere (55, 56). Briefly, telomere length (T/S) was the ratio of the number of repeats in the sample compared to a standard reference with a known number of copies of the repeated sequence (56). The protocol outlines that there were six observations per sample because the aliquots were assayed three different times using duplicate wells in a process repeated for three days using duplicate wells (55, 56). The largest or the smallest T/S value in the set (whichever deviated most from the mean) was a potential outlier and removed before calculating the mean. If the absolute value of the log of the ratio between the recalculated mean (excluding the potential outlier) to the value of the potential outlier was greater than .4, then the value was marked as an outlier (99.8% of all samples contained no outliers). DNA samples were coded, and the lab used blinding to ensure that other measurements in the study did not influence the telomere assay or vice versa. The interassay coefficient of variation was 2.9%. Telomere length was a continuous variable with an approximately normal distribution and a mean of 0.92 (SD=0.20, range=0.49 – 1.67). The lowest tertile of the telomere length (T/S) distribution in the analytic sample was used as a cut point to illustrate *short* telomere length (T/S_{low} = .80).

Study Exposures: Neighborhood Physical Environment

Measures of the neighborhood physical environment included survey-based items and densities of (a) physical activity resources and (b) food environments (see Table 2.2). Each domain included one survey-based item, one Geographic Information System-based (GIS) item, and one composite item. In total, six previously validated (36, 57-60) physical environment measures were evaluated using separate models: walking environment, density of physical activity resources, physical activity environment composite, availability of healthy foods, density of favorable food stores, and food environment composite. All survey-based measures used respondent perceptions of the 1-mile radius surrounding the home, and the final neighborhood-level indicators were census tract-level aggregates of individual-level responses. The GIS-based measures represented densities for the census tract. Information about specific types of recreation facilities and food environments were purchased using the National Establishments Time Series (NETS) data. Conditional empirical Bayes estimates were used to account for census tracts with small sample sizes or poor agreement among residents of the same area (58). Briefly, this method allows unreliable census tracts to borrow information from adjacent areas to improve the estimate. All physical environment measures were continuous items. Higher values indicated better physical environments. The regression models used grand mean centered neighborhood variables (i.e., mean subtracted from each response) and the model coefficients were standardized to one standard deviation unit. Subsequent analyses also used tertiles of each neighborhood measure. There was moderate to high correlation among neighborhood physical environment variables (Pearson correlation range: .42 to .94; see Figure 2.3). Correlation among physical activity environment features was strong; however, the correlation between the survey- and GIS-based measures of the food environment was moderate (Pearson correlation = .42; see Figure 2.3).

(a) Physical activity resources: The physical activity environment was characterized using the walking environment (survey-based) and availability recreational facilities (GIS-based). Respondent-reported ratings of individual perceptions of the walking environment included six items measured on a five-point Likert scale based on previous work (58). The walking environment measure evaluated items such as opportunities to be physically active, aesthetic quality, and overall walkability. This measure was not measure of walkability; it was instead a measure of the physical activity that happens in the neighborhood environment. The availability of locations that promoted walking such as post offices, drug stores and pharmacies, banks, food stores, coffee shops, and restaurants came from lists used in prior work (59) were used to assess the walking environment. Recreational facilities were selected to represent the recreational and physical activity establishments such as indoor conditioning, dance, bowling, golf, team and racquet sports, and water activities derived from lists used in previous studies (36, 57). The composite score for the physical activity environment was the sum of the standardized conditional empirical Bayes survey- and kernel density GIS-based measures.

(b) Food Environment: The food environment was characterized using the availability of both healthy foods (survey-based) and favorable food stores (GIS-based). Respondent-reported ratings of the food environment included two items measured on a five-point Likert scale (60): (1) “A large selection of fresh fruits and vegetables is available in my neighborhood”; and (2) “A large variety of low-fat products is available in my neighborhood”. Food stores were identified using Standard Industrial Classification (SIC) codes that identified supermarkets, grocery stores, fruit and vegetable markets, convenience stores, bakeries, fast food establishments, health food stores, alcoholic drinking places, and liquor stores. The composite score was the sum of the standardized conditional empirical Bayes survey- and kernel density GIS-based measures.

Additional Study Covariates

Neighborhood Socioeconomic Status: Neighborhood socioeconomic status used data from the 2000 US Census. Variables were selected for the construction of a factor-based score as described by Diez Roux *et al*. (61). Six variables representing wealth and income (log of median household income, log of median value of housing units, and percent of households with interest, dividend, or net rental income), education (percent of adults 25 years and older with at least a high school degree and percent of adults 25 years and older with at least a Bachelor's degree), and occupation (percent of employed persons 16 and older in executive, managerial, or professional occupations) were standardized and summed together to create the score (61). An increasing score indicated more socioeconomic advantage. Neighborhood socioeconomic status was a continuous item that was grand mean centered (i.e., mean subtracted from each response) for the regression models. Bivariate analyses and regression models used tertiles of neighborhood socioeconomic status. All built environment features had an orthogonal relationship with neighborhood socioeconomic status (Pearson correlation range: -.13 to .33; see Figure 2.4). Food environment indicators exhibited negative to weak positive correlation with neighborhood socioeconomic status, but physical activity environment features had weak positive correlations (see Figure 2.4).

Sociodemographic Characteristics: Age was calculated using self-reported birth year, and gender was a binary variable (male or female). Self-reported race/ ethnicity was a categorical variable with levels for non-Hispanic Black, Hispanic, and non-Hispanic White. Participants were not permitted to select more than one category to describe their race/ ethnicity. Participants chose their education from 8 categories and continuous years of education was the interval midpoint of the selected category. Education was then re-coded as high school education or less, some college or associate/technical degree, and Bachelor's degree and higher. Per capita income adjusted for the number of people supported per $10,000 [(continuous income/# people supported)/10,000].

Lifestyle Risk Factors: The models included lifestyle factors that exhibited associations with LTL in prior research that are relevant to the built environment characteristics in this study: physical activity (20-22, 62) and diet (62, 63). Physical activity was assessed using the MESA Typical Week Physical Activity Survey adapted from the well-validated Cross-Cultural Activity Participation Study (64). Analyses considered moderate/vigorous physical activity (MET-min/day standardized). Participants who reported more than 18 hours of physical activity per day were removed from the sample as standard practice with MESA data. The Alternative Eating Index was a general diet score. The Alternative Healthy Eating Index provided a scoring criterion based on eleven components (ideal: fruit, vegetable, nuts, omega-3 fats, and polyunsaturated fats; moderate: alcohol; and avoidance: sugar sweetened beverages, red and processed meat, trans fat, and sodium) (65). These measures of physical activity and diet were continuous measures, and higher values indicated more physical activity and better diet, respectively.

Statistical Analyses
Descriptive statistics were calculated to describe the mean or proportion of study participants and neighborhood environments. ANOVA tests were used to describe mean telomere length (T/S ratio) by tertile of each sociodemographic, lifestyle factor, and neighborhood measure.

Linear mixed effect models with a random intercept for neighborhood were used to examine the cross-sectional association between telomere length and indicators of the physical activity and food environments. Neighborhood socioeconomic status estimates were for comparison. Figure 2.2 outlines the proposed relationships between features of residential areas, lifestyle, and telomere length that guided the research questions and analyses. Briefly, age, sex, race/ ethnicity, and individual-level socioeconomic status were confounders; however, the mechanism may have operated through lifestyle factors or via structural confounding from neighborhood socioeconomic status. Figure 2.3, illustrates the directed acyclic graph (DAG) that helped to define the appropriate confounders for statistical adjustment. Individual-level socioeconomic status and other demographic characteristics were included in all models to account for potential bias that may arise from social selection; thus, the neighborhood associations were independent of individual factors.

Sequential models illustrated how the measures of association changed, independent of the individual- and neighborhood-level confounders. First, an unconditional, or empty, model was used to ascertain the intraclass correlation coefficient (ICC) for the proportion of variance in telomere length that was due to between neighborhood variability. Second, an unadjusted model with only the neighborhood variable (model 1) estimated the main effect of each neighborhood variable on telomere length. Third, a conditional model that adjusted for sociodemographic characteristics (age at baseline, sex, race/ ethnicity, income, and education) estimated the measure of association independent of confounders (model 2). Finally, competing hypotheses were tested using individual-level lifestyle factors (AHEI diet score and physical activity MET-min) (model 3) and neighborhood-level socioeconomic status (model 4) to assess whether including additional predictors of telomere length attenuates the measures of association. All regression coefficients were standardized to one standard deviation unit.

Sensitivity analyses tested nonlinearity. Recent research suggested that associations between neighborhood variables and telomere length exhibited a nonlinear trend (51). Thus, the results of models using continuous neighborhood exposures and tertiles of each neighborhood exposure were compared to evaluate the consistency of the research findings and potential dose-response trend.

The sequential, cross-sectional models for subjects, i, nested within neighborhoods, j, are described below. Each model included a random intercept for neighborhood cluster, ζ_j, and fixed predictors for the neighborhood- and individual-level factors.

$$Y_{ij} = \beta_0 + \zeta_j + \epsilon_{ij} \text{ (Unconditional model)}$$
$$Y_{ij} = \beta_0 + \zeta_j + \beta_1 A_j + \epsilon_{ij} \text{ (Model 1)}$$
$$Y_{ij} = \beta_0 + \zeta_j + \beta_1 A_j + \beta_2 \boldsymbol{W}_{ij1} + \epsilon_{ij} \text{ (Model 2)}$$
$$Y_{ij} = \beta_0 + \zeta_j + \beta_1 A_j + \beta_2 \boldsymbol{W}_{ij1} + \beta_3 \boldsymbol{W}_{ij2} + \epsilon_{ij} \text{ (Model 3)}$$
$$Y_{ij} = \beta_0 + \zeta_j + \beta_1 A_j + \beta_2 \boldsymbol{W}_{ij1} + \beta_3 Z_j + \epsilon_{ij} \text{ (Model 4)}$$

Where,

Y_{ij} is telomere length

$\hat{\beta}_0$ is the estimate for the overall intercept
$\hat{\beta}_1$ is the estimate for the associations between one standard deviation unit change in the group mean centered neighborhood characteristic, A_j, and mean telomere length
$\boldsymbol{W}_{ij1}$ is a vector of sociodemographic characteristics (age, sex, race/ ethnicity, education, income)
$\boldsymbol{W}_{ij2}$ is a vector of lifestyle factors (moderate/ vigorous physical activity and AHEI diet score)
Z_j is neighborhood socioeconomic status

All analyses were completed using the *R* software. Linear mixed effects estimates were from the *lme4* and *lmerTest* packages with the restricted maximum likelihood (REML) option and Satterthwaite approximations for degrees of freedom. Statistical significance was defined at p-values < 0.05.

2.3 Results

Table 2.3 summarizes the population characteristics. On average, participants were 62 years old and women accounted for 50% of the sample. The respondents were predominantly of Hispanic ethnicity (45%), but there was a similar distribution of blacks and whites (26% and 29%, respectively). Forty-two percent of participants had high school or less education, 27% completed college or technical school, and 31% completed university or graduate school. Participants originated from 465 census tracts that ranged in size from 1 to 11 persons per census tract.

Table 2.3 also describes trends in mean telomere length by category of each population characteristic. Telomere length decreased with older age (*p*<.0001). Among the youngest age group, mean telomere length was 0.98 (Standard Deviation [SD] = 0.21), compared to 0.93 (SD = 0.19) among middle-aged participants and 0.84 (SD = 0.19) among the oldest age group. Mean telomere length among men was 0.89 (SD=0.2) compared to of 0.94 (SD=0.2) for women (*p*<.001). In this sample, telomeres were shortest among blacks (Mean [SD]= 0.90 [0.20]) as compared to Whites and Hispanics who had a mean telomere length of 0.93 (SD=0.21) and 0.92 (SD=0.21), respectively (p=.043). There were no statistically significant differences in telomere length by education, income, diet, or exercise.

Figure 2.5 illustrates the bivariate trends in mean telomere length, by tertile of the distributions of physical activity resources, food environment, and socioeconomic status measures. The figure also indicates average telomere length was 0.92 (SD=0.21) in the analytic sample and the cut point for short telomeres (i.e., the lowest tertile) was 0.80. Those who lived in the low tertile of the distributions for survey-based measure of walking environment (*p* <.01) and GIS-based measure of physical activity resources (*p* <.001) had the longer telomeres, compared to those in the middle and high tertile whose telomeres were shorter. In addition, the composite measure of the physical activity environment also followed the same inverse patterning of mean telomere length, where those in the low tertile had longer telomeres than subjects in the middle and high tertile of the distribution (*p* <.001). The GIS-based measure of favorable food stores revealed that residents of the middle tertile had the longest telomeres compared to those in the low and middle tertiles (*p*<.001). Mean telomere length did not fall below the *short* T/S threshold in any tertile of physical activity or food environment features. In addition, physical only differed by tertile of the food environment composite (*p*=.04) and diet only differed by tertile of neighborhood socioeconomic status (p<.01), but the lifestyle factors did not exhibit any other statistically significant differences by any other neighborhood indicator (data not shown).

Physical Activity Environment

The results of the linear mixed effects models in Table 2.4 exhibited trends similar to those presented in the bivariate analyses. When the variance-covariance components were partitioned in the unconditional model, 13.3% of the variance in telomere length was between neighborhoods. Table 2.4 summarizes the results of the sequential mixed effects models. Per standard deviation unit increase in the walking environment, there was a .14 unit decrease in mean telomere length (95% Confidence Interval [CI] = -.21, -.07), adjusted for age, sex, race/ethnicity, income, and education (see Table 2.4, Model 2). A similar trend emerged from the GIS-based measure, in which there was a .11 unit decrease in mean telomere length per standard deviation unit increase of physical activity resources (95% CI = -.18, -.04), after controlling for the same sociodemographic covariates (see Table 2.4, Model 2).

Table 2.5 exhibits the results of the regression models that used tertiles of each neighborhood indicator. Overall, the physical activity environment measures showed an inverse dose-response relationship with mean telomere length. Specifically, compared to those in the low tertile of the walking environment, there was a .15 unit decrease in mean telomere length among those in the high tertile, after controlling for sociodemographic confounders (95% CI = -.23, -.07; see Table 2.5, Model 2). The GIS-based measure of physical activity resources showed that among the middle and high tertiles, mean telomere length was shorter compared to the low tertile, which increased in a dose-response fashion independent of sociodemographic covariates (Standardized Beta [Std. β] and 95% CI for middle vs. low was -.11 [-.17, -.04] and -.19 [-.26, -.13] for high vs. low; see Table 2.5, Model 2). The linear mixed effects models for continuous and categorical measures of both GIS- and survey-based measures of physical activity and food environments were stable and the measures of association were not attenuated after additional adjustment for lifestyle factors (see Table 2.4 and Table 2.5, Model 3) or neighborhood socioeconomic status (see Table 2.4 and Table 2.5, Model 4).

Food Environment

Differences in mean telomere length by survey- and GIS-based measures of the food environment continued to the linear mixed effects models shown in Table 2.4. Specifically, the GIS-based measure indicated that per standard deviation unit increase in the availability of favorable food stores, there was a .15 unit decrease in mean telomere length (95% CI = -.22, -.08), adjusted for individual-level sociodemographic characteristics (see Table 2.4, Model 2). This measure of association was not attenuated after adjusting for lifestyle factors or neighborhood-level socioeconomic status. Conversely, the association between the survey-based healthy food availability, which was slightly positive association, was not statistically significant (Std. β (95% CI) = .04 [-.02, .10]; see Table 2.4, Model 2). The categorical GIS-based measure of the availability of favorable food stores revealed that, compared to those living in the low tertile, those living in the high tertile of food environment have shorter telomeres, independent of sociodemographic characteristics (Std. β (95% CI) = -.18 [-.26, -.10]; see Table 2.5, Model 2). The linear mixed effects models for continuous and categorical measures of both GIS- and survey-based measures of physical activity and food environments were stable and the measures of association were not attenuated after additional adjustment for lifestyle factors (see Table 2.4

and Table 2.5, Model 3) or neighborhood socioeconomic status (see Table 2.4 and Table 2.5, Model 4).

Neighborhood Socioeconomic Status

The summary plot in **Figure 2.6** displays the results from all physical environment characteristics in the main model (Model 2 adjusted for age, sex, race/ ethnicity, income, and education) in comparison to neighborhood socioeconomic status. After adjustment for sociodemographic characteristics, socioeconomic status exhibited an association in the opposite direction of most indicators of physical activity resources and food environment. Per standard deviation unit increase in neighborhood socioeconomic status, there was a .08 unit increase in mean telomere length (95% CI= 0.00, 0.16; see Table 2.4, Model 2). Figure 2.7 shows the comparison of the analyses of the categorical neighborhood measures.

2.4 Discussion

The objective of this study was to examine how features of the physical environment were associated with leukocyte telomere length using a cross-sectional sample of adults. The hypothesis was that those who lived in supportive physical activity and food environments would have longer telomeres. However, the main finding suggested that physical activity and food environments were not associated with leukocyte telomere length in the expected direction. Living in an area with better walking conditions (survey), more physical activity resources (GIS), and more favorable food stores (GIS) was associated with shorter telomeres. In contrast, living in a more affluent neighborhood was associated with longer leukocyte telomere length.

This study was the first to examine the relationship between physical activity and food environments, and telomere length. The extant literature included studies that examined other aspects of the built or physical environment such as building densities and population density metrics (see Table 2.1). These findings suggested that higher density of liquor stores (50), higher population density (51) and more urban crowding (51) were associated with shorter telomeres. There have been other relevant studies that examined the level of urbanization (47) and perceived neighborhood physical environment attributes (49), but the results were not statistically significant. Nevertheless, the findings from this research provide an important contribution to the body of literature on built environments and telomere length even though the primary results were not consistent with past research of other neighborhood measures.

The models used continuous and discretized forms of each built environment attribute. Analyses of neighborhood tertiles revealed that telomere length was shortest among those living in better physical environment circumstances, increasing in a dose-response fashion. Notably, these findings were statistically significant for the high versus low tertile comparison. This observation at the extreme tails of the distribution suggests that there was not sufficient variability in telomere length between the low and middle tertiles of the neighborhood variables. A recent study by Lynch *et al*. did not find any statistically significant associations between telomere length and continuous measures of built environment characteristics (as measured by population density, urban crowding, residential stability, and mobility), but quantile regression revealed that those in the lower tails of the distribution had longer telomeres (51). Thus, future research should continue to examine nonlinearity to identify high-risk groups.

This study used survey- and GIS-based measures of the physical activity and food environment to test the consistency of the study's estimates. Overall, the subjective and objective measures of association were inconsistent in magnitude but consistent in direction. The survey-based measure of availability of healthy foods was the lone exception with a slightly positive measure of association that was not statistically significant. Compared to the GIS-based measure that examined density total of the supermarket chain and non-chain and fruit and vegetable markets, the survey-based item assessed the quality and selection of fresh fruits and vegetables. The essential distinction between these two measures helped to validate ratings of neighborhood attributes against objective estimates of availability. Ultimately, this proved problematic for the composite food environment measure, which was close to the null because of the opposite direction of the association for the GIS- and survey-based components. The measures for physical activity resources were not direct analogs either. The survey-based items determined the respondent's subjective assessment of opportunities to engage in physical activity and walking, ratings of the environment for walking (e.g., trees for shade), and social norms among neighbors who participate in walking or physical activity in the neighborhood. Conversely, the GIS-based measure for the density of total of resources for physical activity, instruction, and water activities, measures a different construct. Honing in on perceptions of the quality of physical environment characteristics could provide more compelling findings than objective assessments of densities or even subjective reporting of availability used in this study. Examining availability of versus actual engagement with resources for healthy living only tells part of the complex story of neighborhoods and telomere length. Thus, availability of healthy foods may not translate to the quality of food choices or individual dietary practices. Similarly, opportunities to be physically active may not indicate perceived barriers to engaging in physical activity or individual-level activity. Mixed methods research could highlight underlying factors of the physical activity or food environment that are related to telomere length in an expected direction.

To consider the most relevant competing hypotheses, subsequent models also included lifestyle factors (diet and exercise; Model 3) and neighborhood socioeconomic status (Model 4). First, the hypothesis was that health behaviors might account for some of the variability in telomere length that was due to living in certain physical activity or food environments. Briefly, telomere length was positively associated with physical activity (20) and the Mediterranean diet (18) but negatively associated with the consumption of both sugar-sweetened beverages (66) and processed meats (19). However, neither lifestyle indicator was independently related to telomere length in this study. Furthermore, the measure of association between each neighborhood characteristics and telomere length did not change with lifestyle factors in the model. Second, the explanatory power of neighborhood socioeconomic status was explored to account for heterogeneity within physical contexts and structural confounding. Neighborhood socioeconomic status was independently associated with telomere length despite a lack of evidence in the extant literature (45, 46). However, adjustment for neighborhood socioeconomic status (Model 4) did not attenuate any of the physical environment-telomere length associations. Overall, the measures of association were robust to statistical adjustment for the main confounders and other mechanisms.

No study is without limitation, and many approaches were used to mitigate biases that may have ensued from social selection, confounding, and misclassification. Cross-sectional neighborhood analyses have to consider the practical challenges of social selection. Adjusting for individual-level socioeconomic status in adulthood and other sociodemographic factors such as age, sex, and race/ ethnicity helped to account for factors that may confer selection into certain neighborhood contexts (67). Longitudinal designs that take advantage of contextual changes could surmount the bias associated with selection factors (68). Residual confounding builds on the issue of social selection. This study used a directed acyclic graph (DAG) and *a priori* knowledge to select the minimally sufficient set of covariates needed to estimate an unbiased measure of association (see Figure 2.2 and Figure 2.3). The most parsimonious model only included demographic characteristics and individual-level socioeconomic status. To consider the most relevant competing hypotheses, subsequent models also included lifestyle factors (diet and exercise; Model 3) and neighborhood socioeconomic status (Model 4). Future research should also consider other etiologically relevant factors because residual confounding may still arise. The design of this study considered misclassification carefully. The survey-based items were census tract-level aggregates of respondents' perception of their neighborhood (i.e., 1-mile radius). The census tract is a suitable proxy for a neighborhood (58), but some disconnect may still exist. Future research should consider using a 1-mile buffer and contiguous census tracts in sensitivity analyses to examine whether the boundary of a neighborhood influences results. Misclassification may have also occurred when the composite measures were considered in analyses for the food environment because the survey- and GIS-based measures were not strongly correlated. Any bias resulting from misclassification of the exposure was likely to be nondifferential, and the measures of association may have been drawn towards or away from the null. For telomere length, misclassification may have occurred from categorizing subjects into standard and short telomere length categories. The cut point for short telomere length was an arbitrary measure that may not be externally valid. Future research should derive clinically meaningful thresholds for short telomere length using population-based cohorts or findings from experimental studies. This study does not represent causal conclusions, but it brings into focus that investment in the walking environment, availability of healthy foods, and density of favorable food stores may *not* have similar gains in biological aging.

2.5 Conclusion

This study was the first to examine the relationship between neighborhood physical activity and food environments and telomere length. The findings suggested that living in an area with better recreational and food environments were associated with shorter telomeres. Future research should consider measurement instruments that directly assess the quality and utilization of neighborhood physical activity and healthy food resources to develop a holistic description of how built environments and behaviors predict telomere length using longitudinal data.

2.6 Tables and figures

Tables

Table 2.1 Summary of Findings From Studies That Examined Associations Between Neighborhood Features and Telomere Length (N=7)

Author, Year, Journal	Study Population	Key Findings	Design	Assay and cell type
Theall K, *et al.,* 2013 **(46)**	African American children aged 4-14 from 5 urban schools in New Orleans, Louisiana (n = 99)	Concentrated neighborhood disadvantage (ns) Neighborhood disorder (-, s)	Cross-sectional	qPCR, saliva
Needham B, *et al.,* 2014 **(45)**	Men and women aged 45-84 from subset of MESA of African American, White, or Hispanic descent (n=978)	Neighborhood SES (ns) Poor social environment (-, s)	Cross-sectional	qPCR, leukocyte
Park M, *et al*., 2015. **(47)**	Men and women ages 18-65, (n = 2,901)	Perceived neighborhood quality (+, s) Neighborhood appraisal, duration of residence, level of urbanization (ns)	Cross-sectional	qPCR, leukocyte
Geronimus A, *et al*., 2015 **(49)**	Black, white, or Mexican adults from a stratified, multistage probability sample of 3 Detroit neighborhoods (n=239)	Perceived physical environment (heavy car or truck traffic, air pollution, contaminated land, vacant homes and lots in the neighborhood, noise pollution, well-maintained homes and clean streets, sidewalks, and vacant lots) (ns)	Cross-sectional	qPCR, leukocyte
Gebreab S, *et al*., 2016**(48)**	African American men and women aged 30-55 from the Morehouse School of Medicine Study (n=233)	*Among women only* Neighborhood problems (-, s) Unfavorable neighborhood perception (-, s) Social cohesion (+, ns)	Cross-sectional	qPCR, leukocyte

Author, Year, Journal	Study Population	Key Findings	Design	Assay and cell type
Lynch S, *et al*., 2017(**51**)	Pooled three samples: (1) Non-Hispanic white women from rural Appalachia, (2) Non-Hispanic white, African American prostate cancer patients, and (3) Population-based sample of non-Hispanic households and a strata sample of Hispanic households (n=1,488)	Population density, urban crowding (-, s) Residential stability, mobility (+, s)	Cross-sectional	Southern Blot, leukocyte
Theall K, *et al*., 2017(**50**)	African American children aged 5-16 from 52 neighborhoods in New Orleans Louisiana (n=85)	Density of liquor stores (-, s) Domestic violence (-, s) Violent crime (-, s)	Cross-sectional	qPCR, saliva

Notes. The following symbols describe the key findings of each study: "+" indicates a positive association in which higher values of the neighborhood exposure are associated with longer telomeres; "-" identifies findings in which higher values of the neighborhood exposure are associated with shorter telomeres; "s" describes statistically significant measures of association; and "ns" denotes a measure of association that has not reached the threshold for statistical significance. SES = socioeconomic status.

Table 2.2 Definitions of Physical Environment Measures Used in Analyses of Baseline Data From the Multi-Ethnic Study of Atherosclerosis' Longitudinal Neighborhoods Study (2000-2002)

Neighborhood Feature	Scale Summary and Items	Unit
Food Environment		
Availability of Healthy Foods, S	1. A large selection of fresh fruits and vegetables is available in my neighborhood. 2. A large selection of low-fat products is available in my neighborhood.	Census tract
Favorable Food Stores, G	Kernel density total of supermarket chain and non-chain and fruit and vegetable markets. The unit of measure is number of facilities per square mile.	Census tract
Healthy Food Environment, G/S*	Composite measure of GIS-based and survey-based scores for Favorable Food Stores + Availability of Healthy Foods. Sum of standardized conditional empirical Bayes scale score and kernel density estimates.	Census tract
Physical activity Environment		

Neighborhood Feature	Scale Summary and Items	Unit
Walking Environment, S	1. My neighborhood offers many opportunities to be physically active. 2. Local sports clubs and other facilities in my neighborhood offer many opportunities to get exercise. 3. The trees in my neighborhood provide enough shade. 4. In my neighborhood it is easy to walk [to] places. 5. I often see other people walking in my neighborhood. 6. I often see other people exercising (for example, jogging, bicycling, playing sports) in my neighborhood.	Census tract
Physical Activity Resources, G	Kernel density total of resources for physical activity, instruction, and water activities. The unit of measure is number of facilities per square mile.	Census tract
Physical Activity Environment, G/S*	Composite measure of GIS-based and survey-based scores for Physical Activity Resources + Walking Environment. Sum of standardized conditional empirical Bayes scale score and kernel density estimates. Does not include parks.	Census tract

Note. G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure

Table 2.3 Summary of Population Characteristics and Mean Telomere Length in the Multi-Ethnic Study of Atherosclerosis, 2000-2002 (N=835)

Characteristic	Study Population		Telomere Length	
	Mean (SD)	*N (%)*	*Mean (SD)*	*P*
Age	61.66 (9.47)			**<.0001**
45-54		227 (27.2)	0.98 (0.21)	
55-64		263 (31.5)	0.93 (0.19)	
65 and older		345 (41.3)	0.84 (0.19)	
Race/ ethnicity				**0.043**
White		244 (29.2)	0.93 (0.21)	
Black		216 (25.9)	0.90 (0.20)	
Hispanic		375 (44.9)	0.92 (0.21)	

Characteristic	Study Population		Telomere Length	
Gender				**<.001**
Female		421 (50.4)	0.94 (0.20)	
Male		414 (49.6)	0.89 (0.20)	
Education				0.206
High school or less		353 (42.3)	0.91 (0.21)	
College or technical school		221 (26.5)	0.93 (0.21)	
University or graduate		261 (31.3)	0.91 (0.19)	
Adjusted per capita income (Per $10,000)	2.37 (1.82)			0.816
Low tertile (<1.375)		279 (33.4)	0.90 (0.21)	
Middle tertile (1.375-2.183)		278 (33.3)	0.92 (0.20)	
High tertile (>2.183)		278 (33.3)	0.92 (0.20)	
Alternative Healthy Eating Index score	53.08 (11.30)			0.749
Low tertile (<48.1)		279 (33.4)	0.91 (0.21)	
Middle tertile (48.1-57.5)		278 (33.3)	0.92 (0.20)	
High tertile (>57.5)		278 (33.3)	0.93 (0.20)	
Physical activity (MET-min/day standardized)	4,820.53 (3,831.16)			0.800
Low tertile (<2,565)		279 (33.4)	0.92 (0.20)	
Middle tertile (2,565-5,580)		278 (33.3)	0.91 (0.20)	
High tertile (>5,580)		278 (33.3)	0.92 (0.22)	

Note. P-values obtained via ANOVA test for the differences in means, by category of each population characteristic. Post-hoc tests were not administered.

Table 2.4 Associations of Neighborhood Built Environment Features and Telomere Length in MESA, 2000-2002 (N=835)

	Model 1	**Model 2**	**Model 3**	**Model 4**
	Std. β (95% CI)	**Std. β (95% CI)**	**Std. β (95% CI)**	**Std. β (95% CI)**
Socioeconomic Status	0.04 (-0.03, 0.12)	**0.08 (0.00, 0.16)**	**0.08 (0.00, 0.16)**	--
Physical Activity Environment				
Walking Environment, S	**-0.15 (-0.22, -0.07)**	**-0.14 (-0.21, -0.07)**	**-0.14 (-0.21, -0.07)**	**-0.16 (-0.23, -0.09)**
Physical Activity Resources, G	**-0.14 (-0.21, -0.07)**	**-0.11 (-0.18, -0.04)**	**-0.11 (-0.18, -0.04)**	**-0.13 (-0.2, -0.06)**
Physical Activity	**-0.16 (-0.23, -0.08)**	**-0.14 (-0.21, -0.07)**	**-0.14 (-0.21, -0.07)**	**-0.16 (-0.23, -0.09)**

Environment, GS*				
Food Environment				
Availability of Healthy Foods, S	0.03 (-0.05, 0.11)	0.04 (-0.03, 0.11)	0.04 (-0.03, 0.11)	0.03 (-0.05, 0.1)
Favorable Food Stores, G	**-0.17 (-0.24, -0.09)**	**-0.15 (-0.22, -0.08)**	**-0.15 (-0.22, -0.08)**	**-0.14 (-0.21, -0.08)**
Healthy Food Environment, GS*	**-0.12 (-0.2, -0.05)**	**-0.11 (-0.17, -0.04)**	**-0.11 (-0.17, -0.04)**	**-0.1 (-0.17, -0.03)**

Notes. Bolded items are statistically significant ($p \leq .05$). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. L = Low tertile; M = Middle tertile; H = High tertile. Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood variable
Model 2: neighborhood variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood variable, age, sex, race/ ethnicity, income, education, diet, and physical activity
Model 4: neighborhood variable, age, sex, race/ ethnicity, income, education, and neighborhood socioeconomic status

Table 2.5 Associations by Tertile of Neighborhood Built Environment Features and Telomere Length in MESA, 2000-2002 (N=835)

	Level	Model 1 Std. β (95% CI)	Model 2 Std. β (95% CI)	Model 3 Std. β (95% CI)	Model 4 Std. β (95% CI)
Socioeconomic	M	0.01 (-0.07, 0.1)	0.01 (-0.07, 0.09)	0.01 (-0.06, 0.09)	--
Status	H	0.04 (-0.04, 0.13)	0.07 (-0.02, 0.16)	0.07 (-0.02, 0.16)	--
Physical Activity Environment					
Walking	M	-0.04 (-0.12, 0.05)	-0.03 (-0.11, 0.05)	-0.03 (-0.11, 0.05)	-0.02 (-0.1, 0.05)
Environment, S	H	**-0.14 (-0.23, -0.06)**	**-0.15 (-0.23, -0.07)**	**-0.15 (-0.23, -0.07)**	**-0.16 (-0.23, -0.08)**
Physical	M	-0.07 (-0.15, 0.01)	**-0.09 (-0.17, -0.02)**	**-0.09 (-0.16, -0.02)**	**-0.09 (-0.16, -0.01)**
Activity Resources, G	H	**-0.25 (-0.33, -0.17)**	**-0.23 (-0.31, -0.16)**	**-0.23 (-0.31, -0.16)**	**-0.22 (-0.3, -0.15)**
Physical	M	-0.05 (-0.13, 0.03)	-0.06 (-0.14, 0.01)	-0.06 (-0.14, 0.02)	-0.06 (-0.13, 0.02)
Activity Environment, GS*	H	**-0.2 (-0.28, -0.12)**	**-0.19 (-0.27, -0.11)**	**-0.19 (-0.27, -0.11)**	**-0.18 (-0.26, -0.11)**
Food Environment					
Availability of	M	0.05 (-0.04, 0.13)	0.05 (-0.03, 0.13)	0.05 (-0.03, 0.13)	0.06 (-0.03, 0.14)
Healthy Foods, S	H	0.07 (-0.01, 0.16)	0.07 (-0.01, 0.15)	0.07 (-0.01, 0.15)	0.06 (-0.02, 0.14)
Favorable Food	M	-0.03 (-0.11, 0.05)	-0.05 (-0.13, 0.03)	-0.05 (-0.13, 0.03)	-0.04 (-0.12, 0.04)

Stores, G	H	**-0.18 (-0.27, -0.1)**	**-0.18 (-0.26, -0.1)**	**-0.18 (-0.26, -0.1)**	**-0.17 (-0.25, -0.09)**
Healthy Food	M	0.05 (-0.03, 0.14)	0.05 (-0.03, 0.13)	0.05 (-0.03, 0.12)	0.06 (-0.02, 0.14)
Environment, GS*	H	**-0.13 (-0.21, -0.05)**	**-0.13 (-0.21, -0.05)**	**-0.13 (-0.21, -0.05)**	**-0.11 (-0.19, -0.03)**

Notes. Each tertile is compared to the referent tertile, low. Bolded items are statistically significant ($p \leq .05$). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. L = Low tertile; M = Middle tertile; H = High tertile. Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood variable
Model 2: neighborhood variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood variable, age, sex, race/ ethnicity, income, education, diet, and physical activity
Model 4: neighborhood variable, age, sex, race/ ethnicity, income, education, and neighborhood socioeconomic status

Figures

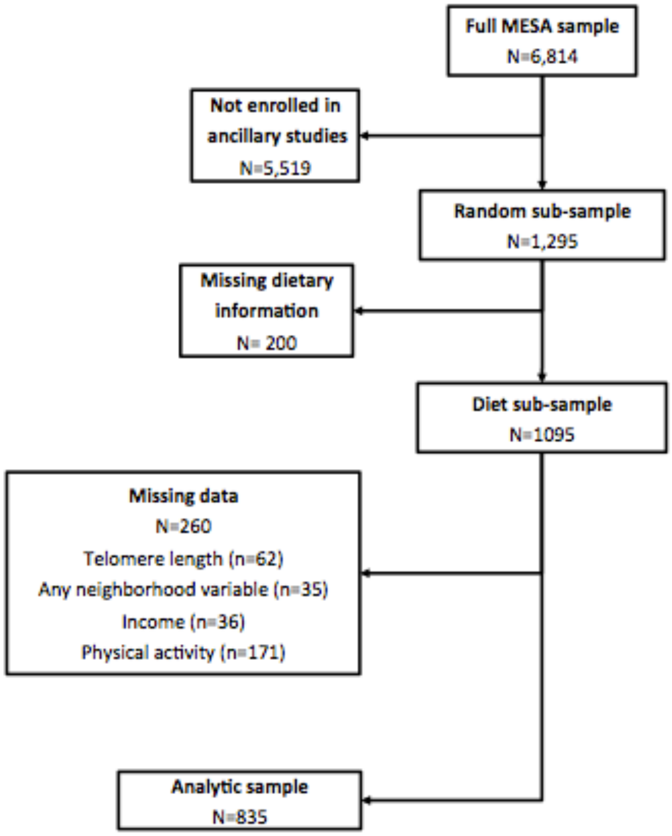

Figure 2.1 Data for these analyses originated from the baseline exam of the Multi-Ethnic Study of Atherosclerosis, 2000-2002. The analytic sample included data from a random sub-sample of subjects. Any respondent that was missing data on telomere length, neighborhood characteristics, demographic information, or lifestyle factors was excluded from the final sample. Overall, 835 subjects were used to examine the research objectives. *Note*. MESA = Multi-Ethnic Study of Atherosclerosis

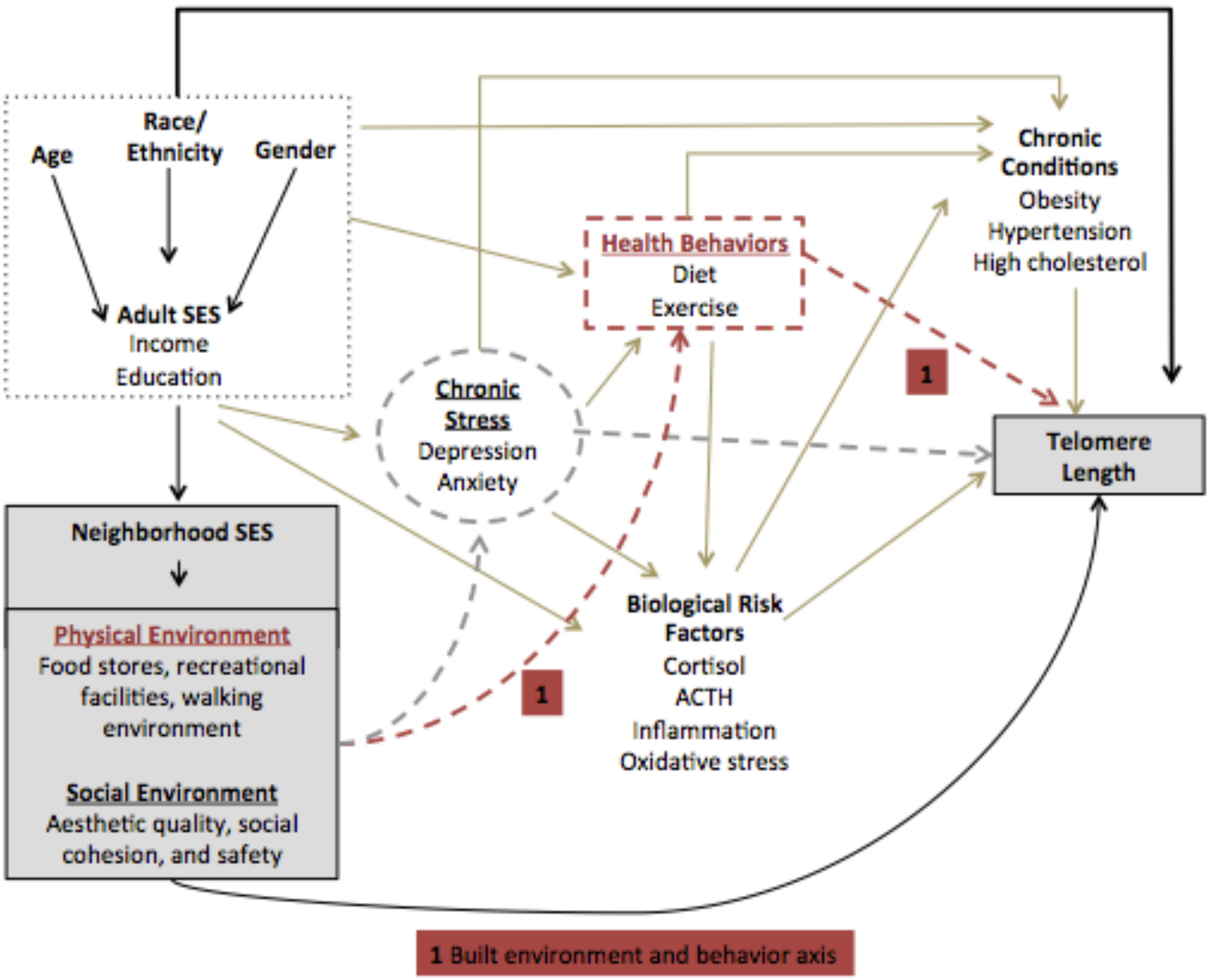

Figure 2.2 The conceptual framework that guided the analyses of neighborhood physical activity and food environments considered the following confounders: age, race/ ethnicity, gender, and individual-level socioeconomic status. Health behaviors (diet and exercise) and neighborhood socioeconomic status were included in subsequent models. All neighborhood physical environment features were modeled separately. Telomeres and neighborhoods also have numerous interrelationships with psychosocial stress, biological risk factors, and comorbidities; however, these relationships were not the focus of this research. *Note*. SES = socioeconomic status.

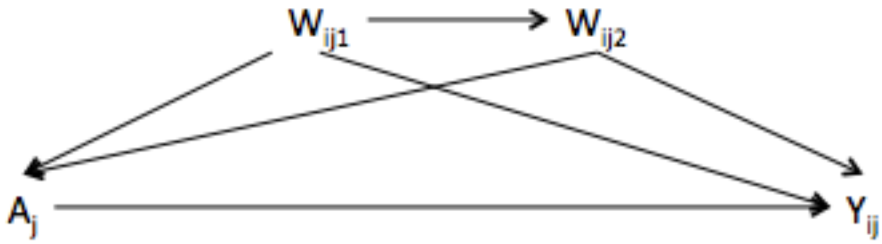

Figure 2.3 This DAG describes the cross-sectional association between neighborhood physical environment characteristics and telomere length for each subject, i, nested within neighborhood, j. In this diagram, $\boldsymbol{W_{ij1}}$ is a vector of individual-level demographic characteristics (age, sex, race/ ethnicity), $\boldsymbol{W_{ij2}}$ is a vector of individual-level socioeconomic status variables (income and education), $\boldsymbol{A_j}$ is a physical environment exposure, and $\boldsymbol{Y_{ij}}$ is telomere length. Subsequent models that included lifestyle factors and neighborhood socioeconomic status are not part of this illustration.

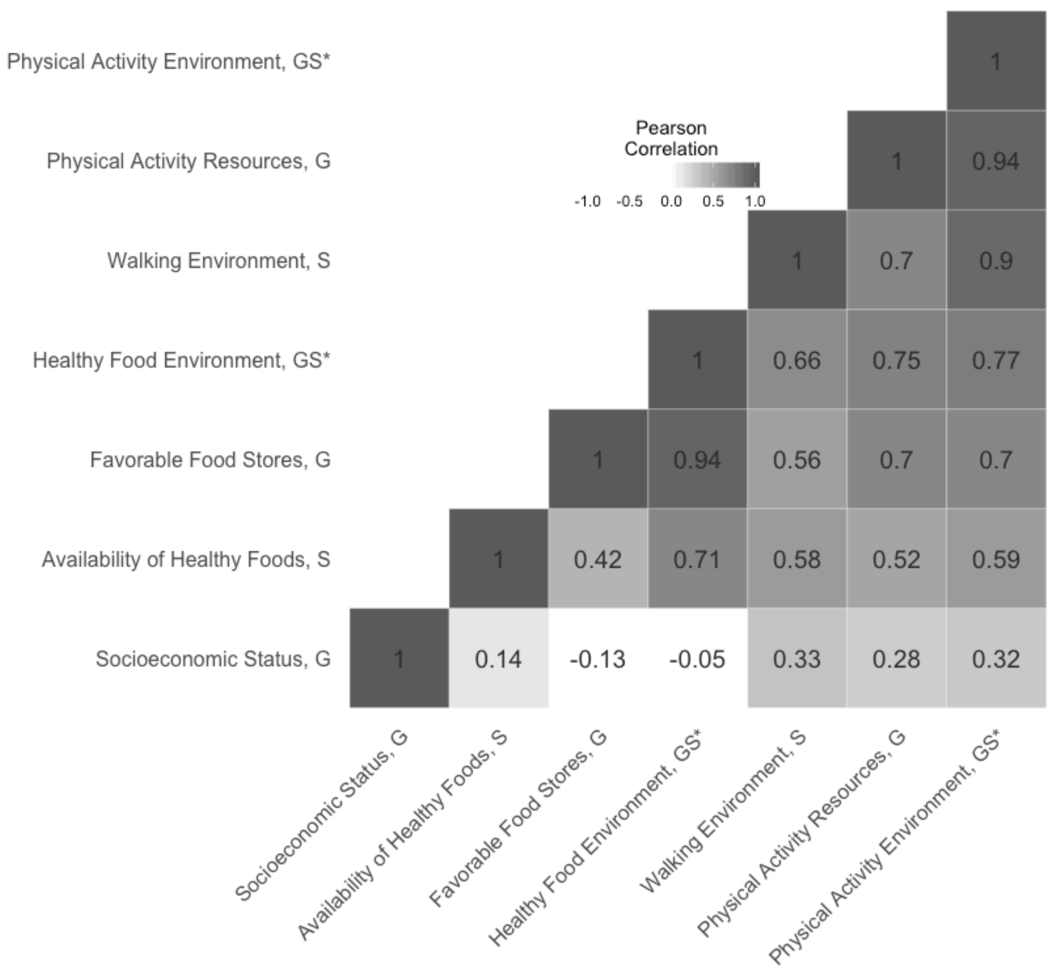

Figure 2.4 Pearson Correlation Among Physical Environment Characteristics and Neighborhood Socioeconomic Status (N=835)
Note. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure.

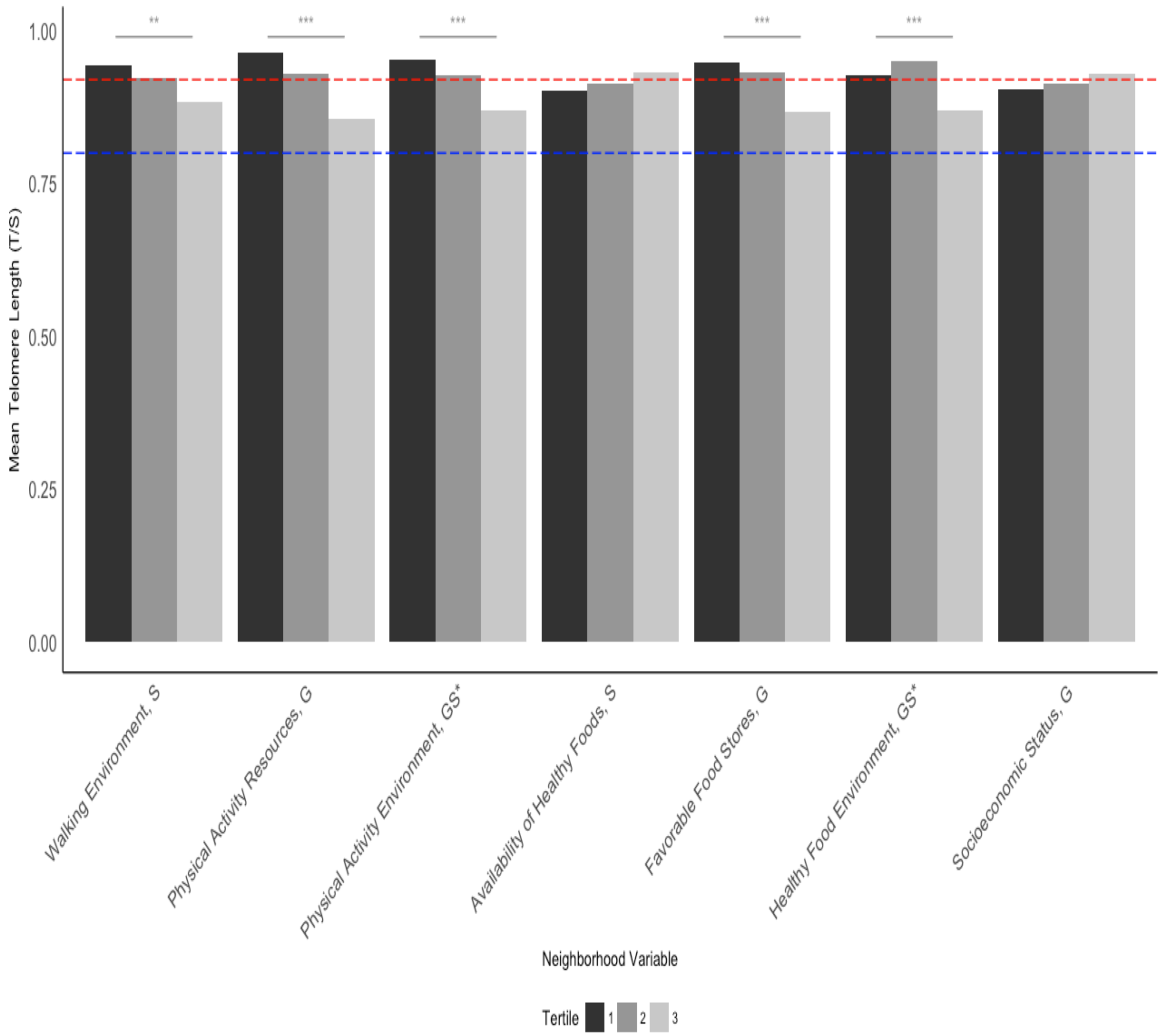

Figure 2.5 Mean telomere length differed by tertile of each neighborhood characteristic. The red horizontal line indicates the overall mean telomere length in the sample, .92 (SD = .20). The blue horizontal line indicates the threshold for short telomere length for those in the lowest tertile of the distribution (T/S=.80). *Notes*. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Statistical significance thresholds for the ANOVA tests were set at * for *p*<.05, ** for *p*<.01, and *** *p*<.001.

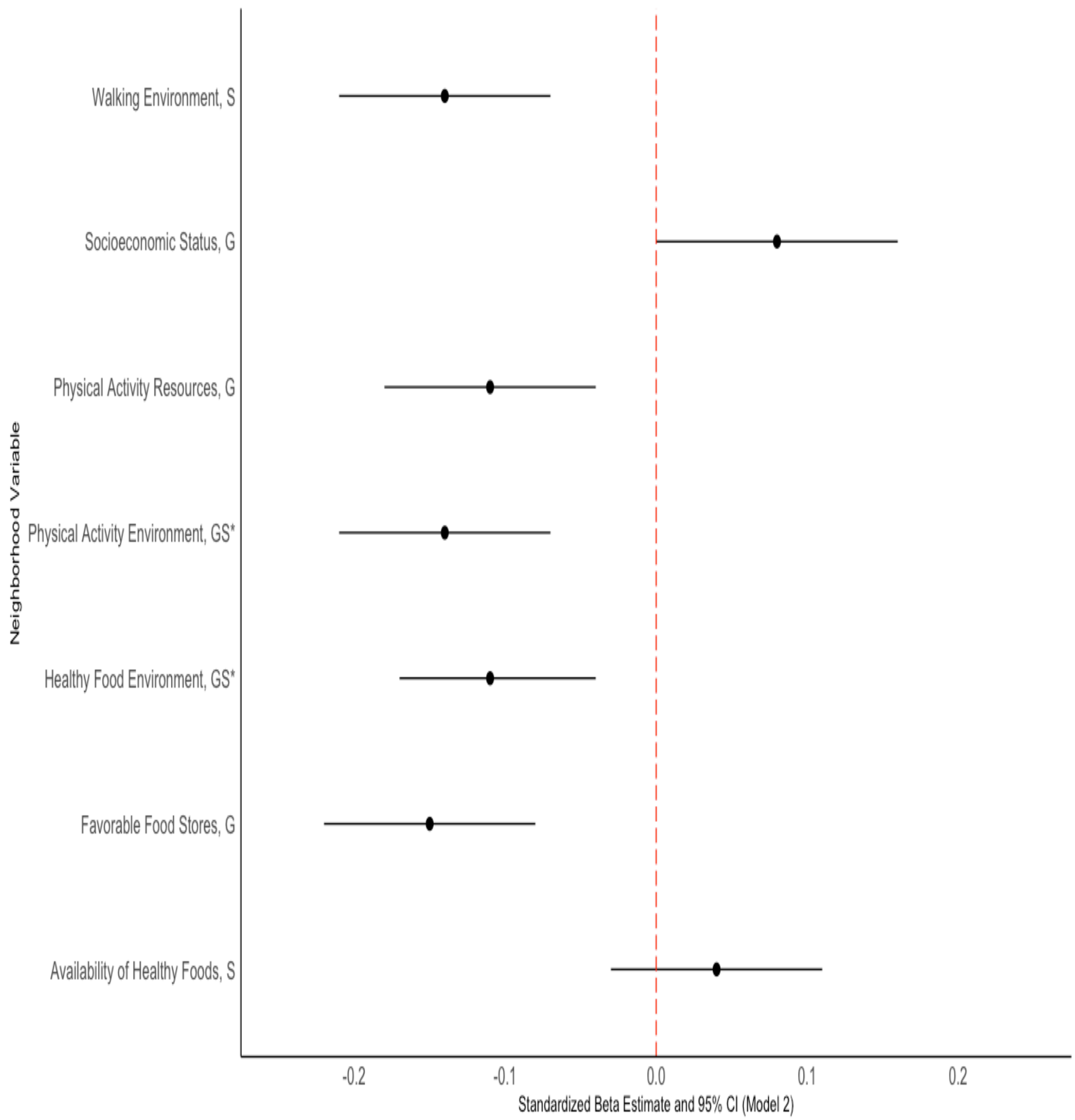

Figure 2.6 Summary of Associations of Built Environment Features and Telomere Length in MESA, 2000-2002 (N=835) *Notes*. Each linear mixed effect model included a random intercept for census tract. The models presented in this figure were adjusted for age, gender, race/ ethnicity, income, and education. All measures were grand mean centered and model estimates were standardized to 1 standard deviation unit. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Statistical significance was set at p<.05 and the red vertical line indicates the null.

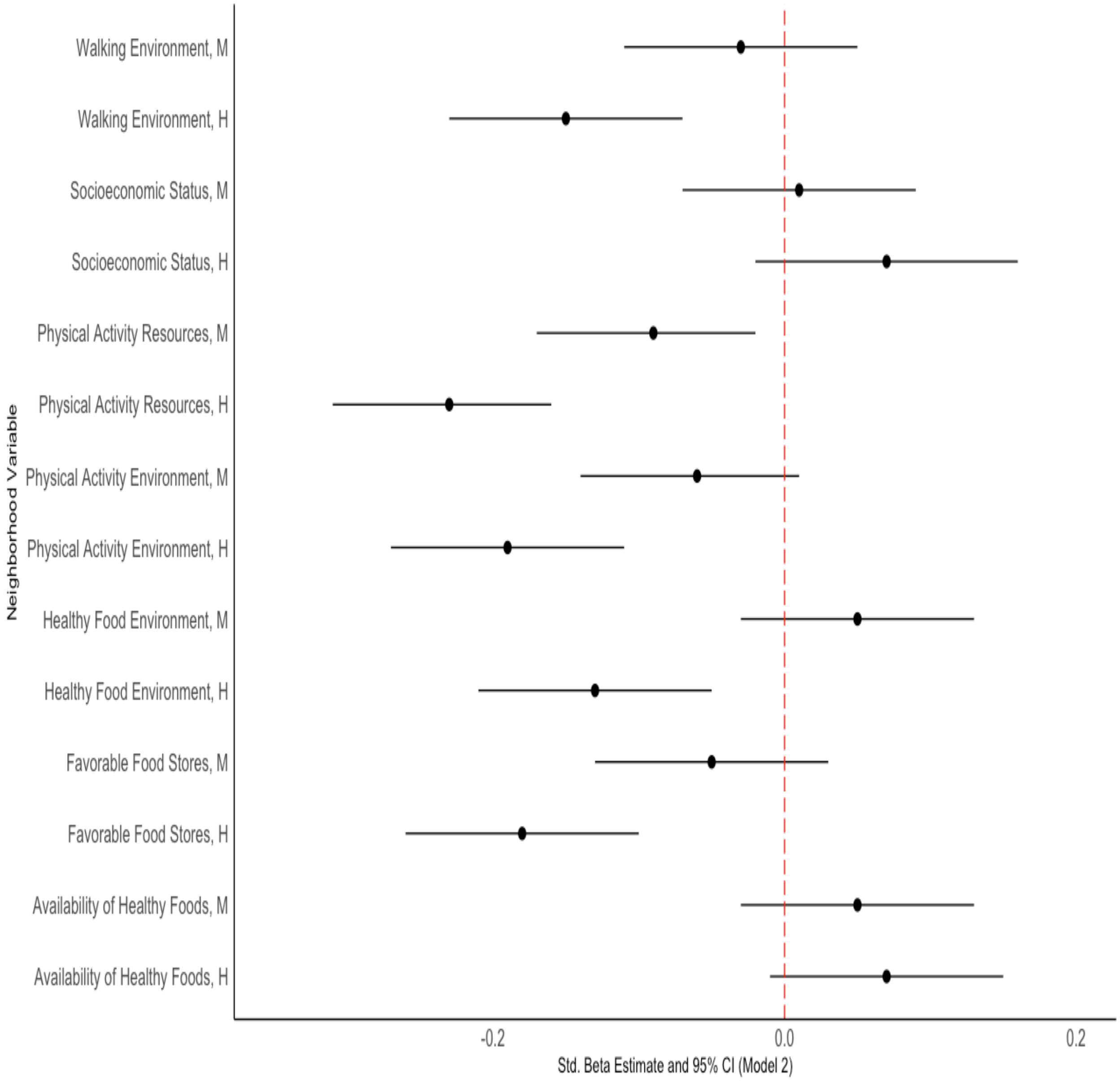

Figure 2.7 Summary of Associations of Tertile of Built Environment Features and Telomere Length in MESA, 2000-2002 (N=835) *Notes*. Each linear mixed effect model included a random intercept for census tract. The models in this figure were adjusted for age, gender, race/ ethnicity, income, and education. All measures were grand mean centered and model estimates were standardized to 1 standard deviation unit. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Tertiles were defined as H for high and M for middle. The reference category was the low tertile of the distribution of each physical environment variable. Statistical significance was set at $p<.05$ and the red vertical line indicates the null.

Chapter 3 Changes in availability and perceptions of physical activity and healthy food resources may slow leukocyte telomere length attrition

3.1 Background

In 2016, health expenditure the United States was almost 18% of the total Gross Domestic Product (GDP). Spending on hospitalization and care will continue to rise as the population ages. Thus, understanding points of intervention to slow the aging process is at the center of the modern epidemiology paradigm. A shift in focus from health management to prevention will help to reduce the burden of disease that currently weighs heavily on the most disadvantaged population groups. Beyond pharmacological interventions, it is often controversial to suggest that morbidity or premature mortality can be prevented or managed. However, lifestyle factors, such as adequate physical activity and healthy dietary choices are modifiable behaviors with wide-ranging health benefits that have emerged as part of a global strategy to prevent chronic diseases (69). Telomere length and the rate of telomere shortening are indicators of biological aging that are sensitive to various exposures, including diet (16-19) and low moderate/vigorous physical activity (14, 16, 20-25). Features of the neighborhood environments are shown to support healthy lifestyles, but it remains unknown whether changes in the physical activity and food environments are related to changes in telomere dynamics.

To date, no study has examined whether improvements in the physical activity or food environments could be axes to slow telomere length attrition. There is evidence of an association between physical environment characteristics and telomere length in cross-sectional analyses. These studies have examined whether neighborhood context is related to leukocyte telomere length. A high density of liquor stores (50), high population density (51), more urban crowding (51), high level of urbanization (47) (not statistically significant), and poor perceived neighborhood physical environment (49) are linked to shorter telomeres. There are no longitudinal assessments of neighborhood features and telomere length.

Studies of neighborhood change are rare. The Moving to Opportunity Study was one example in which study participants were randomized into specific contexts. Spatial randomization studies are onerous; thus, researchers must take advantage of observational studies that exhibit a change in neighborhood exposures over time to establish temporal ordering. Intra-neighborhood change may result from forces such as gentrification (e.g., an influx of high SES residents to optimal urban locations) or resident-motivated neighborhood improvement strategies (e.g., building new parks). Studies of long-term change in telomere length are also equally rare. Telomeres shorten with each replicative phase, but the enzyme telomerase helps depleted telomeres by adding base pairs. The prospect of long-term lengthening is the most attractive, but also the most controversial, part of telomere research. It is hypothesized that health-promoting behaviors may provide an additional boost to telomerase activity and slow LTL attrition (70). Thus, this study presents a unique opportunity to overcome the gaps in both neighborhoods and telomere research to understand how community-level changes in access to physical activity and food resources influence the malleability of biological aging.

The goal of this study was to investigate whether changes in the physical activity and food environments were associated with the 10-year change in telomere length. Competing hypotheses were tested to examine the influence of built environment change independent of baseline levels of individual health behaviors (diet and physical activity) and change in neighborhood socioeconomic status. Moving status was used as a treatment to assess the added impact of an acute change in context using a difference-in-differences estimator. The principal hypothesis was that improvements in the physical activity and food environments would slow telomere attrition over 10 years and that there would be even less telomere length shortening among movers compared to non-movers.

3.2 Methods

Study Sample

Data for these analyses were from the Multi-Ethnic Study of Atherosclerosis (MESA) (N=6,814). Details about the design and population characteristics of this cohort of adults aged 45-84 at baseline are available elsewhere (54). Briefly, subjects were recruited from New York, New York; Los Angeles, California; and Baltimore, Maryland and followed for 10 years and exam data were collected in two-year increments. This study used a subsample of participants who participated in the MESA Stress and MESA Neighborhood ancillary studies (N=1,295). Only 1,095 of these participants had data available on dietary choices. Subjects who had telomere length data available (N missing = 97) at Exam 1 (July 2000 – August 2002) and Exam 5 (April 2010 – December 2011) from these subsamples were part of the sampling scheme. The subsample participants were of non-Hispanic Black, Hispanic, and non-Hispanic White racial/ ethnic backgrounds and originated from New York, New York and Los Angeles, California. Thirty-two percent of the sample was missing data from at least one study variable: change in telomere length, sociodemographic characteristics, exercise, or neighborhood change indicators (see Figure 2.1). The final analytic sample used complete case analysis and included 747 individuals. Missing data were not imputed.

Study Variables

Study Outcome: Change in Leukocyte Telomere Length

Blood samples were from baseline and Exam 5, and the visits were10 years apart. The University of California, San Francisco conducted the telomere length assay using quantitative polymerase chain reaction (PCR) (55, 56). Both samples were assayed at the same time. Storage and batch effects were carefully considered to ensure sample integrity. Each sample was assayed three times on three different days on duplicate wells. Mean T/S ratio was calculated using non-outlier samples. The interassay coefficient of variation was 2.9%. The laboratory assays were conducted independently of all other study functions.

The crude and adjusted measures of change in telomere length were used in all analyses to ensure consistency and validity. Crude change was the difference between follow-up and baseline measures, $\Delta T/S_{crude} = Y_{tij} - Y_{t-1,ij}$. Adjusted telomere length change also calculated to account for potential regression to the mean (71). The adapted equation for adjusted telomere change was:

$$\Delta T/S_{adjusted} = \rho\left(Y_{tij} - \overline{Y_{tij}}\right) - \left(Y_{t-1,ij} - \overline{Y_{t-1,ij}}\right)$$

Where,

$$\rho = \frac{2rS_{tij}S_{t-1,ij}}{S_{tij}^2 + S_{t-1,ij}^2}$$

$$r = corr(Y_{tij}, Y_{t-1,ij})$$

Y is telomere length
t is visit
i is subject
j is neighborhood

S is standard deviation
r is Pearson correlation coefficient

In this sample, persons with shorter telomeres at baseline also had short telomeres at follow up (data not shown). In addition, respondents who had longer telomeres at baseline shortened more after 10 years. These observations were consistent with existing telomere research and provide an argument for calculating an adjusted telomere length to account for regression to the mean. The crude and adjusted change in T/S measures exhibited a strong linear relationship (Pearson's r = .91). Three additional change in telomere length cutoffs were derived to illustrate its public health relevance and to provide context for the overall study population. First, telomere length (T/S) was converted to base pairs using the formula: $basePairs = 3274 + 2413 \times \frac{T}{S}$. Second the 10-year percent change in base pairs since baseline, $[(Y_{tij} - Y_{t-1,ij})/Y_{t-1,ij}] \times 100\%$, was discretized into three categories to examine the proportion of the study population that lengthened more than 10%, changed within +/- 10%, and shortened more than 10%. Finally, the lowest tertile of the change in T/S distribution ($\Delta T/S_{low} < -.28$) was used for illustrative purposes in the bivariate analyses that compared the change in telomere length and tertile of change in each neighborhood variable.

Study Exposures: Neighborhood Factors

Change in Neighborhood Physical Environment

Table 3.1 describes the physical environment variables in detail. Measures of the neighborhood physical environment included survey- and GIS-based items of physical activity resources and food environments. Each domain included one survey-based item, one Geographic Information System-based (GIS) item, and one composite item. In total, six previously validated (36, 57-60) physical environment measures were evaluated using separate models: walking environment, density of physical activity resources, physical activity environment composite, availability of healthy foods, density of favorable food stores, and food environment composite. All survey-based measures used assessments of a 1-mile radius surrounding the home, and neighborhood-level indicators were aggregates from the census-tract level. GIS-based measures represented kernel densities for the census tract. Information about specific types of recreation facilities and food environments were purchased using the National Establishments Time Series (NETS) data. Conditional empirical Bayes estimates were used to account for census tracts with small sample sizes or poor agreement among residents of the same area. Briefly, this method allows unreliable census tracts to borrow information from adjacent areas to improve the estimate.

Neighborhood change was: $A_{tj} - A_{t-1,j}$ (i.e., the change in each neighborhood variable score between Exam 5, t, and baseline, $t - 1$). All physical environment measures were continuous items, and higher values indicated better environments. Tertiles of each neighborhood change variable were used to illustrate dose-response relationships. The regression models used grand mean centered (i.e., mean subtracted from each response) neighborhood variables and the model coefficients were standardized to one standard deviation unit. Correlation among change in physical environment characteristics ranged from -.18 to .83 (see Figure 3.3). Changes in the GIS-based measures of physical activity and food environments were not correlated, but the survey-based measures had a moderate correlation. Changes in physical activity measures exhibited a weak, negative correlation and changes in the food environment variables had a weak, positive correlation.

(a) Physical activity resources: The physical activity environment was characterized using the walking environment (survey-based) and availability recreational facilities (GIS-based). Respondent-reported ratings of individual perceptions of the walking environment included six items measured on a five-point Likert scale based on previous work (58). The walking environment measure evaluated items such as opportunities to be physically active, aesthetic quality, and overall walkability. The availability of locations that promoted walking such as post offices, drug stores and pharmacies, banks, food stores, coffee shops, and restaurants were from lists used in prior work (59) to assess the walking environment. Recreational facilities represented the recreational and physical activity establishments such as indoor conditioning, dance, bowling, golf, team and racquet sports, and water activities derived from lists used in previous studies (36, 57). The composite score for the physical activity environment was the sum of the standardized conditional empirical Bayes survey- and kernel density GIS-based measures.

(b) Food Environment: The food environment was characterized using the availability of both healthy foods (survey-based) and favorable food stores (GIS-based). Respondent-reported ratings of the food environment included two items measured on a five-point Likert scale (60): (1) "A large selection of fresh fruits and vegetables is available in my neighborhood"; and (2) "A large selection of low-fat products is available in my neighborhood." Food stores were identified using Standard Industrial Classification (SIC) codes that identified supermarkets, grocery stores, fruit and vegetable markets, convenience stores, bakeries, fast food establishments, health food stores, alcoholic drinking places, and liquor stores. The composite score was the sum of the standardized conditional empirical Bayes survey- and kernel density GIS-based measures.

Additional Study Covariates

Change in Neighborhood Socioeconomic Status

Variables were selected for the construction of a factor-based score as described by Diez Roux *et al*. (61). Baseline data and boundaries were from the 2000 US Census. Exam 5 data were from the American Community Survey (ACS) 2007-2011 using the 2010 US Census boundaries. Six variables representing wealth and income (log of median household income, log of median value of housing units, and percent of households with interest, dividend, or net rental income), education (percent of adults 25 years and older with at least a high school degree and percent of adults 25 years and older with at least a Bachelor's degree), and occupation (percent of employed persons 16 and older in executive, managerial, or professional occupations) were standardized and summed together to create the score. An increasing score indicated a more socioeconomically advantaged area. Change neighborhood socioeconomic status was a continuous measure the difference between the baseline and follow-up measure. Bivariate analyses used tertile of neighborhood socioeconomic status. Neighborhood socioeconomic status exhibited weak to moderate correlations with the change in physical activity resources and change in food environment measures (Pearson correlation ranged from 0 to .48 and -.1 to -.18, respectively; see Figure 3.3).

Moving status

A *mover* was a participant who changed census tracts between baseline and follow-up (treatment group) to examine an acute change in context. An individual who moved to the same census tract or did not move at all was considered a non-mover (control group).

Baseline Sociodemographic Characteristics
All sociodemographic characteristics were time-constant covariates measured at baseline. Age was a continuous measure, and gender was a binary variable (male or female). Self-reported race/ ethnicity as from the baseline exam with levels for Black, Hispanic, and White. Participants were not permitted to select more than one category to describe their race/ ethnicity. Education had eight categories, and these values were re-coded as high school education or less, some college or associate/technical degree, and Bachelor's degree and higher. Per capita income adjusted for the number of people supported per $10,000 [(continuous income/# people supported)/10,000

Lifestyle Risk Factors: Lifestyle factors were from baseline. Physical activity was assessed using the MESA Typical Week Physical Activity Survey adapted from the well-validated Cross-Cultural Activity Participation Study (64). Analyses considered moderate/vigorous physical activity (MET-min/day standardized). Participants who reported more than 18 hours of physical activity per day were removed from the sample as standard practice with MESA data. The Alternative Eating Index was a general diet score. The Alternative Healthy Eating Index provided a scoring criterion based on eleven components (ideal: fruit, vegetable, nuts, omega-3 fats, and polyunsaturated fats; moderate: alcohol; and avoidance: sugar sweetened beverages, red and processed meat, trans fat, and sodium) (65). These measures of physical activity and diet were continuous measures, and higher values indicated more physical activity and better diet, respectively.

Statistical analyses
Means and proportions were used to the describe distribution of the study sample across population characteristics. ANOVA assessed differences in mean change in telomere length (T/S ratio) by each study variable. Two-level mixed effects models were used to compare 10-year changes in built environment features with the change in telomere length.

The two-level mixed effects models included a random intercept for census tract. Regression coefficients described mean change in telomere length per standard deviation unit change in each grand mean centered neighborhood variable. An unconditional model was used to estimate the proportion of the total variance in change in telomere length that was due to between-neighborhood variation. Sequential models were presented to show whether lifestyle factors or change in neighborhood socioeconomic status attenuated the association between changes in neighborhood environments and change in telomere length. The first model only included the neighborhood change variable of interest. The second model, the primary model, examined the neighborhood change variable and adjusted for baseline sociodemographic characteristics, such as age, sex, race/ ethnicity, income, and education. The third model had the neighborhood change variable and baseline measures of individual-level sociodemographic characteristics, diet, and physical activity. The fourth model examined the association of neighborhood change variable, independent of sociodemographic characteristics and change in neighborhood socioeconomic status. Each built environment feature was in a separate model. All measures of association were tested using crude and adjusted change in telomere length.

$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1(A_{tj} - A_{t-1,j}) + \epsilon_{tij} \text{ (Model 1)}$$
$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1(A_{tj} - A_{t-1,j}) + \beta_2 \boldsymbol{W}_{ij1} + \epsilon_{tij} \text{ (Model 2)}$$

$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1\left(A_{tj} - A_{t-1,j}\right) + \beta_2 \boldsymbol{W}_{ij1} + \beta_3 \boldsymbol{W}_{ij2} + \epsilon_{tij} \text{ (Model 3)}$$
$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1\left(A_{tj} - A_{t-1,j}\right) + \beta_2 \boldsymbol{W}_{ij1} + \beta_3\left(Z_{tj} - Z_{t-1,j}\right) + \epsilon_{tij} \text{ (Model 4)}$$

Where,
t is the time index
i is the subject
j is the neighborhood cluster
$Y_{tij} - Y_{t-1,ij}$ is the change in telomere length between follow-up, t, and baseline, $t-1$
β_0 is the overall intercept
ζ_j is the neighborhood-specific intercept (random effect)
β_1 is the coefficient for the association between a standard deviation unit change in neighborhood characteristic, $A_{tj} - A_{t-1,j}$, and the mean change in telomere length between baseline and follow-up
$\boldsymbol{W}_{tij1}$ is a vector of time constant (age, sex, race/ ethnicity, education, and income) sociodemographic characteristics
$\boldsymbol{W}_{tij2}$ is a vector of lifestyle factors (moderate/ vigorous physical activity and AHEI diet score)
$Z_{tj} - Z_{t-1,j}$ is change in neighborhood socioeconomic status

Additional models examined moving status. The treatment group included those who moved between exams and the control group includes subjects who moved within the same census tract or did not move between assessments. The approach used a difference-in-difference (DD) model. This specification added two predictors to Model 2: an indicator variable for moving status and a cross-product term for neighborhood change and moving status. The statistical significance of the cross-product term, β_4, tested the effect of neighborhood change due to moving from one context to another on the change in telomere length.

$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1\left(A_{tj} - A_{t-1,j}\right) + \beta_2 \boldsymbol{W}_{ij1} + \beta_3 M_{tij} + \beta_4\left(A_{tj} - A_{t-1,j}\right) \times M_{tij} + \epsilon_{tij} \text{ (Model DD)}$$

Where,
M_{tij} is the indicator for moving status (1=mover, treatment; 0=non-mover, control)
β_4 is the coefficient the exhibit the mean change in telomere length associated with a one standard deviation unit change in neighborhood change among movers

Sensitivity analyses ensured the validity of the study results. Associations with tertiles of each neighborhood variable helped to assess nonlinearity and dose-response relationships. Regression to the mean was a significant concern for measuring the change in LTL over time, particularly with respect to telomere lengthening. All linear mixed effects models were run using a corrected measure of LTL change that adjusts for regression to the mean (71) to assess bias in the estimates of association.

All analyses were completed using the R software using the *lme4* and *lmerTest* packages with the restricted maximum likelihood (REML) option and Satterthwaite approximations for degrees of freedom. Statistical significance was defined at p-values <.05, and statistically significant cross-product terms were defined at p-values <.1.

3.3 Results

Table 3.2 describes the population characteristics. Participants had a mean age of 61.7 years. Fifty-one percent of respondents were women, and most were from racial/ ethnic minority backgrounds (45% Hispanic, 25% black, and 31% white). Eighteen percent of the sample had moved at least once between baseline and follow-up visits (data not shown). Participants originated from 427 census tracts that ranged in size from 1 to 11 persons per census tract. Mean follow-up time was 9.5 years (Range: 8 to 11 years; data not shown).

Average crude telomere length change was -.21 (Standard Deviation [SD] = .19) and the mean adjusted change in T/S ratio was -0.01 (SD=0.18). When converted to base pairs, telomere there was a 9% decline in telomere length on average. Using the categorical distribution of percent change in base pairs, 45.6% of the sample experienced more than a 10% reduction, 53.4% had +/- 10% change, and only .009% lengthened more than 10%. These data were not shown. All descriptions below use crude change in telomere length unless stated otherwise.

Telomere shortening, measured by crude change in T/S ratio, occurred most rapidly among those in the middle age tertile (range: 55-64 years; Mean [SD]: -.24 [.18]), compared to other age groups (p=.014). Men shortened more than women during the 10-year period (p=.047), and telomere attrition was slowest among blacks, followed by Hispanics, and then whites (p<.0001). There were no bivariate associations between change in telomere length and income, education, diet, or physical activity. Participants who moved did not experience more telomere shortening than those who stayed in the same neighborhood (data not shown; $p > .05$).

During the 10-year period, only the GIS-based measure of favorable food environment became worse. All other indicators of physical activity and food environments improved between baseline and Exam 5 (data not shown). Figure 3.4 compared the mean change in telomere length by tertile of change in each built environment feature. In general, persons in the middle or high tertile of built environment change (i.e., the most improvement) experienced the most telomere shortening compared to those in the low tertile (survey-based walking environment: $p < .001$, survey-based availability of healthy foods: $p < .001$, GIS-based favorable food stores: $p < .01$, and food environment composite: p<.001). The only exception was that those in the high tertile of change in the GIS-based measured of physical activity resources experienced the least telomere shortening ($p < .001$) compared to those in the middle and low tertiles. There was a similar trend for neighborhood socioeconomic status where people from the most improved areas experienced the least shortening (p<.05). The bivariate associations between mean change in telomere length and tertile of change in physical activity and food environment did not differ by moving status (all p >.05, see Figure 3.5). However, mean change in telomere length among movers in the high tertile of walking environment change and middle tertile of the food environment composite measure surpassed the threshold for the lowest tertile of the change in T/S distribution ($\Delta T/S_{low} < -.28$).

The linear mixed effects models exhibited consistent trends across model specifications. The ICC for the proportion of variance in the change in telomere length due to between-neighborhood variability was 26.4%. The results of the linear mixed effects and difference-in-differences model, by neighborhood domain, are below.

Physical activity environment

The physical environment did not influence changes in telomere length uniformly. The GIS-based measure of physical activity resources and the survey-based measure of the walking environment were opposite in direction and differed in magnitude. Per standard deviation unit increase in the change in neighborhood walking environment, there was .17 unit decrease in mean change telomere length, after adjusting for age, sex, and individual-level socioeconomic status (95% Confidence Interval [CI]= -.24, -.10; see Table 3.3, Model 2). Conversely, the GIS-based measure of physical activity resource availability had a positive association with change in telomere length (Standardized Beta [Std. β] and 95% CI=.08 [.01, .16]; see Table 3.3, Model 2), independent of age, sex, and individual-level socioeconomic status. Diet and physical activity did not attenuate either association, but the change in neighborhood-level socioeconomic status attenuated the association of change in physical activity resources (see Table 3.3, Models 2-4). Models that used adjusted telomere length exhibited similar patterns (see Table 3.4; Models 2-4).

Tertiles of physical environment characteristics showed a clear dose-response trend for the change in walking environment. When compared to the low tertile of change in walking environment, the high and medium tertiles the Std. β (95% CI) were -.17 (-.26, -.08) and -.09 (-.18, -.01), respectively, after adjustment for age, sex, gender, and individual-level socioeconomic status (see Table 3.5, Model 2). Only the high versus low tertile comparisons for the GIS-based indicator of physical activity resources yielded a statistically significant association (Std. β [95% CI] =.14 [.05, .22]), which was in the same direction and almost two times the magnitude of the continuous measure. Additional adjustment for diet, physical activity, and change in neighborhood socioeconomic status did not attenuate the associations of tertiles of physical activity resources and the change in telomere length (see Table 3.5, Models 2-4). Models that used the adjusted telomere length as the dependent variable exhibited similar patterns (see Table 3.6, Models 2-4).

Further inspection of this association among movers and non-movers, using the difference-in-differences approach did not reveal any statistically significant cross-product terms (all $p > .05$; see **Table 3.7** and **Table 3.8**).

Food environment

Similar to the physical activity environment, measures of the change in survey-based food environment measures exhibited a stronger magnitude of association than the change in the GIS-based measure. Per standard deviation unit increase in the change in the availability of healthy foods, there was a .15 decrease in mean change telomere length, after adjusting for age, sex, gender, and individual-level socioeconomic status (95% CI=-.23, -.08; see Table 2.4, Model 2). Diet, physical activity, and neighborhood-level socioeconomic status did not attenuate this association. Change in favorable food stores was only associated with the crude, but not the adjusted change in telomere length (see and Table 3.4 and Table 3.4).

The analyses revealed a dose-response relationship of tertiles of change in the food environment. Specifically, compared to those in the low tertile, those in the middle and high tertile of change in the availability of healthy foods experienced more telomere shortening, -.09 (95% CI =-.18, -.01) and -.17 (95% CI =-.26, -.09), respectively. Similarly, the compared to the low tertile of change in the GIS-based measure of favorable food stores, there was a 0.1 unit decrease in mean change in telomere length among the middle tertile (95% CI =-0.19, -0.02; see Table 3.5, Model 2). Including diet, physical activity, and change in neighborhood socioeconomic status did not attenuate the results of the tertile analyses. However, the comparison of the high versus low tertile of favorable food stores was only statistically significant when the adjusted change in telomere length was the outcome (see Table 3.6, Models 2-4).

There were no statistically significant cross-product terms between changes in neighborhood exposures and moving status (all $p > .05$; see **Table 3.7** and **Table 3.8**). However, the GIS-based measure of physical activity resources exhibited a trend towards dissimilarity across strata of moving status. The models showed that among those who stayed in the same neighborhood, there was a larger positive effect of change in physical activity resources on change in telomere length, independent of age, sex, race/ ethnicity, income, and education (Std. β [95% CI] Non-movers: 0.12 [0.03, 0.2] and Std. β [95% CI] Movers: 0.01 (-0.16, 0.18); see **Table 3.7**). These findings, albeit not statistically significant, were similar even when the adjusted measure of change in telomere length was used (see **Table 3.8**). It is important to note that fifty percent movers went to a neighborhood with similar physical activity resources, so there was little information to gain from these subjects.

3.4 Discussion

This study examined whether changes in physical activity and food environments were associated with the 10-year change in telomere length using a racially/ ethnically and socioeconomically diverse sample of middle-aged and older adults. The principal hypothesis was that improvements in built environment features would result in less telomere length shortening or maintenance over time. The results suggested that increased availability of physical activity resources was associated with telomere maintenance, but improvements in perceived physical activity and food environments slowed telomere shortening. These findings were robust to adjustments for sociodemographic characteristics, lifestyle factors, and change in neighborhood socioeconomic status. Moving did not have any added influence on these associations. This study was the first to examine the relationship between change in the built environment and change in telomere length.

A few points are needed to provide context to interpret these results. First, the average crude change in T/S was -.21 and -.01 for the adjusted change. The lowest tertile of unadjusted change in T/S was -.28. Positive neighborhood changes helped to slow telomere shortening since the standardized regression coefficients in the crude change in T/S models ranged from -.17 to .08 and -.17 to .09 in the models that used the adjusted change in T/S. Second, about 1% of the sample experienced an increase in base pairs that was greater than 10% of their baseline value. Thus, positive regression coefficients should be perceived as *maintenance,* not *lengthening*. The more negative a coefficient, the more shortening occurred in response to the neighborhood improvement; whereas, telomeres shortened less or maintained their length when measures of association were closer to the null. Third, the crude and adjusted measures of change in telomere length yielded results that were similar in magnitude. As a result, the results were valid even if regression towards the mean was present. Finally, moving from one context to another did not impact the change-in-change analyses, so interpretation of the pooled analyses is suitable.

The underlying assumption for these analyses was that neighborhood features and subjective experiences of neighborhood contexts might influence health via two potential pathways: (1) psychosocial stress resulting from exposure to adverse built and social contexts, and (2) inadequate access to resources for healthy lifestyle choices (1). This study focused on the latter pathway to examine whether changes in access to or perceptions of neighborhood resources for healthy living was related to the change in telomere length, independent of sociodemographic characteristics, lifestyle, and change in neighborhood socioeconomic status. The hypothesis was that telomeres would shorten over time, but improvements in the physical activity and food environments would help to lessen telomere attrition over 10 years. In a five-year randomized control trial of men with prostate cancer, comprehensive changes in diet, exercise, stress management, and social support were reported to increase telomere length (72). Studies of long-term telomere lengthening have received criticism because of the consistent association between telomere shortening and increased age (6, 70, 73). Indeed, the telomere-telomerase dynamic suggests that there may be a compensatory activation of telomerase that rebuilds telomeres over a short duration (70); however, this assertion is problematic over the life course because there is an overall inverse association between LTL and age. Depending on a study's duration, one may observe conflicting results due to the oscillation of telomere length during short observation periods. Rather, it is more reasonable to suggest that certain health promoting behaviors and improved access to resources that support healthy living may slow but not completely prevent telomere attrition. In this study, improvements in the availability of physical activity resources, the perception of physical activity resources, and subjective assessments of the food environment exhibited associations with the change in telomere length.

Neighborhoods frame access to resources for healthy living. Residents of high-walkability neighborhoods engage in more physical activity than persons who reside in low-walkability neighborhoods (74). Similarly, individuals who lived in environments with more access to healthy foods have better diets (75). A systematic review of the association between telomere length and exercise uncovered few longitudinal studies (20). There was evidence of a positive association between physical activity and LTL in both human and animal models, but some studies identified a linear association while others indicated a U-shaped dose-response curve (20). Cross-sectional studies that examined diet found that consumption of processed meats was associated with shorter LTL (19), drinking sugar-sweetened beverages was related to short LTL (66), and the Mediterranean diet was positively associated with longer LTL (18). Neither diet nor exercise was related to the change in telomere length in this study; however, the models retained these lifestyle variables given the *a priori* knowledge that suggested otherwise in cross-sectional analyses. Also, built environment contexts are not homogeneous; thus, accounting for socioeconomic heterogeneity was key to estimating unbiased measures of association. The physical characteristics of neighborhoods vary across the spectrum of socioeconomic status (58). There is evidence to suggest that the location of recreational resources differed by neighborhood socioeconomic status. Specifically, fee-requiring activities in recreational facilities were predominant in high-income areas; whereas, park-based free activities were more prevalent in low-income areas (76). There was a similar trend for the availability of healthy foods. Access to healthy foods is not equitable across levels of neighborhood socioeconomic status or by racial/ ethnic composition (77). It is detrimental to conflate the built environment resources of a neighborhood with its socioeconomic composition; thus, future research should also consider effect modification, by the level of change in neighborhood socioeconomic status.

Studies of neighborhood change are rare, and this study attempted to leverage the econometric difference-in-differences approach to examine the added influence of moving (treatment group). The difference-in-differences estimation technique had a few key assumptions: (1) there should be a sharp change in exposure, (2) the difference between groups should be constant over time (parallel trends), and (3) there should be an exogenous source of variation in exposure. Unfortunately, the parallel trends assumption of the double difference approach was unverifiable because only two time points of data were available. This study assumed that baseline neighborhood exposure was representative of past exposure (67). Mobility across neighborhood contexts was limited; thus, it was unlikely that there was a violation of the parallel trends assumption. During the study period, however, most movers migrated to areas with similar levels of physical environment resources. Thus, the change in telomere length among people who moved was comparable to those who stayed in the same context.

Certainly, no study is without limitation. Some limitations of this study were related to information bias, confounding, selection, and external validity. First, this study used both surveys and GIS-based measures of the physical activity and food environments to exhibit the robustness of the results and juxtapose objective and subjective measures. The GIS-based measures represented densities of the actual presence of physical activity resources and outlets for healthy foods. The survey-based measures of the walking environment and availability of healthy foods measured the presence and quality of the available neighborhood resources. The distinction between these measures was also present in the empirical results, in which the magnitude of survey-based items was almost twice that observed for GIS-based measures. Put simply, the associations of attitudes towards availability were more pronounced than the actual densities of resources. Future research should consider the types, qualities, costs, and attractiveness of neighborhood resources (76). Furthermore, resources in adjacent neighborhoods or in an area where individuals work or attend school (78) could also help to reduce the gap between perceptions versus utilization of neighborhood resources. Telomere length was measured at two time points, spaced 10 years apart. Sample degradation and stability from freeze-thaw cycles were a concern. However, a number of stringent laboratory methods were utilized to ensure that the data were not compromised. It is not likely that misclassification differed by the outcome or exposure, so the resulting measures of association may be biased towards or away from the null. Second, the measures of association were shown to operate independent of lifestyle factors (physical activity and diet) and change in neighborhood socioeconomic status, but residual confounding may still exist. In addition, income was treated as a time-constant covariate although neighborhood change could also influence financial resources via employment or other mechanisms. Third, social selection was a concern, and novel methods were used to surmount this potential source of bias. Questions remained as to whether the moving was a random phenomenon and if health status motivated the decision to move. Furthermore, only two time points of data were available. Future research should consider at least three, moderately spaced measurements to delve into both short- and long-term variability. Fourth, the study's population characteristics limit the external validity of these results. The sample comprised of middle-aged and older adults who lived in urban settings; thus, extrapolations to other populations may be biased.

3.5 Conclusion

This study was the first to examine change in telomere length in response to changes in both physical activity resources and food environments. Improvement in the availability of physical activity resources was associated with telomere length maintenance over 10 years. Positive changes in perceptions of physical activity resources and food environments also helped to slow telomere length attrition. Future research should consider utilization of physical activity and food resources. Using shorter time intervals and more time points of observation can also help to refine the understanding of cell aging trajectories in response to changes in residential areas.

3.6 Tables and figures

Tables

Table 3.1 Definitions of Physical Environment Measures Used in Analyses of Baseline Data From the Multi-Ethnic Study of Atherosclerosis' Longitudinal Neighborhoods Study (2000-2010)

Neighborhood Feature	Scale Summary and Items	Unit
Food Environment		
Availability of Healthy Foods, S	1. A large selection of fresh fruits and vegetables is available in my neighborhood. 2. A large selection of low-fat products is available in my neighborhood.	Census tract
Favorable Food Stores, G	Kernel density total of supermarket chain and non-chain and fruit and vegetable markets. The unit of measure is number of facilities per square mile.	Census tract
Healthy Food Environment, G/S*	Composite measure of GIS-based and survey-based scores for Favorable Food Stores + Availability of Healthy Foods. Sum of standardized conditional empirical Bayes scale score and kernel density estimates.	Census tract
Physical activity Environment		
Walking Environment, S	1. My neighborhood offers many opportunities to be physically active. 2. Local sports clubs and other facilities in my neighbourhood offer many opportunities to get exercise. 3. The trees in my neighborhood provide enough shade. 4. In my neighborhood it is easy to walk [to] places. 5. I often see other people walking in my neighborhood. 6. I often see other people exercising (for example, jogging, bicycling, playing sports) in my neighborhood.	Census tract
Physical Activity Resources, G	Kernel density total of resources for physical activity, instruction, and water activities. The unit of measure is number of facilities per square mile.	Census tract
Physical Activity Environment, G/S*	Composite measure of GIS-based and survey-based	Census tract

Neighborhood Feature	Scale Summary and Items	Unit
	scores for Physical Activity Resources + Walking Environment. Sum of standardized conditional empirical Bayes scale score and kernel density estimates. Does not include parks.	

Note. G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure

Table 3.2 Summary of Population Characteristics and Mean Telomere Length in the Multi-Ethnic Study of Atherosclerosis, 2000-2010 (N=747)

Characteristic	Study Population		Telomere Length	
	Mean (SD)	***N (%)***	***Mean (SD)***	***P***
Age	61.73 (9.43)			**0.014**
45-54		201 (26.9)	-0.21 (0.2)	
55-64		235 (31.5)	-0.24 (0.18)	
65 and older		311 (41.6)	-0.19 (0.18)	
Race/ ethnicity				**<.0001**
White		229 (30.7)	-0.23 (0.19)	
Black		185 (24.8)	-0.17 (0.17)	
Hispanic		333 (44.6)	-0.23 (0.18)	
Gender				**0.047**
Female		379 (50.7)	-0.23 (0.17)	
Male		368 (49.3)	-0.2 (0.2)	
Education				0.057
High school or less		316 (42.3)	-0.22 (0.18)	
College or technical school		191 (25.6)	-0.23 (0.21)	
University or graduate		240 (32.1)	-0.19 (0.17)	
Adjusted per capita income (Per $10,000)	2.38 (1.84)			0.439
Low tertile (<1.375)		249 (33.3)	-0.22 (0.18)	
Middle tertile (1.375-2.183)		249 (33.3)	-0.22 (0.2)	
High tertile (>2.183)		249 (33.3)	-0.20 (0.18)	
Alternative Healthy Eating Index score	53.23 (11.14)			0.445
Low tertile (<48.3)		249 (33.3)	-0.21 (0.19)	

Characteristic	Study Population		Telomere Length	
	Mean (SD)	***N (%)***	***Mean (SD)***	***P***
Middle tertile (48.3-57.8)		249 (33.3)	-0.21 (0.19)	
High tertile (>57.8)		249 (33.3)	-0.23 (0.18)	
Physical activity (MET-min/day standardized)	4811.55 (3858.72)			0.762
Low tertile (<2,530)		249 (33.3)	-0.22 (0.18)	
Middle tertile (2,530-5,528)		249 (33.3)	-0.21 (0.18)	
High tertile (>5,528)		249 (33.3)	-0.21 (0.2)	

Note. P-values obtained via ANOVA test for the differences in means, by category of each population characteristic. Post-hoc tests were not administered.

Table 3.3 Associations of Change in Neighborhood Built Environment Features and Change Telomere Length in MESA, 2000-2010 (N=747)

	Model 1	**Model 2**	**Model 3**	**Model 4**
	Std. β (95% CI)	**Std. β (95% CI)**	**Std. β (95% CI)**	**Std. β (95% CI)**
Physical Activity Environment				
Walking Environment, S	**-0.19 (-0.27, -0.12)**	**-0.17 (-0.24, -0.10)**	**-0.17 (-0.24, -0.09)**	**-0.17 (-0.24, -0.09)**
Physical Activity Resources, G	**0.09 (0.01, 0.16)**	**0.08 (0.01, 0.16)**	**0.08 (0.01, 0.15)**	0.04 (-0.04, 0.12)
Physical Activity Environment, GS*	-0.07 (-0.15, 0.00)	-0.06 (-0.13, 0.02)	-0.05 (-0.13, 0.02)	**-0.11 (-0.19, -0.03)**
Food Environment				
Availability of Healthy Foods, S	**-0.18 (-0.26, -0.11)**	**-0.15 (-0.23, -0.08)**	**-0.15 (-0.22, -0.08)**	**-0.14 (-0.21, -0.06)**
Favorable Food Stores, G	**-0.1 (-0.17, -0.02)**	**-0.08 (-0.15, -0.01)**	**-0.08 (-0.15, -0.01)**	-0.07 (-0.14, 0.00)
Healthy Food Environment, GS*	**-0.19 (-0.26, -0.11)**	**-0.16 (-0.23, -0.09)**	**-0.16 (-0.23, -0.09)**	**-0.15 (-0.22, -0.07)**

Notes. Bolded items are statistically significant ($p \leq .05$). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood variable
Model 2: neighborhood variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood variable, age, sex, race/ ethnicity, income, education, diet, and physical activity
Model 4: neighborhood variable, age, sex, race/ ethnicity, income, education, and change in neighborhood socioeconomic status

Table 3.4 Associations of Change in Neighborhood Built Environment Features and Adjusted Change Telomere Length in MESA, 2000-2010 (N=747)

	Model 1 Std. β (95% CI)	Model 2 Std. β (95% CI)	Model 3 Std. β (95% CI)	Model 4 Std. β (95% CI)
Physical Activity Environment				
Walking Environment, S	**-0.2 (-0.27, -0.12)**	**-0.17 (-0.24, -0.09)**	**-0.16 (-0.24, -0.09)**	**-0.16 (-0.23, -0.09)**
Physical Activity Resources, G	**0.09 (0.02, 0.17)**	**0.09 (0.01, 0.16)**	**0.08 (0.01, 0.16)**	0.04 (-0.05, 0.12)
Physical Activity Environment, GS*	-0.07 (-0.15, 0)	-0.05 (-0.12, 0.02)	-0.05 (-0.12, 0.02)	**-0.11 (-0.19, -0.04)**
Food Environment				
Availability of Healthy Foods, S	**-0.17 (-0.25, -0.1)**	**-0.14 (-0.21, -0.06)**	**-0.14 (-0.21, -0.06)**	**-0.12 (-0.19, -0.05)**
Favorable Food Stores, G	**-0.08 (-0.16, -0.01)**	-0.07 (-0.14, 0)	-0.07 (-0.14, 0)	-0.06 (-0.13, 0.01)
Healthy Food Environment, GS*	**-0.18 (-0.25, -0.1)**	**-0.14 (-0.22, -0.07)**	**-0.14 (-0.21, -0.07)**	**-0.13 (-0.2, -0.05)**

Notes. Bolded items are statistically significant (p≤.05). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood variable
Model 2: neighborhood variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood variable, age, sex, race/ ethnicity, income, education, diet, and physical activity
Model 4: neighborhood variable, age, sex, race/ ethnicity, income, education, and change in neighborhood socioeconomic status

Table 3.5 Associations by Tertile of Neighborhood Built Environment Features and Telomere Length in MESA, 2000-2010 (N=835)

	Level	Model 1 Std. β (95% CI)	Model 2 Std. β (95% CI)	Model 3 Std. β (95% CI)	Model 4 Std. β (95% CI)
Physical Activity Environment					
Walking	M	**-0.1 (-0.19, -0.01)**	**-0.09 (-0.18, -0.01)**	**-0.09 (-0.18, -0.01)**	**-0.1 (-0.19, -0.02)**
Environment, S	H	**-0.19 (-0.28, -0.11)**	**-0.17 (-0.26, -0.08)**	**-0.17 (-0.25, -0.08)**	**-0.16 (-0.25, -0.08)**
Physical Activity Resources, G	M	0 (-0.08, 0.08)	0 (-0.08, 0.08)	0 (-0.08, 0.08)	0 (-0.08, 0.09)
	H	**0.14 (0.06, 0.23)**	**0.14 (0.05, 0.22)**	**0.14 (0.05, 0.22)**	**0.11 (0.02, 0.21)**
Physical	M	-0.02 (-0.11, 0.06)	-0.02 (-0.1, 0.07)	-0.02 (-0.1, 0.07)	-0.03 (-0.12, 0.05)

Activity Environment, GS*	H	-0.06 (-0.15, 0.03)	-0.05 (-0.13, 0.04)	-0.04 (-0.13, 0.04)	-0.09 (-0.18, -0.01)
Food Environment					
Availability of Healthy Foods, S	M	**-0.12 (-0.21, -0.03)**	**-0.09 (-0.18, -0.01)**	**-0.09 (-0.18, -0.01)**	**-0.09 (-0.18, -0.01)**
	H	**-0.21 (-0.29, -0.12)**	**-0.17 (-0.26, -0.09)**	**-0.17 (-0.26, -0.09)**	**-0.16 (-0.24, -0.07)**
Favorable Food Stores, G	M	**-0.12 (-0.2, -0.03)**	**-0.1 (-0.19, -0.02)**	**-0.1 (-0.19, -0.02)**	-0.07 (-0.16, 0.01)
	H	**-0.1 (-0.18, -0.01)**	-0.08 (-0.16, 0)	-0.08 (-0.17, 0)	-0.06 (-0.15, 0.03)
Healthy Food Environment, GS*	M	**-0.2 (-0.28, -0.11)**	**-0.18 (-0.26, -0.09)**	**-0.18 (-0.26, -0.09)**	**-0.16 (-0.25, -0.08)**
	H	**-0.2 (-0.28, -0.11)**	**-0.16 (-0.25, -0.07)**	**-0.16 (-0.25, -0.07)**	**-0.14 (-0.23, -0.05)**

Notes. Each tertile is compared to the referent tertile, low. Bolded items are statistically significant (p≤.05). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. L = Low tertile; M = Middle tertile; H = High tertile. Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood variable
Model 2: neighborhood variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood variable, age, sex, race/ ethnicity, income, education, diet, and physical activity
Model 4: neighborhood variable, age, sex, race/ ethnicity, income, education, and change in neighborhood socioeconomic status

Table 3.6 Associations by Tertile of Neighborhood Built Environment Features and Adjusted Telomere Length in MESA, 2000-2010 (N=835)

	Level	Model 1 Std. β (95% CI)	Model 2 Std. β (95% CI)	Model 3 Std. β (95% CI)	Model 4 Std. β (95% CI)
Physical Activity Environment					
Walking Environment, S	M	**-0.1 (-0.19, -0.01)**	**-0.1 (-0.19, -0.02)**	**-0.1 (-0.19, -0.02)**	**-0.12 (-0.2, -0.03)**
	H	**-0.18 (-0.26, -0.09)**	**-0.15 (-0.24, -0.07)**	**-0.15 (-0.24, -0.07)**	**-0.15 (-0.23, -0.06)**
Physical Activity Resources, G	M	-0.01 (-0.09, 0.07)	0 (-0.08, 0.08)	-0.01 (-0.09, 0.07)	0 (-0.08, 0.08)
	H	**0.15 (0.06, 0.23)**	**0.14 (0.06, 0.22)**	**0.14 (0.05, 0.22)**	**0.1 (0.01, 0.2)**
Physical Activity Environment, GS*	M	0 (-0.08, 0.09)	-0.01 (-0.1, 0.07)	-0.01 (-0.09, 0.07)	-0.03 (-0.11, 0.05)
	H	-0.05 (-0.14, 0.03)	-0.04 (-0.12, 0.05)	-0.04 (-0.12, 0.05)	-0.09 (-0.18, 0)
Food Environment					
Availability of Healthy Foods,	M	**-0.13 (-0.21, -0.04)**	**-0.1 (-0.18, -0.01)**	**-0.09 (-0.18, -0.01)**	**-0.09 (-0.17, -0.01)**
	H	**-0.2 (-0.29, -0.11)**	**-0.16 (-0.25, -0.08)**	**-0.16 (-0.25, -0.08)**	**-0.14 (-0.23, -0.06)**

S					
Favorable Food	M	**-0.13 (-0.21, -0.04)**	**-0.1 (-0.18, -0.02)**	**-0.1 (-0.18, -0.02)**	-0.07 (-0.15, 0.02)
Stores, G	H	**-0.11 (-0.2, -0.03)**	**-0.09 (-0.17, -0.01)**	**-0.09 (-0.17, -0.01)**	-0.06 (-0.15, 0.02)
Healthy Food	M	**-0.24 (-0.32, -0.15)**	**-0.2 (-0.29, -0.12)**	**-0.2 (-0.29, -0.12)**	**-0.19 (-0.27, -0.1)**
Environment, GS*	H	**-0.18 (-0.27, -0.09)**	**-0.14 (-0.22, -0.05)**	**-0.13 (-0.22, -0.05)**	**-0.11 (-0.2, -0.03)**

Notes. Each tertile is compared to the referent tertile, low. Bolded items are statistically significant (p≤.05). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. L = Low tertile; M = Middle tertile; H = High tertile.
Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood variable
Model 2: neighborhood variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood variable, age, sex, race/ ethnicity, income, education, diet, and physical activity
Model 4: neighborhood variable, age, sex, race/ ethnicity, income, education, and change in neighborhood socioeconomic status

Table 3.7 Difference-in-Differences Approach of Associations Among Built Environment Features and Change in Telomere Length, by Moving Status in MESA, 2000-2010 (N=835)

Characteristic	Movers (N=138) Std. β (95% CI)	Non-movers (N=609) Std. β (95% CI)	P-value Interaction
Physical Activity Environment			
Walking Environment, S	-0.06 (-0.24, 0.13)	**-0.19 (-0.27, -0.11)**	0.330
Physical Activity Resources, G	0.01 (-0.16, 0.18)	**0.12 (0.03, 0.2)**	0.145
Physical Activity Environment, GS*	-0.02 (-0.19, 0.16)	-0.07 (-0.16, 0.01)	0.356
Food Environment			
Availability of Healthy Foods, S	-0.09 (-0.26, 0.09)	**-0.16 (-0.24, -0.08)**	0.893
Favorable Food Stores, G	**-0.18 (-0.34, -0.01)**	-0.04 (-0.12, 0.05)	0.201
Healthy Food Environment, GS*	-0.17 (-0.34, 0)	**-0.15 (-0.23, -0.07)**	0.852

Notes. Bolded items are statistically significant (p<.05) and statistically significant cross-product terms were defined at p<.1
Std. β = grand mean centered regression coefficient standardized to one standard deviation unit
Model: neighborhood change variable, mover, mover x neighborhood change variable age, sex, race/ ethnicity, income, education
P-value interaction: p-value for mover x neighborhood change variable interaction coefficient in the model

Table 3.8 Difference-in-Differences Approach of Associations Among Built Environment Features and Adjusted Change in Telomere Length, by Moving Status in MESA, 2000-2010 (N=835)

Characteristic	Movers (N=138) Std. β (95% CI)	Non-movers (N=609) Std. β (95% CI)	P-value Interaction
Physical Activity Environment			
Walking Environment, S	-0.05 (-0.23, 0.13)	**-0.19 (-0.27, -0.11)**	0.338
Physical Activity Resources, G	0.04 (-0.13, 0.2)	**0.12 (0.04, 0.2)**	0.154
Physical Activity Environment, GS*	0.01 (-0.17, 0.18)	-0.07 (-0.15, 0.01)	0.342
Food Environment			
Availability of Healthy Foods, S	-0.1 (-0.27, 0.07)	**-0.14 (-0.22, -0.06)**	0.987
Favorable Food Stores, G	-0.1 (-0.27, 0.07)	-0.05 (-0.13, 0.03)	0.715
Healthy Food Environment, GS*	-0.12 (-0.29, 0.05)	**-0.14 (-0.22, -0.07)**	0.781

Notes. Bolded items are statistically significant (p<.05) and statistically significant cross-product terms were defined at p<.1
Std. β = grand mean centered regression coefficient standardized to one standard deviation unit

Model: neighborhood change variable, mover, mover x neighborhood change variable age, sex, race/ ethnicity, income, education
P-value interaction: p-value for mover x neighborhood change variable interaction coefficient in the model

Table 3.9 Transition proportion table for movers, by tertile of access to physical activity resources (N=138)

		Exam 5 ***Neighborhood physical activity resources***		
		L	**M**	**H**
Exam 1 ***Neighborhood physical activity resources***	**L**	Consistently low 29.0%	Moderate increase 7.2%	High increase 2.9%
	M	Moderate decrease 15.9%	Consistently moderate 13.8%	Moderate increase 7.2%
	H	High decrease 2.9%	Moderate decrease 8.7%	Consistently high 12.3%

Figures

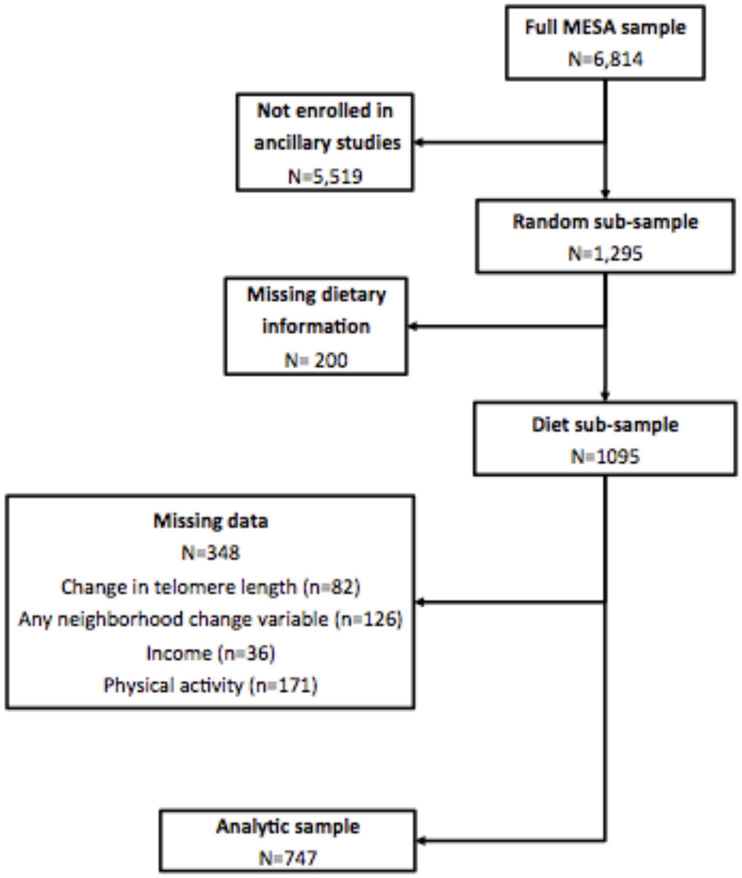

Figure 3.1 Data for these analyses originated from the baseline exam of the Multi-Ethnic Study of Atherosclerosis, 2000-2010. The analytic sample included data from a random sub-sample of subjects. Any respondent that was missing data on telomere length, neighborhood characteristics, demographic information, or lifestyle factors was excluded from the final sample. Overall, 747 subjects were used to examine the research objectives. *Note*. MESA = Multi-Ethnic Study of Atherosclerosis

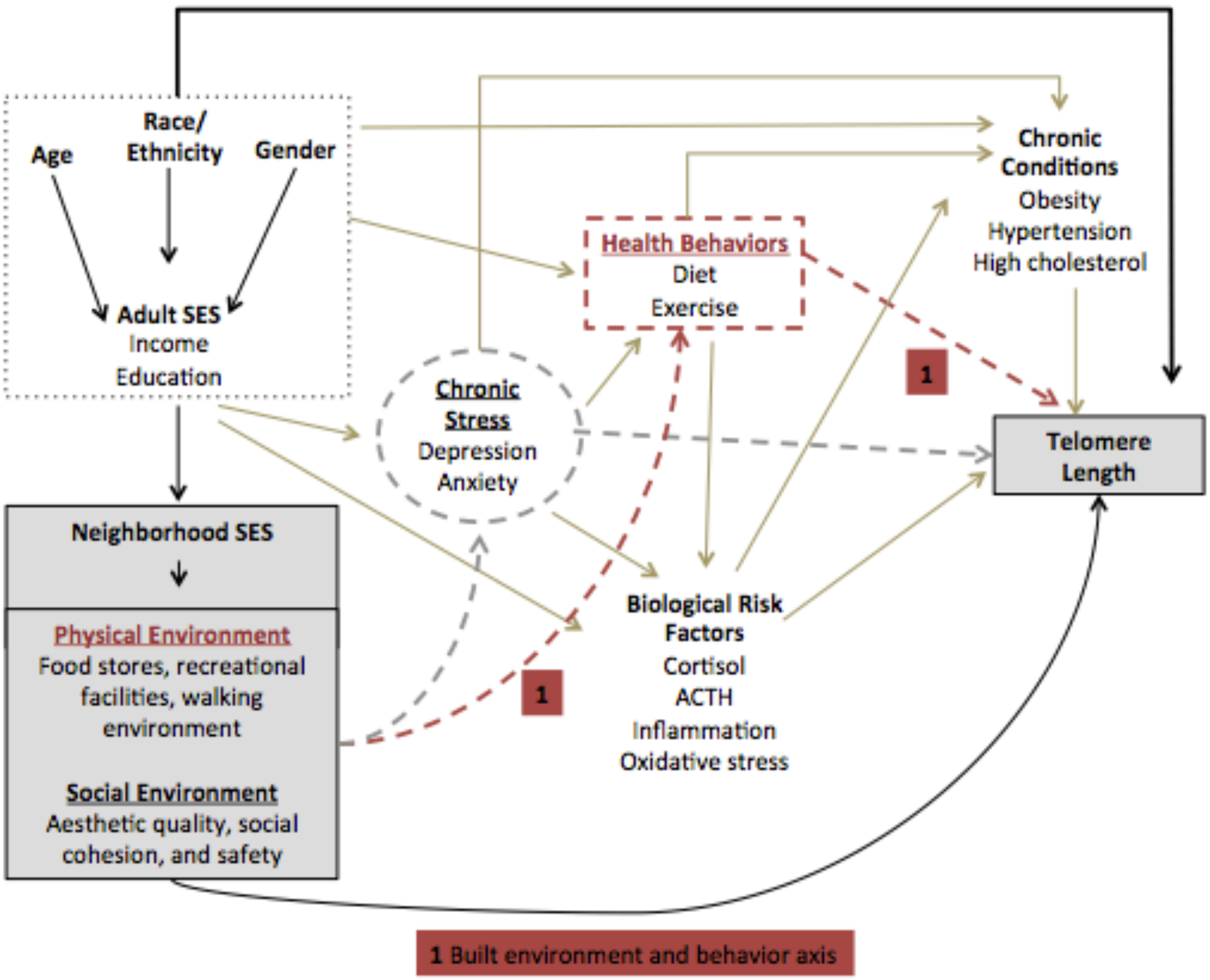

Figure 3.2 The conceptual framework that guided the analyses of neighborhood physical activity and food environments considered the following confounders: age, race/ ethnicity, gender, and individual-level socioeconomic status. Health behaviors (diet and exercise) and neighborhood socioeconomic status were included in subsequent models. All neighborhood physical environment features were modeled separately. Telomeres and neighborhoods also have numerous interrelationships with psychosocial stress, biological risk factors, and comorbidities; however, these relationships were not the focus of this research. Temporal ordering was assumed, but not shown in this diagram. *Note*. SES = socioeconomic status.

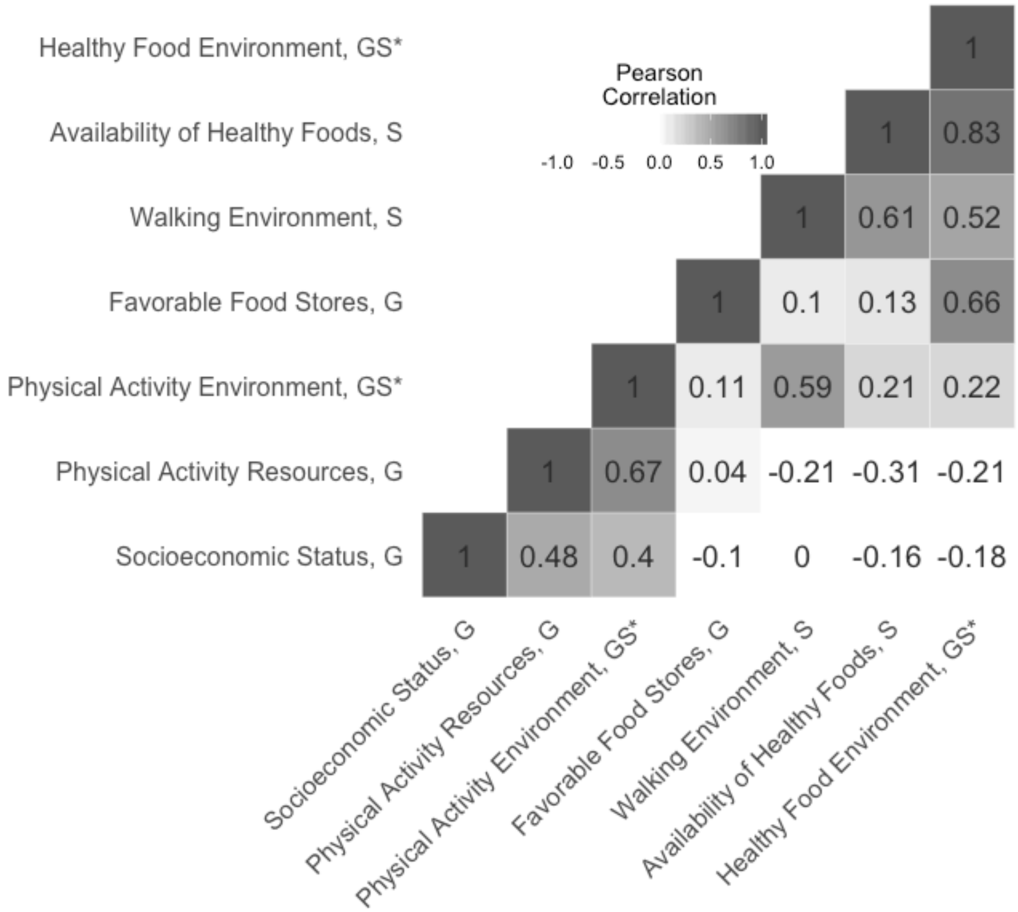

Figure 3.3 Pearson Correlation Among Change in Physical Environment Characteristics and Change in Neighborhood Socioeconomic Status (N=747) *Note*. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure.

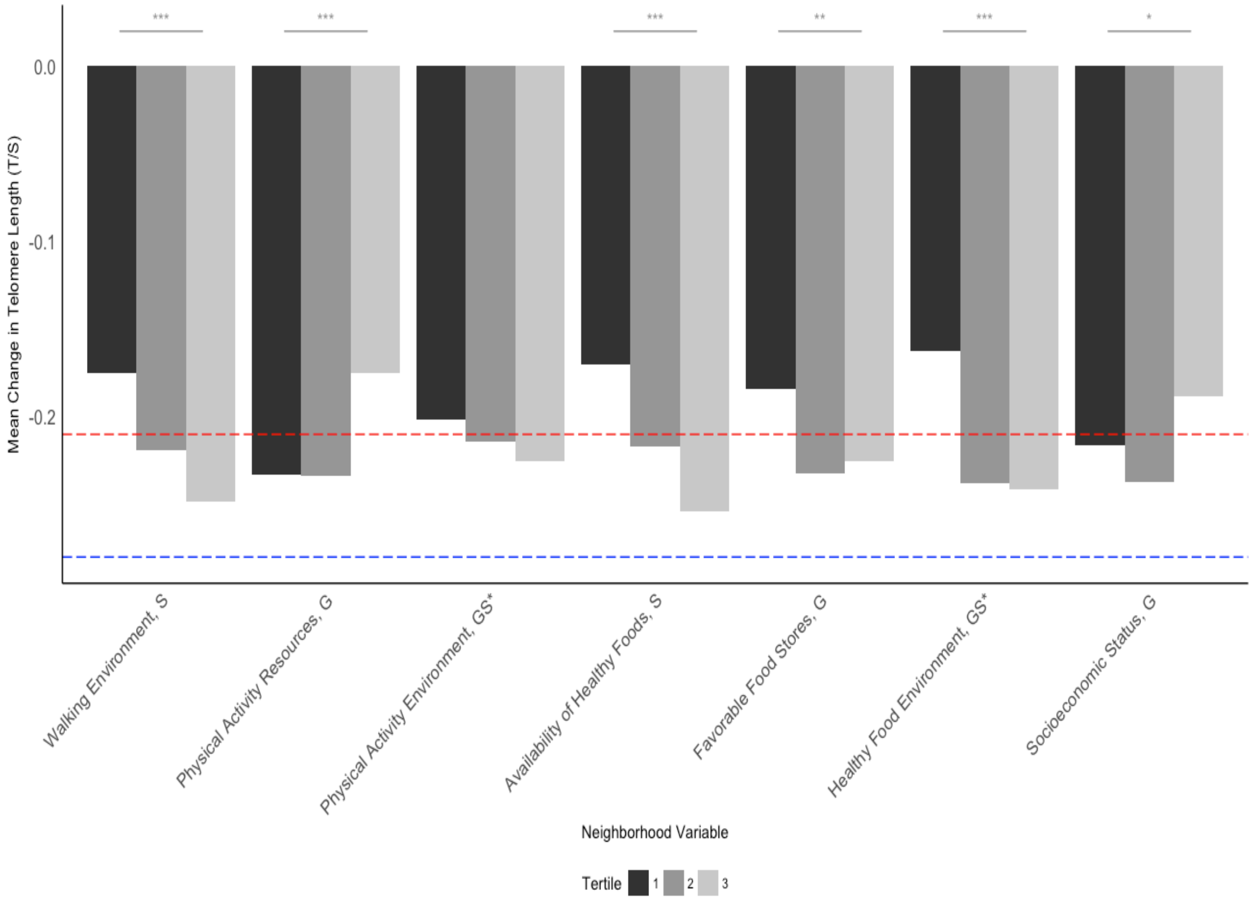

Figure 3.4 Mean change in telomere length (crude T/S) differed by tertile of change in each neighborhood characteristic. The red horizontal line indicates the overall mean change telomere length in the sample, -.21 (SD = .18). The blue horizontal line indicates the threshold for short telomere length for those in the lowest tertile of the distribution (T/S=-.28). *Notes*. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Statistical significance thresholds for the ANOVA tests were set at * for $p<.05$, ** for $p<.01$, and *** $p<.001$.

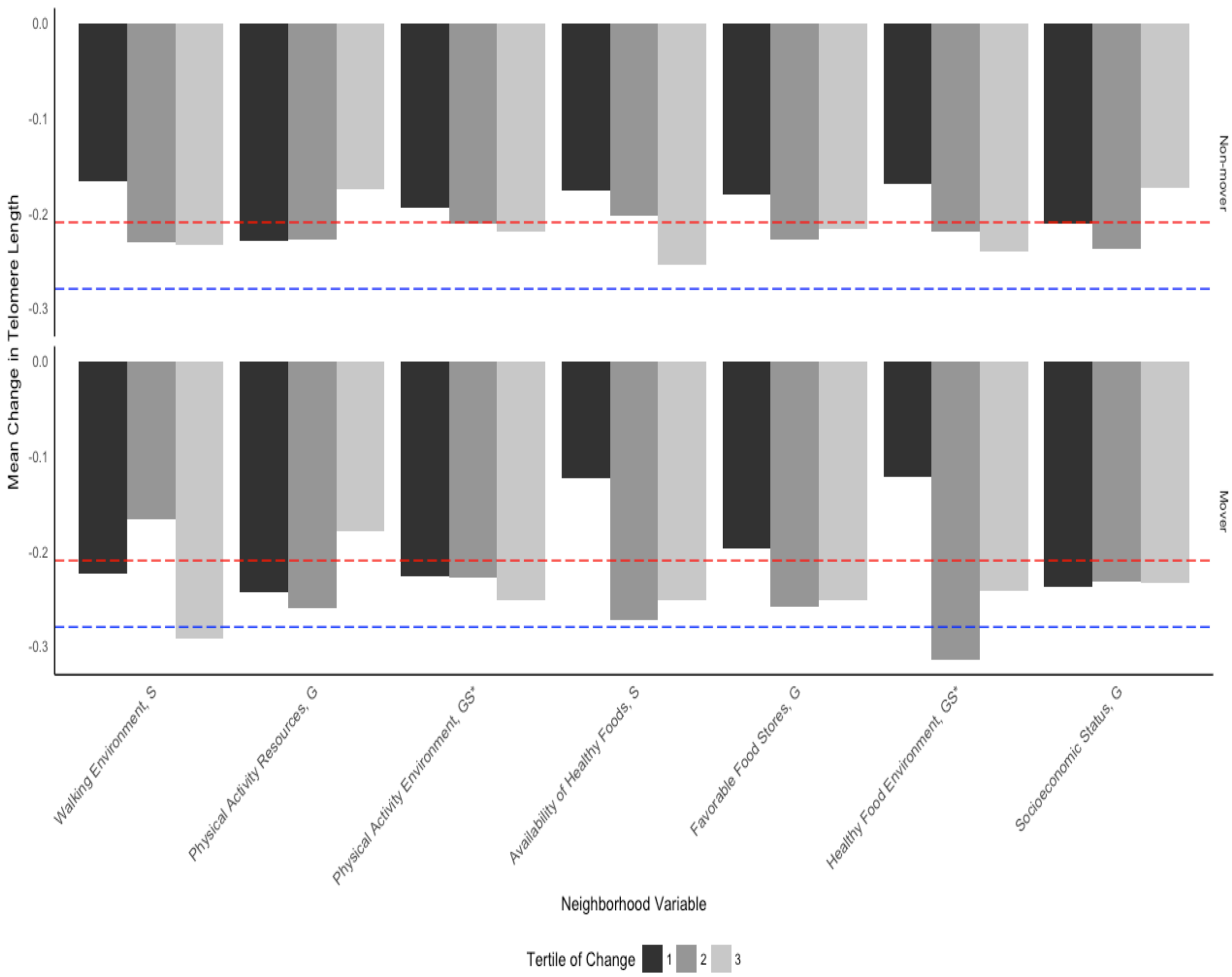

Figure 3.5 There were no statistically significant differences in mean change in telomere length (crude T/S) by tertile of change in each neighborhood characteristic and moving status. The red horizontal line indicates the overall mean change telomere length in the sample, -.21 (SD = .18). The blue horizontal line indicates the threshold for short telomere length for those in the lowest tertile of the distribution (T/S=-.28). Mean change in telomere length among movers in the highest tertile of walking environment change and middle tertile of the food environment composite measure surpassed the lowest tertile of the distribution (i.e., decrease in T/S ratio was among the highest in the study population). There were 138 movers and 609 non-movers in the sample. *Notes*. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Statistical significance thresholds for the ANOVA tests were set at * for $p<.05$, ** for $p<.01$, and *** $p<.001$.

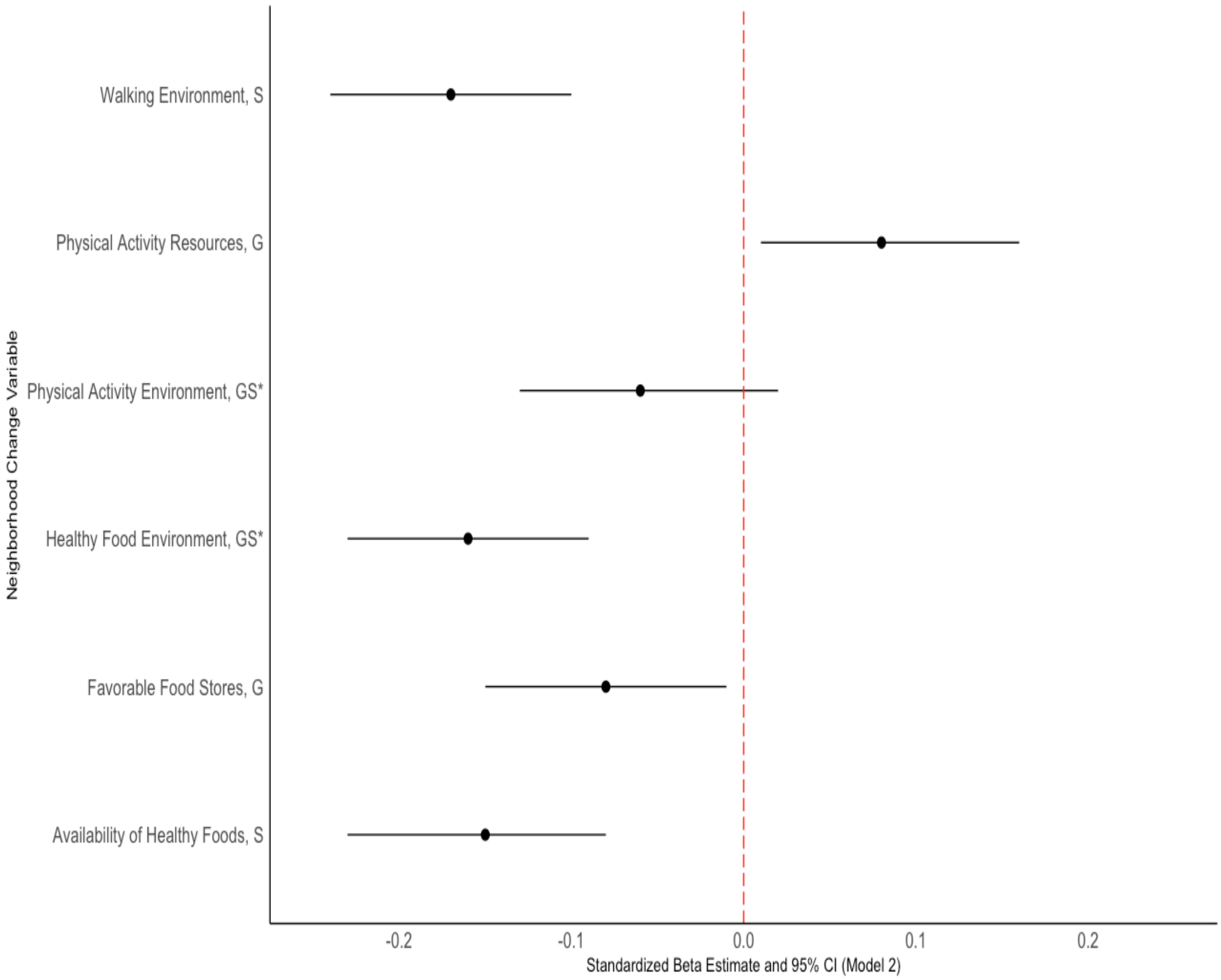

Figure 3.6 Summary of Associations of Change in Built Environment Features and Change in Telomere Length in MESA, 2000-2010 (N=747) *Notes*. Each linear mixed effect model included a random intercept for census tract. The models presented in this figure were adjusted for baseline measures of age, gender, race/ ethnicity, income, and education. Neighborhood change measures were grand mean centered and model estimates were standardized to 1 standard deviation unit. Neighborhood variables were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Statistical significance was set at $p<.05$ and the red vertical line indicates the null.

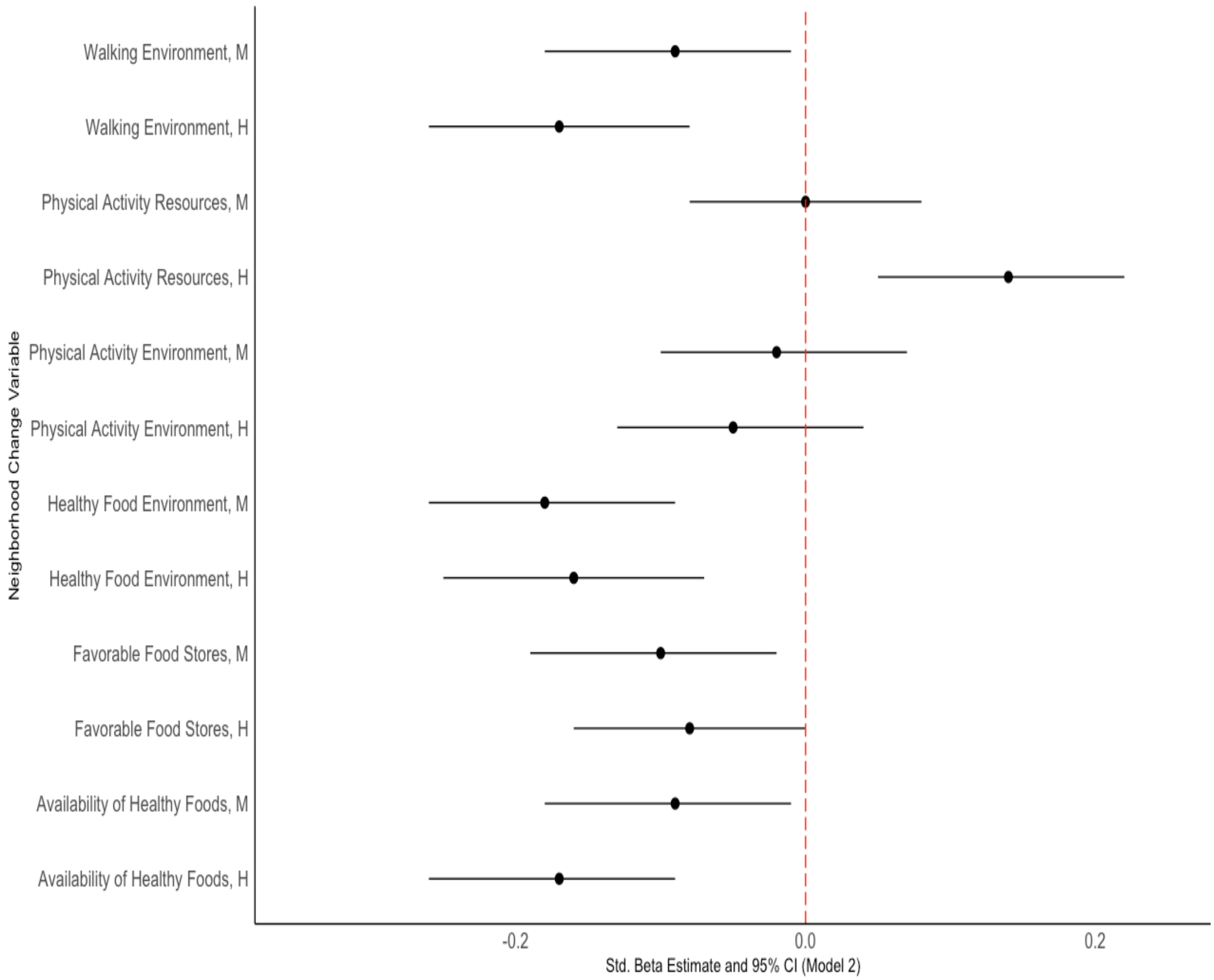

Figure 3.7 Summary of Associations of Tertile of Change in Built Environment Features and Change in Telomere Length in MESA, 2000-2010 (N=747) *Notes*. Each linear mixed effect model included a random intercept for census tract. The models in this figure were adjusted for age, gender, race/ ethnicity, income, and education. All measures were grand mean centered and model estimates were standardized to 1 standard deviation unit. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Tertiles were defined as H for high and M for middle. The reference category was the low tertile of the distribution of each physical environment variable. Statistical significance was set at $p<.05$ and the red vertical line indicates the null.

Chapter 4 Change in leukocyte telomere length is related to changes in neighborhood safety and socioeconomic status

4.1 Background

There is a growing need to examine the plasticity of aging. In 2014, chronic health conditions dominated the leading causes of death. Many of these diseases are preventable, but early indicators of adverse health trajectories remain understudied in the literature. Telomeres are the repeat sequence at the ends of DNA. This non-coding region helps to ensure that valuable information encoded in DNA remain after each replicative cycle. If telomeres shorten and reach a critically short phase, then the cell will enter senescence or apoptosis. Thus, telomere length and the rate at which telomere attrition occurs serve as biomarkers of susceptibility to age-related diseases (5, 70). In particular, telomeres measured in leukocytes provide insight into immune health (52, 53). Many studies have examined the association between telomere length and psychosocial health, healthy behaviors, morbidity, and premature mortality using observational and experimental designs (5-28). However, risk factors for accelerated biological aging can originate at multiple levels, and there is little information about how risk acquired at the neighborhood level affects cell aging (45-51). The impetus for this research was the lack of understanding of how changes in socioeconomic and social environments influence telomere length dynamics, independent of multi-level predictors. Tackling the place-based barriers to healthy aging is one way to reduce disparities in morbidity and mortality that affect disadvantaged communities.

Attention must be given to specific attributes, and not just composite measures of neighborhood social and socioeconomic contexts. Living in better social environments exhibited consistent associations with longer telomeres. Needham and colleagues identified that poor social environment (a composite measure that included aesthetic quality, safety, and social cohesion) was associated with shorter telomeres (45). Measures of adverse neighborhood attributes provided evidence in the opposite direction and suggested that neighborhood disorder (46), violent crime (50), and perceived problems (48) were associated with shorter telomeres. Poor neighborhood perception was also among the predictors related to shorter telomeres in at least three studies (47-49). However, no study empirically linked neighborhood socioeconomic status to telomere length (45, 46). This study used indicators of perceived neighborhood social attributes, including independent measures of aesthetic quality, social cohesion, and safety to examine if changes in neighborhood-level measures of subjective assessments were associated with changes in telomere length. A census-based measure of socioeconomic status was also used to provide an overarching assessment of neighborhood quality that transcended multiple domains.

Many methodological and empirical concerns hindered the impact of prior work on neighborhoods and telomere length. First, few studies concomitantly tested associations among telomere length and robust measures of the social and socioeconomic environments. Empirical models should consider multiple measures of the social and socioeconomic contexts to rule out competing hypotheses. Second, all seven studies that examined the relationship between neighborhoods and telomere length were cross-sectional, a limiting factor for establishing temporal ordering. Third, measuring neighborhood change is subject to bias and novel methodological approaches are required to capture the nuance of changing contexts.

The goal of this research was to examine whether changes in neighborhood social (as measured by aesthetic quality, social cohesion, and safety) and socioeconomic contexts were associated with changes in telomere length. The central hypothesis was that those who experienced improvements in neighborhood exposures would have less telomere shortening and that this association would differ by moving status.

4.2 Methods

Study Sample

Data for this study were from the Multi-Ethnic Study of Atherosclerosis (MESA), a sample of 6,814 United States adults aged 45-84 years at the time of recruitment. Study participants were free of subclinical cardiovascular disease at baseline and were followed for ten years using exam visits spaced two years apart. This study used data from a subset of the MESA cohort that participated in the Stress and the Neighborhood ancillary studies. The random subsample (N=1,295) included white, black, and Hispanic adults from New York, New York and Los Angeles, California. In addition, 1,095 of these participants had data available on dietary practices. Only those who also had two waves of data (Exam 1 and Exam 5) and stored blood samples for the telomere length assay were considered for the study sample. Baseline respondent data and blood samples were collected beginning in July 2000 – August 2002, and follow-up data were collected in April 2010 – December 2011. The final sample included participants were not missing data on telomere length, sociodemographic characteristics (age, sex, race/ ethnicity, income, and education), and neighborhood features (N=1,031). No imputations methods were used to address missing data.

Study Variables

Study Outcome: Change in Leukocyte Telomere Length

Blood samples were collected and stored at baseline (2000-2002) and Exam 5 (2010-2011). Both samples were assayed at the same time. Telomere length was ascertained using quantitative polymerase chain reaction (PCR) at the University of California, San Francisco. Each sample was compared to a known reference DNA aliquot to obtain the T/S ratio. The laboratory protocol was described in detail elsewhere (55, 56). Storage and batch effects were carefully considered to ensure sample integrity. Each sample was assayed three times on three different days on duplicate wells (55, 56). Mean T/S ratio was calculated using non-outlier samples. The laboratory tests were conducted independently of all other study functions.

The study used two measures of change in telomere length. The unadjusted change was measured as the difference between follow-up and baseline measures, $Y_{tij} - Y_{t-1,ij}$. Adjusted telomere length change also calculated to account for potential regression to the mean (71). The adapted equation for adjusted telomere change was:

$$\Delta T/S_{adjusted} = \rho\left(Y_{tij} - \overline{Y_{tij}}\right) - \left(Y_{t-1,ij} - \overline{Y_{t-1,ij}}\right)$$

Where,

$$\rho = \frac{2rS_{tij}S_{t-1,ij}}{S_{tij}^2 + S_{t-1,ij}^2}$$

$$r = corr(Y_{tij}, Y_{t-1,ij})$$

Y is telomere length

t is visit
i is subject
j is neighborhood
S is standard deviation
r is Pearson correlation coefficient

There were three additional telomere length measures for post-hoc comparisons: (1) telomere length in base pairs ($3274 + 2413 \times \frac{T}{S}$); (2) a three-level categorical variable of the 10-year percent change in base pairs that described the proportion that lengthened more than 10%, changed within +/- 10%, and shortened more than 10%; and (3) the low tertile of the change in T/S distribution ($\Delta T/S_{low} < -.28$).

Study Exposures: Neighborhood Factors
Census tracts defined neighborhood boundaries. Conditional empirical Bayes estimates were used to account for census tracts with small sample sizes or poor agreement among residents of the same area. Briefly, this method allows unreliable census tracts to borrow information from adjacent areas to improve the estimate. Neighborhood change was the difference between Exam 5 and baseline. Analyses used both a continuous and a categorical measure tertiles of the sample distribution. Neighborhood change was grand mean centered (i.e., mean subtracted from each response) and results in the linear mixed effects models were standardized to one standard deviation unit.

Change in Neighborhood Social Environment
Table 4.1 describes the social environment features in detail. Information on neighborhood dimensions was ascertained using a survey asking participants to rate the area within approximately one mile around their home. The survey items were averaged for all participants within a census tract to produce a neighborhood-level measure using conditional empirical Bayes estimates. Neighborhood dimensions included aesthetic quality, safety, and social cohesion. Scales were based on previous work (58) and had acceptable internal consistency (Cronbach's alpha .64-.82). Aesthetic quality used respondent-reported ratings of individual perceptions and included four items measured on a five-point Likert scale. The items examined cleanliness, noise, and overall attractiveness of the neighborhood. Three items were used to examine social cohesion using a five-point Likert scale. The items examined relationships among neighbors and feelings towards crime. Respondents were asked to examine neighborhood safety using three questions that were measured on a 5-point Likert scale. These questions directly assessed sentiments regarding safety while walking, violence, and crime. The neighborhood social environment composite was the sum of standardized conditional empirical Bayes estimate (CEB) scales for aesthetic quality, safety, and social cohesion. Increasing scores in these items indicated a better social environment. Figure 4.2 exhibited that correlation among the change in specific social environment indicators ranged from .49 to .54.

Change in Neighborhood Socioeconomic Status
Variables were selected for the construction of a factor-based score as described by Diez Roux et al (61). Baseline data and boundaries were from the 2000 US Census. Exam 5 data were from the American Community Survey (ACS) 2007-2011 using the 2010 US Census boundaries. Six variables representing wealth and income (log of median household income, log of median value

of housing units, and percent of households with interest, dividend, or net rental income), education (percent of adults 25 years and older with at least a high school degree and percent of adults 25 years and older with at least a Bachelor's degree), and occupation (percent of employed persons 16 and older in executive, managerial, or professional occupations) were standardized and summed together to create the score. An increasing score indicated more socioeconomic advantage. The correlation matrix in Figure 4.2 shows that there was a weak, positive correlation between change in neighborhood socioeconomic status and change in social environment characteristics (Range: .09 to .27). On average, neighborhood socioeconomic contexts improved in the study sample (data not shown).

Additional Study Covariates

Moving status

A mover (treatment group) was a subject who changed census tracts between visits. A non-mover (control group) moved to the same census tract or did not move at all.

Sociodemographic Characteristics

Sociodemographic characteristics were from baseline and included in models as time-constant covariates. Age was a continuous variable that was calculated using self-reported birth year at each exam and gender was a binary variable (male or female). Self-reported race/ ethnicity included levels for Black, Hispanic, and White. Participants were not permitted to select more than one category to describe their race/ ethnicity. Participants chose their education from 8 levels and responses were grouped into three levels: high school education or less, some college or associate/technical degree, and Bachelor's degree and higher. Income adjusted for the number of people supported per $10,000 [(continuous income/ number of people supported)/10,000].

Statistical analyses

Means and proportions were used to describe the distribution of the study sample across population characteristics. ANOVA was used to assess differences in mean change in telomere length (T/S ratio) by each study variable.

All models included a random intercept for census tract. Regression coefficients described mean change in telomere length per standard deviation unit change in each grand mean centered neighborhood variable. An unconditional model was used to estimate the proportion of the total variance in change in telomere length that was due to between-neighborhood variation. Sequential models were presented to show whether other variables attenuated the association between changes in neighborhood environments and change in telomere length. First, the unadjusted model tested the association between the neighborhood change variable and change in telomere length in Model 1. Second, the minimally sufficient set of time-constant confounders (age, sex, race/ ethnicity, income, and education) were included in Model 2 to estimate an adjusted measure of association between neighborhood change and change in telomere length. Finally, Model 3 addressed structural confounding by adding the change in neighborhood socioeconomic status to the Model 2 variables (neighborhood change measure, age, sex, race/ ethnicity, income, and education). These models were repeated using two modifications: tertiles of each neighborhood change exposure was used to examine dose-response and both adjusted and unadjusted changes in telomere length were used as outcomes. Thus, each series of three sequential models had four variations, and five different neighborhood change variables were tested. The main results from the study came from Model 2 when the adjusted and unadjusted telomere length model iterations produced similar results.

An additional model was used to examine the difference-in-differences (DD) estimator. This specification added two predictors to Model 2: an indicator variable for moving status and a cross-product term for the neighborhood change variable and moving status. The statistical significance of the cross-product term, β_4, tested the added effect of neighborhood change due to moving (treatment group) from one context to another on the change in telomere length. The results of these analyses were presented in a table stratified by moving status. The models were replicated using unadjusted and adjusted change in telomere length.

$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1(A_{tj} - A_{t-1,j}) + \epsilon_{tij} \text{ (Model 1)}$$
$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1(A_{tj} - A_{t-1,j}) + \beta_2 \boldsymbol{W}_{ij1} + \epsilon_{tij} \text{ (Model 2)}$$
$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1(A_{tj} - A_{t-1,j}) + \beta_2 \boldsymbol{W}_{ij1} + \beta_3(Z_{tj} - Z_{t-1,j}) + \epsilon_{tij} \text{ (Model 3)}$$

$$Y_{tij} - Y_{t-1,ij} = \beta_0 + \zeta_j + \beta_1(A_{tj} - A_{t-1,j}) + \beta_2 \boldsymbol{W}_{ij1} + \beta_3 M_{tij} + \beta_4(A_{tj} - A_{t-1,j}) \times M_{tij} + \epsilon_{tij} \text{ (DD Model)}$$

Where,
t is the time index
i is the subject
j is the neighborhood cluster
$Y_{tij} - Y_{t-1,ij}$ is the change in telomere length between follow-up, t, and baseline, $t-1$
β_0 is the overall intercept
ζ_j is the neighborhood-specific intercept (random effect)
β_1 is the coefficient for the association between a standard deviation unit change in neighborhood characteristic, $A_{tj} - A_{t-1,j}$, and the mean change in telomere length between baseline and follow-up
$\boldsymbol{W}_{ij1}$ is a vector of time constant (age, sex, race/ ethnicity, education, and income) sociodemographic characteristics
$Z_{tj} - Z_{t-1,j}$ is change in neighborhood socioeconomic status
M_{tij} is the indicator for moving status (1=mover, treatment; 0=non-mover, control)
β_4 is the coefficient the exhibit the mean change in telomere length associated with a one standard deviation unit change in neighborhood change among movers

All analyses were completed using the R software using the *lme4* and *lmerTest* packages with the restricted maximum likelihood (REML) option and Satterthwaite approximations for degrees of freedom. Statistical significance was defined at p-values <0.05 and statistically significant cross-product terms were defined at p-values <0.1.

4.3 Results

A summary of the population characteristics is in Table 4.2. Mean age was 61 years, more than half the participants were women (53%), and the racial/ethnic makeup was: 43% Hispanic, 30% black, and 27% white. Educational attainment among sample participants was varied. Forty-one percent of respondents had a high school diploma or less, nearly 30% had a college diploma or attended technical school, and almost 30% completed a Bachelor or graduate degree. Almost twenty-one percent of respondents moved between exams. Mean follow-up time was 9.5 years. Subjects originated from 507 census tracts that ranged in size from 1 to 14.

Mean change in telomere length (T/S) was -.21 (Standard Deviation [SD]=.18) for the unadjusted measure and -.0007 (SD=.18) for the adjusted measure. Average percent change in base pairs was 7.4%. Forty-three percent of the participants experienced greater than a 10% loss in base pairs compared to their baseline telomere length, 56% changed within +/-10%, and less than 1% lengthened more than 10%. The threshold for accelerated telomere shortening (i.e., those in the low tertile of the unadjusted change in telomere length distribution) was -.28. These data are not shown.

Change in telomere length over 10 years exhibited some patterning by key sociodemographic characteristic. Those who were older (high tertile) experienced the least telomere shortening (Mean [SD]=-.19 [.17]) compared to the young and middle age tertiles, who had similar changes in telomere length (Mean [SD]=-.21 [.20]) and -.22 [.19], respectively; p=.032). There was a statistically significant difference in change in telomere shortening by race/ ethnicity (p=002) in which blacks shortened the least (Mean [SD]=-0.18 [0.18]), followed by Hispanics (Mean [SD]=-0.22 [0.18]) and whites (Mean [SD]=-0.22 [0.19]) who shortened at a similar rate. Those who completed university or graduate school experienced the least telomere shortening with a mean change of -0.18 (SD=0.17), compared to those with lower levels of educational attainment (p=.037). No discernable trends emerged by gender or income (all p>.05). Telomere shortening did not differ by moving status (p>.05).

Figure 4.3 exhibited the results of the bivariate analyses of tertile of change in neighborhood feature and crude mean change in telomere length. Those who experienced a change in neighborhood socioeconomic advantage in the high tertile (most improvement) experienced the least 10-year telomere shortening (p<.01). However, those in the low tertile of change in aesthetic quality (p<.05) and safety (p<.001) shortened the least. There was no trend in change in telomere length by tertiles of change in neighborhood social cohesion. Figure 4.4 shows that movers and non-movers exhibited similar trends in telomere shortening (all p>.05). No subgroup exceeded the threshold for excessive telomere length attrition in either the one- or two-way analyses.

Neighborhood socioeconomic status

The results of the linear mixed effects models are in Table 4.3. Per standard deviation unit increase in the change in neighborhood socioeconomic advantage, there was a .14-unit increase in mean change telomere length (95% Confidence Interval [CI]=.06, .19), independent of age, sex, race/ ethnicity, and individual-level socioeconomic status (see Table 4.3, Model 2). In assessments of nonlinearity, the comparison of high versus low tertile change in neighborhood socioeconomic status revealed that there was a .09 unit increase in mean change in telomere length (95% CI=0.02, 0.17), after adjusting for sociodemographic characteristics (see Table 4.4, Model 2). The adjusted change in telomere length exhibited similar results.

The difference-in-differences approach did not suggest that the association between change in neighborhood socioeconomic status and change in telomere length differed by moving status (see Table 4.7 and Table 4.8). Further inspection of the types of movers revealed that movers tended to migrate to similar socioeconomic contexts. Fifty-seven percent of movers entered neighborhoods with the same socioeconomic composition as the one they left (i.e., transitions represented consistently low, middle, or high neighborhood socioeconomic exposure). Only 24% of respondents were able to enter an environment with a better socioeconomic status than the one where they resided at baseline. Nineteen percent of individuals moved to an area that was worse than the one they left (see Table 4.9).

Social Environment

The mixed effects models presented in Table 4.3 highlighted that among social environment features, only changes in neighborhood safety was related to change in telomere length in the main model. The relationship exhibited that a positive change in neighborhood safety was associated with a .10 unit decrease in telomere length after ten years (95% CI=-0.17, -0.04), adjusted for age, sex, race/ ethnicity, and individual-level socioeconomic status (see Table 4.3, Model 2). Further adjustment for the change in neighborhood socioeconomic status did not attenuate the measure of association for neighborhood safety. However, a statistically significant association for change in aesthetic quality emerged only after adjustment for sociodemographic characteristics and neighborhood socioeconomic status (Standardized Beta [Std. β] and 95% CI=-0.08 (-0.14, -0.01); see Table 4.3, Model 3).

Tertile analyses mirrored the continuous trends. Those living in the high tertile of change in neighborhood safety experienced a .13 unit decrease in mean telomere length, compared to those residing in the low tertile of change (95% CI=-.20, -.05), independent of demographic characteristics and individual-level socioeconomic status (see Table 4.4, Model 2). This measure of association remained after further adjustment for change in neighborhood socioeconomic status. Findings for aesthetic quality suggested that compared to the low tertile of change, the middle and high tertile were associated with a .08 unit and .09 unit change in mean telomere length, independent of individual-level sociodemographic predictors and neighborhood socioeconomic status (95% CI for middle= -0.16, -0.01and 95% CI for high=-0.17, -0.02; see Table 4.4, Model 3). Similar results were obtained using the adjusted measure of change in telomere length (see Table 4.6).

The tests of effect measure modification by moving status did not reveal any statistically significant differences across strata using both the unadjusted and adjusted measures of change in telomere length (see Table 4.7 and Table 4.8). However, the influence of the change in social cohesion was only apparent among those who moved, albeit not statistically significant (p-for-interaction=.168 in crude and .102 in adjusted models; see Table 4.7 and Table 4.8). There was low plasticity in the change in the social environment among movers because 63% moved to an area with an identical level of social cohesion (see Table 4.10).

4.4 Discussion

The goal of this study was to understand how improvements in socioeconomic and social environments were associated with the change in telomere length over 10 years. A positive change in neighborhood socioeconomic status was related to telomere length maintenance, and improved safety helped to slow telomere shortening. These findings did not differ by moving status. The results of this research are generalizable to middle aged and older adults that live in urban settings.

Few studies examined neighborhood determinants of telomere length (45-51), and all were cross-sectional. While there is evidence to suggest individual-level socioeconomic status is associated with telomere length (79-82), no study was able to empirically link neighborhood-level socioeconomic status to telomere length (45, 46). In this study, change in neighborhood-level socioeconomic status was positively associated with telomere length maintenance after 10 years, independent of sociodemographic characteristics. This study contributed to the extant literature as the first to establish a statistically significant relationship between neighborhood socioeconomic status and telomere length. Also, these results were obtained using two time points of data, which is another first for this body of work.

When specific features of the social environment were examined, only changes in neighborhood safety and aesthetic quality were associated with the change in telomere length, independent of sociodemographic characteristics and change in neighborhood socioeconomic status. In the literature, poor social environments were related to shorter telomeres in a separate, cross-sectional study that used MESA data (45). Similarly, adverse neighborhood exposures such as neighborhood disorder (46), violent crime (50), and perceived problems (48) were associated with shorter telomeres in the extant literature. This research identified that a positive change in neighborhood safety was associated with less telomere shortening than expected. Again, this is the first study to establish these associations, and it did so while using two observations.

Telomere length malleability is an important part of biological aging. In response to psychosocial or physiological stress, telomerase helps to rebuild telomeres over a short time (70). Leukocytes, in particular, depend on this mechanism because they are often under attack. Thus, the telomere-telomerase regulatory process helps to ensure immune health. However, it is notable that telomere length and telomere dynamics are cell and site specific. For example, the up regulation of telomerase in cancer cells helps to provide tumor cells with immortality. Nevertheless, short-term observational and experimental studies of hematopoietic cells have provided valuable contributions to the overall understanding of telomeres as a biomarker of aging that is sensitive to internal and external stressors. Indeed, telomeres shorten with increasing age (6, 70, 73). However, a five-year study of lifestyle changes (as measured by diet, exercise, stress management, and social support), found that telomeres lengthened among men with prostate cancer in the treatment arm (72). Research findings that suggest long-term lengthening are rare, and they sometimes come under intense speculation.

In this study, less than 1% of the sample experienced telomere lengthening that was greater than a 10% increase in base pairs after 10 years. Most of the sample participants experienced telomere maintenance within +/-10% (56%) or shortening greater than 10% (43%) compared to their baseline values. On average, the unadjusted mean change telomere length in this sample was -.21, and the threshold for short telomeres using the sample distribution for the low tertile was -.28. However, the adjusted change in telomere length exhibited that, on average there was little or no change in telomere length after 10 years (Mean (SD)=-.0007 (.18)). To place the results of the multivariate linear mixed effects tests into context, the regression coefficient for change in socioeconomic status was a .14 unit increase in mean change telomere length (95% Confidence Interval [CI]=.06, .19) and .10 unit decrease (95% CI=-0.17, -0.04) for change in safety, adjusted for age, sex, race/ ethnicity, income, and education. The mean number of base pairs decreased by 52.6 per year for an average of 9.5 years of follow-up (assuming a linear decline). Expected change in telomere length in a healthy population is a reduction of 30-60 base pairs per year. In contrast, leukocyte telomere length decreased by 42 base pairs per year in a five-year cohort of 608 adults with coronary heart disease (83). Another study of young adults that were aged 20-40 years at baseline found that after around six years of follow-up the mean change in base pairs was a 40.7 unit decrease (84). As a result, it appears that mean telomere length attrition in this study was similar to what was observed in other cohorts.

Considered together, the main findings from this work support the hypothesis that changes in features of the socioeconomic and social environments have varied and, at times, inconsistent implications on biological aging. Improvement in neighborhood socioeconomic status was associated with telomere length maintenance. However, the cumulative impact of living in an unsafe neighborhood throughout the life course may be biologically "embedded" and could not be reversed by acute or even gradual neighborhood changes. Thus, improvements in neighborhood safety were only able to *slow* the rate of biological aging. Even the most concerted efforts to improve neighborhood safety, perhaps through other social factors such as improving aesthetic quality or social cohesion, may not have a direct impact at the individual level. The biological dysregulation that stems from living in a stressful neighborhood social environment (e.g., elevated cortisol levels, high blood pressure, elevated levels of inflammatory response markers) is complicated. Nevertheless, this study made significant contributions to the body of work on social and socioeconomic environments and telomere length. First, this is the only study to use multiple time points of data and focus on change in context. Second, specific measures of the social environment were considered, independent of neighborhood socioeconomic status. Third, the study duration was long enough to examine meaningful changes. Finally, the sample was a socioeconomically and racially/ ethnically diverse cohort of older adults who lived in urban centers in the United States.

No study is without limitation, and this research faced many challenges such as residual confounding, misclassification, social selection, and external validity. Social environment features were modeled separately in to avoid collinearity, but neighborhood features do not change in an isolated fashion. For example, the influence of the change in aesthetic quality was unveiled when the change in neighborhood socioeconomic status was also included as a structural confounder. In that series of analyses, adjusting for individual-level factors alone did not reveal a statistically significant association between aesthetic quality and telomere length. Psychosocial stress was not included in this study, and this is not uncommon since few studies accounted for psychosocial influences in the neighborhood-telomere length models (47). Future research should also consider whether the social environment acts independently of stress. Overall, these factors may have led to an underestimation of the measure of association and biased the results towards the null. Measurement of the social environment included previously validated scales of respondent reports (58). The summary scores were aggregated to the census tract level and applied as neighborhood-level measures. One limitation of this approach was that the census tract might not be indicative a personal assessment of the neighborhood boundary (67). A second measurement challenge was that subjective assessments of neighborhood social environments might be biased. For example, a respondent's perception of safety may differ from the incidence of crime. In addition, assessments of social cohesion may vary from actual engagement with neighbors or attendance at community events. Another concern was that measurement of neighborhood socioeconomic status may have also introduced some bias. In the United States, race/ ethnicity and neighborhood socioeconomic status are inextricably linked; thus, race-specific neighborhood socioeconomic status may help to reduce bias from positivity violations. Concerning telomere length, the 10-year gap between baseline sample collection and the assay may have introduced bias. Some approaches made in the laboratory setting to ensure accuracy were randomizing aliquot placement in the wells, blinding the technician, running repeats of each sample, and re-running samples that produced improbable values. Misclassification resulting from this study was likely nondifferential and the measures of association could have been biased towards or away from the null. These analyses leveraged data from two time points, concomitantly considered the influence of moving between contexts, and adjusted for individual-level selection factors to handle bias from social selection. However, two time points were not sufficient to assess both short- and long-term trajectories in the rate of change in telomere length and neighborhood features. Cross product terms with moving status accounted for the type of neighborhood change: (1) an acute shift in exposure from moving or (2) chronic exposure to the same context that happened to transform over time. Unfortunately, the issues related to randomization of exposure (i.e., whether the impetus to move was random) could not be verified. Independent selection factors such as age, sex, race/ ethnicity, and individual-level socioeconomic status were considered in multivariate analyses; however, additional selection factors may still exist. Finally, this study population was not representative of the general population. The sample was older and more racially/ ethnically diverse than other studies. Not only do these caveats affect comparability in the extant literature, but these considerations also limit external validity.

4.5 Conclusion

Few studies have successfully connected biological aging to the broader social and socioeconomic climate. This study was the first to examine how changes in the social environment patterned change in leukocyte telomere length. Telomere length attrition was most amenable to modifications in neighborhood socioeconomic status and safety. Moving status did not modify these associations. Future research should consider competing pathways using additional measures of the social environment.

4.6 Tables and figures

Tables

Table 4.1 Definitions of Socioeconomic and Social Environment Measures Used in Analyses of Baseline Data From the Multi-Ethnic Study of Atherosclerosis' Longitudinal Neighborhoods Study (2000-2010)

Neighborhood Feature	Scale Summary and Items	Unit
Socioeconomic Status, G	Six variables representing wealth and income (log of median household income, log of median value of housing units, and percent of households with interest, dividend, or net rental income), education (percent of adults 25 years and older with at least a high school degree and percent of adults 25 years and older with at least a Bachelor's degree), and occupation (percent of employed persons 16 and older in executive, managerial, or professional occupations) were standardized and summed together to create the score.	Census tract
Aesthetic Quality, S	1. There is a lot of trash and litter on the street in my neighborhood.^{R} 2. There is a lot of noise in my neighborhood.^{R} 3. In my neighborhood the buildings and homes are well-maintained. 4. The buildings and houses in my neighborhood are interesting. 5. My neighborhood is attractive.	Census tract
Social Cohesion, S	1. People around here are willing to help their neighbors. 2. Violence is not a problem in my neighborhood. 3. My neighborhood is safe from crime.	Census tract
Safety, S	1. I feel safe walking in my neighborhood, day or night. 2. Violence is not a problem in my neighborhood. 3. My neighborhood is safe from crime.	Census tract
Social Environment, S*	A composite score that contained standardized measures of aesthetic quality, safety, and social cohesion.	Census tract

Note. ^{R} Reverse-coded item; G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure

Table 4.2 Summary of Population Characteristics and Mean Telomere Length in the Multi-Ethnic Study of Atherosclerosis, 2000-2010 (N=1,031)

Characteristic	Study Population		Telomere Length	
	Mean (SD)	*N (%)*	*Mean (SD)*	*P*
Age	61.04 (9.36)			**0.032**
45-54		303 (29.4)	-0.21 (0.2)	
55-64		324 (31.4)	-0.22 (0.19)	
65 and older		404 (39.2)	-0.19 (0.17)	
Race/ ethnicity				**0.002**
White		294 (28.5)	-0.22 (0.19)	
Black		305 (29.6)	-0.18 (0.18)	
Hispanic		432 (41.9)	-0.22 (0.18)	
Gender				0.072
Female		550 (53.3)	-0.22 (0.17)	
Male		481 (46.7)	-0.20 (0.2)	
Education				**0.037**
High school or less		416 (40.3)	-0.21 (0.18)	
College or technical school		308 (29.9)	-0.22 (0.2)	
University or graduate		307 (29.8)	-0.18 (0.17)	
Adjusted per capita income (Per $10,000)	2.41 (1.84)			0.161
Low tertile (<1.375)		249 (33.3)	-0.22 (0.18)	
Middle tertile (1.375-2.183)		249 (33.3)	-0.21 (0.19)	
High tertile (>2.183)		249 (33.3)	-0.19 (0.18)	

Note. P-values obtained via ANOVA test for the differences in means, by category of each population characteristic. Post-hoc tests were not administered.

Table 4.3 Associations of Change in Neighborhood Socioeconomic and Social Environment Features and Change Telomere Length in MESA, 2000-2010 (N=1,031)

Characteristic	Model 1	Model 2	Model 3
	Std. β (95% CI)	Std. β (95% CI)	Std. β (95% CI)
Socioeconomic Status, G	**0.12 (0.05, 0.18)**	**0.13 (0.06, 0.19)**	--
Social Environment			
Aesthetic Quality, S	-0.06 (-0.12, 0.01)	-0.05 (-0.11, 0.02)	**-0.08 (-0.14, -0.01)**
Social Cohesion, S	0 (-0.07, 0.07)	0.01 (-0.06, 0.07)	-0.01 (-0.08, 0.05)
Safety, S	**-0.13 (-0.19, -0.06)**	**-0.1 (-0.17, -0.04)**	**-0.11 (-0.17, -0.05)**

Social Environment, S*	**-0.08 (-0.14, -0.01)**	-0.06 (-0.12, 0.01)	**-0.08 (-0.15, -0.02)**

Notes. Bolded items are statistically significant (p≤.05). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood change variable
Model 2: neighborhood change variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood change variable, age, sex, race/ ethnicity, income, education, and change in neighborhood socioeconomic status

Table 4.4 Associations of Change in Neighborhood Socioeconomic and Social Environment Features and Adjusted Change Telomere Length in MESA, 2000-2010 (N=1,031)

Characteristic	Model 1	Model 2	Model 3
	Std. β (95% CI)	Std. β (95% CI)	Std. β (95% CI)
Socioeconomic Status, G	**0.12 (0.06, 0.19)**	**0.14 (0.07, 0.2)**	--
Social Environment			
Aesthetic Quality, S	-0.07 (-0.13, 0)	-0.05 (-0.11, 0.02)	**-0.08 (-0.14, -0.01)**
Social Cohesion, S	0 (-0.07, 0.06)	0.02 (-0.04, 0.08)	0 (-0.07, 0.06)
Safety, S	**-0.12 (-0.19, -0.06)**	**-0.09 (-0.15, -0.03)**	**-0.1 (-0.16, -0.04)**
Social Environment, S*	**-0.08 (-0.14, -0.01)**	-0.05 (-0.11, 0.02)	**-0.07 (-0.14, -0.01)**

Notes. Bolded items are statistically significant (p≤.05). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood change variable
Model 2: neighborhood change variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood change variable, age, sex, race/ ethnicity, income, education, and change in neighborhood socioeconomic status

Table 4.5 Associations by Tertile of Neighborhood Socioeconomic and Social Environment Features and Telomere Length in MESA, 2000-2002 (N=1,031)

		Model 1	**Model 2**	**Model 3**
		Std. β (95% CI)	**Std. β (95% CI)**	**Std. β (95% CI)**
Socioeconomic Status, G	M	-0.02 (-0.09, 0.05)	-0.01 (-0.08, 0.07)	--
	H	**0.08 (0, 0.16)**	**0.09 (0.02, 0.17)**	--
Social Environment				
Aesthetic Quality, S	M	**-0.09 (-0.16, -0.01)**	-0.07 (-0.15, 0)	**-0.08 (-0.16, -0.01)**
	H	-0.08 (-0.16, 0)	-0.06 (-0.14, 0.01)	**-0.09 (-0.17, -0.02)**
Social Cohesion, S	M	-0.02 (-0.1, 0.05)	-0.02 (-0.09, 0.05)	-0.03 (-0.1, 0.04)
	H	-0.01 (-0.09, 0.07)	0.01 (-0.07, 0.08)	-0.02 (-0.09, 0.06)
Safety, S	M	-0.06 (-0.14, 0.02)	-0.05 (-0.13, 0.02)	-0.05 (-0.13, 0.02)
	H	**-0.14 (-0.22, -0.07)**	**-0.13 (-0.2, -0.05)**	**-0.14 (-0.21, -0.07)**
Social Environment, S*	M	-0.08 (-0.15, 0)	-0.07 (-0.15, 0)	-0.08 (-0.15, 0)
	H	**-0.09 (-0.17, -0.02)**	-0.07 (-0.14, 0.01)	**-0.09 (-0.17, -0.02)**

Notes. Each tertile is compared to the referent tertile, low. Bolded items are statistically significant (p≤.05). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. L = Low tertile; M = Middle tertile; H = High tertile. Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood change variable
Model 2: neighborhood change variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood change variable, age, sex, race/ ethnicity, income, education, and change in neighborhood socioeconomic status

Table 4.6 Associations by Tertile of Neighborhood Socioeconomic and Social Environment Features and Adjusted Telomere Length in MESA, 2000-2002 (N=1,031)

		Model 1	Model 2	Model 3
		Std. β (95% CI)	Std. β (95% CI)	Std. β (95% CI)
Socioeconomic Status, G	M	-0.02 (-0.09, 0.06)	-0.01 (-0.08, 0.06)	--
	H	**0.09 (0.01, 0.16)**	**0.1 (0.03, 0.18)**	--
Social Environment				
Aesthetic Quality, S	M	**-0.09 (-0.17, -0.02)**	**-0.08 (-0.16, -0.01)**	**-0.09 (-0.17, -0.02)**
	H	**-0.08 (-0.16, -0.01)**	-0.06 (-0.14, 0.01)	**-0.1 (-0.17, -0.02)**
Social Cohesion, S	M	-0.04 (-0.12, 0.03)	-0.04 (-0.11, 0.03)	-0.05 (-0.12, 0.02)
	H	0 (-0.08, 0.08)	0.03 (-0.04, 0.11)	0.01 (-0.07, 0.08)
Safety, S	M	-0.07 (-0.15, 0)	-0.07 (-0.14, 0.01)	-0.07 (-0.14, 0)
	H	**-0.14 (-0.22, -0.07)**	**-0.12 (-0.19, -0.05)**	**-0.13 (-0.2, -0.06)**
Social Environment, S*	M	-0.07 (-0.15, 0)	-0.07 (-0.14, 0)	**-0.08 (-0.15, -0.01)**
	H	**-0.08 (-0.16, -0.01)**	-0.05 (-0.12, 0.03)	-0.08 (-0.15, 0)

Notes. Each tertile is compared to the referent tertile, low. Bolded items are statistically significant ($p \leq .05$). G = GIS-based measure; S = Survey-based measure; GS = Combined GIS- and survey-based measure; *= Composite measure. L = Low tertile; M = Middle tertile; H = High tertile.
Std. β = grand mean centered regression coefficient standardized to one standard deviation unit.
Model 1: neighborhood change variable
Model 2: neighborhood change variable, age, sex, race/ ethnicity, income, and education
Model 3: neighborhood change variable, age, sex, race/ ethnicity, income, education, and change in neighborhood socioeconomic status

Table 4.7 Difference-in-Differences Approach of Associations Among Change Social and Socioeconomic Environment Features and Change in Telomere Length, by Moving Status in MESA, 2000-2010 (N=1,031)

Characteristic	Movers (N=212) Std. β (95% CI)	Non-movers (N=819) Std. β (95% CI)	P-value Interaction
Socioeconomic Status, G	0.09 (-0.05, 0.24)	**0.15 (0.07, 0.22)**	0.549
Social Environment			
Aesthetic Quality, S	-0.03 (-0.17, 0.11)	-0.05 (-0.12, 0.03)	0.814
Social Cohesion, S	0.09 (-0.05, 0.23)	-0.01 (-0.08, 0.07)	0.168
Safety, S	-0.11 (-0.26, 0.03)	**-0.09 (-0.16, -0.01)**	0.669
Social Environment, S*	-0.02 (-0.17, 0.12)	-0.06 (-0.13, 0.02)	0.670

Notes. Bolded items are statistically significant ($p<.05$) and statistically significant cross-product terms were defined at $p<.1$
Std. β = grand mean centered regression coefficient standardized to one standard deviation unit
Model: neighborhood change variable, mover, mover x neighborhood change variable age, sex, race/ ethnicity, income, education
P-value interaction: p-value for mover x neighborhood change variable interaction coefficient in the model

Table 4.8 Difference-in-Differences Approach of Associations Among Change Social and Socioeconomic Environment Features and Adjusted Change in Telomere Length, by Moving Status in MESA, 2000-2010 (N=1,031)

Characteristic	Movers (N=212) Std. β (95% CI)	Non-movers (N=819) Std. β (95% CI)	P-value Interaction
Socioeconomic Status, G	0.12 (-0.02, 0.26)	**0.15 (0.08, 0.23)**	0.516
Social Environment			
Aesthetic Quality, S	-0.04 (-0.17, 0.1)	-0.04 (-0.11, 0.03)	0.928
Social Cohesion, S	0.12 (-0.02, 0.26)	0 (-0.07, 0.07)	0.102

Safety, S	-0.11 (-0.25, 0.04)	-0.07 (-0.14, 0)	0.588
Social Environment, S*	-0.01 (-0.15, 0.13)	-0.05 (-0.12, 0.03)	0.681

Notes. Bolded items are statistically significant (p<.05) and statistically significant cross-product terms were defined at p<.1
Std. β = grand mean centered regression coefficient standardized to one standard deviation unit
Model: neighborhood change variable, mover, mover x neighborhood change variable age, sex, race/ ethnicity, income, education
P-value interaction: p-value for mover x neighborhood change variable interaction coefficient in the model

Table 4.9 Transition proportion table for movers, by tertile of neighborhood socioeconomic status (N=212)

		Exam 5 ***Neighborhood socioeconomic status***		
		L	**M**	**H**
Exam 1 ***Neighborhood socioeconomic status***	**L**	Consistently low 15.6%	Moderate increase 10.8%	High increase 3.7%
	M	Moderate decrease 8.0%	Consistently moderate 17.9%	Moderate increase 9.0%
	H	High decrease 2.8%	Moderate decrease 8.5%	Consistently high 23.6%

Table 4.10 Transition proportion table for movers, by tertile of neighborhood social cohesion (N=212)

		Exam 5 ***Neighborhood social cohesion***		
		L	**M**	**H**
Exam 1 ***Neighborhood social cohesion***	**L**	Consistently low 21.2%	Moderate increase 10.4%	High increase 3.3%
	M	Moderate decrease 2.8%	Consistently moderate 16.0%	Moderate increase 11.8%
	H	High decrease 1.9%	Moderate decrease 7.1%	Consistently high 25.5%

Figures

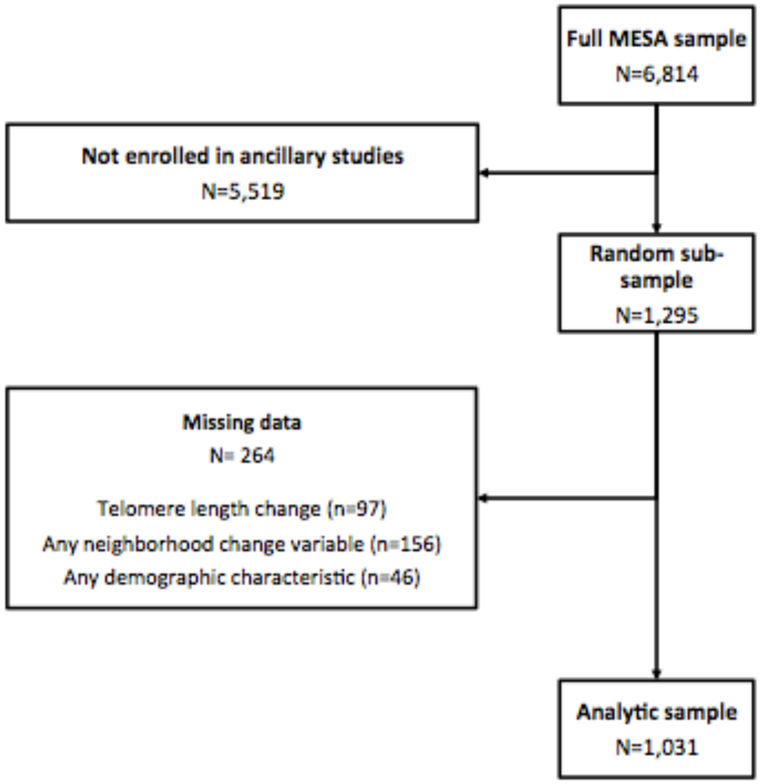

Figure 4.1 Data for these analyses originated from the baseline exam of the Multi-Ethnic Study of Atherosclerosis, 2000-2010. The analytic sample included data from a random sub-sample of subjects. Any respondent that was missing data on telomere length, neighborhood characteristics, or demographic information from the final sample. Overall, 1,031 subjects were used to examine the research objectives. *Note*. MESA = Multi-Ethnic Study of Atherosclerosis

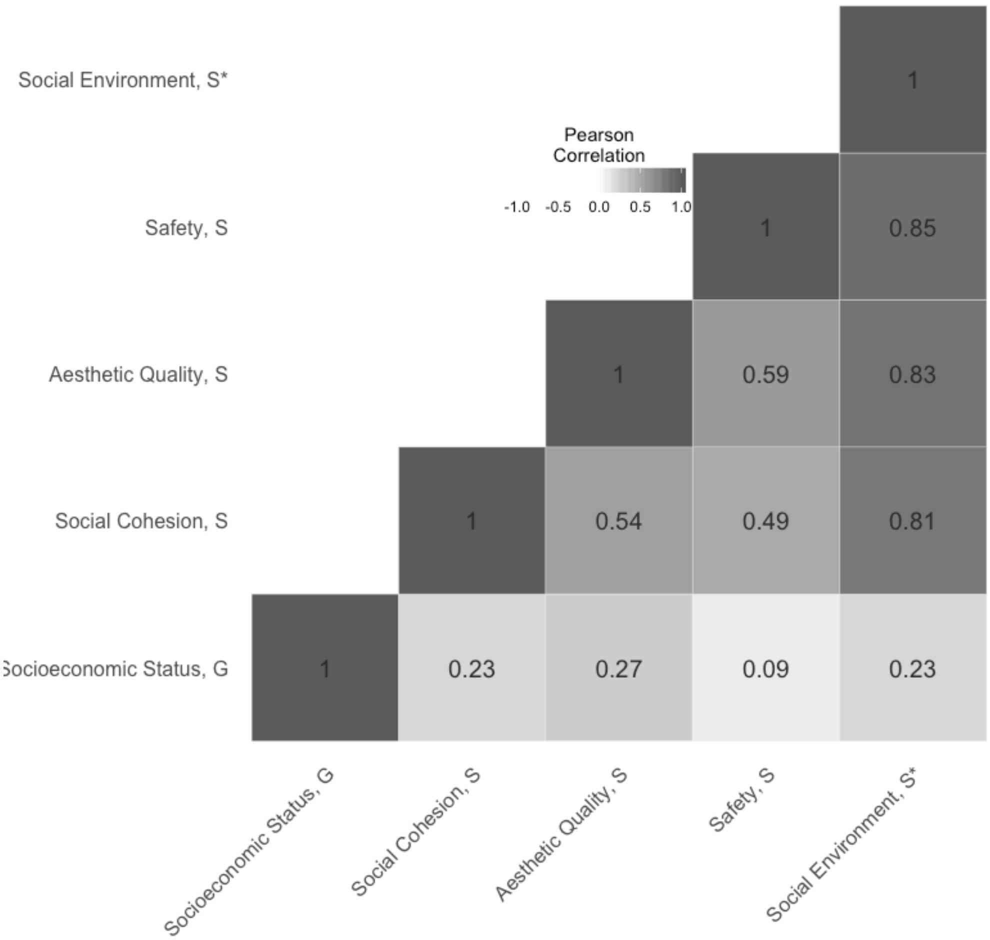

Figure 4.2 Pearson Correlation Among Change in Social Environment Characteristics and Change in Neighborhood Socioeconomic Status (N=1,031) *Note*. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure.

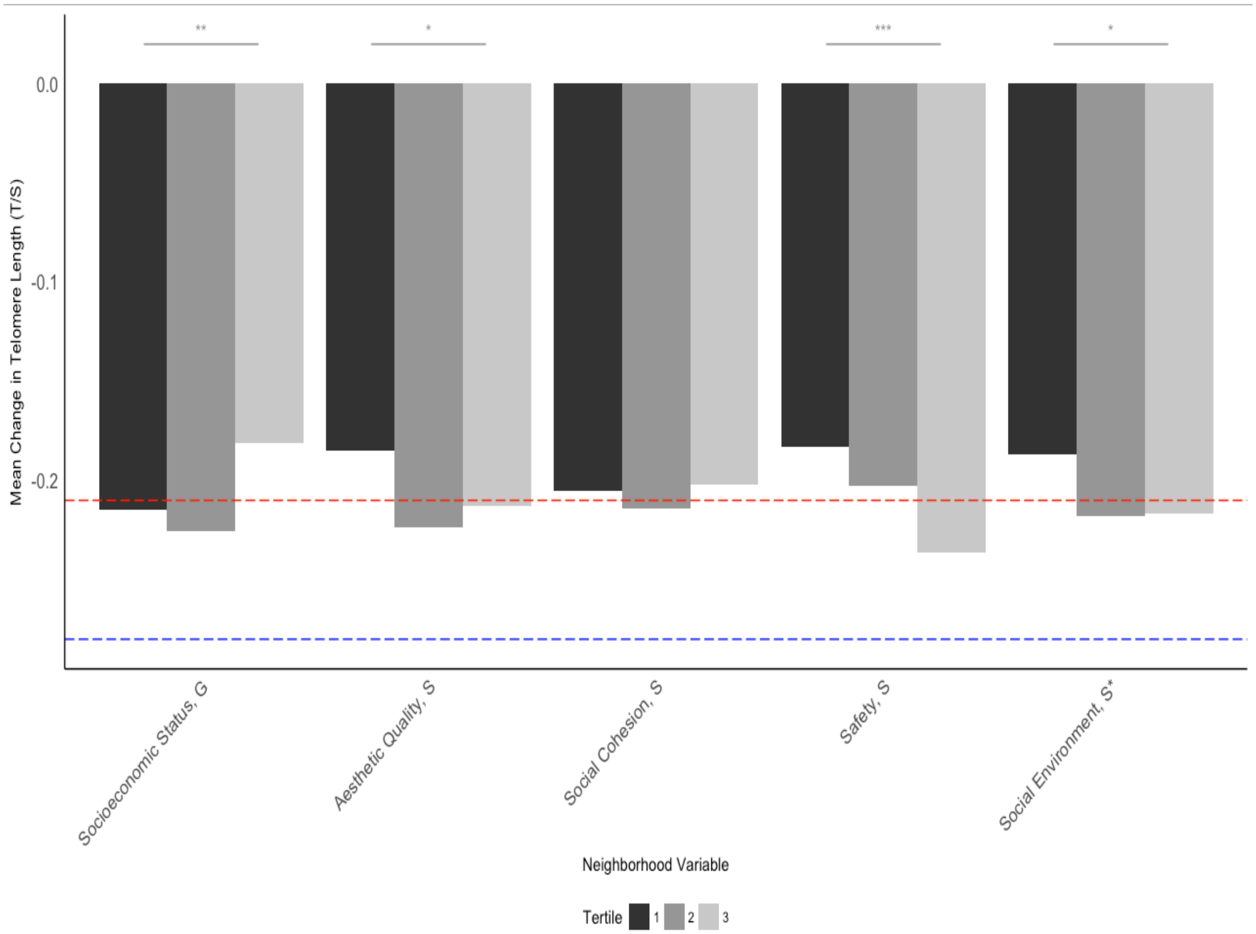

Figure 4.3 Mean change in telomere length (crude T/S) differed by tertile of change in each neighborhood characteristic. The red horizontal line indicates the overall mean change telomere length in the sample, -.21 (SD = .18). The blue horizontal line indicates the threshold for short telomere length for those in the lowest tertile of the distribution (T/S=-.28). *Notes*. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Statistical significance thresholds for the ANOVA tests were set at * for p<.05, ** for p<.01, and *** p<.001.

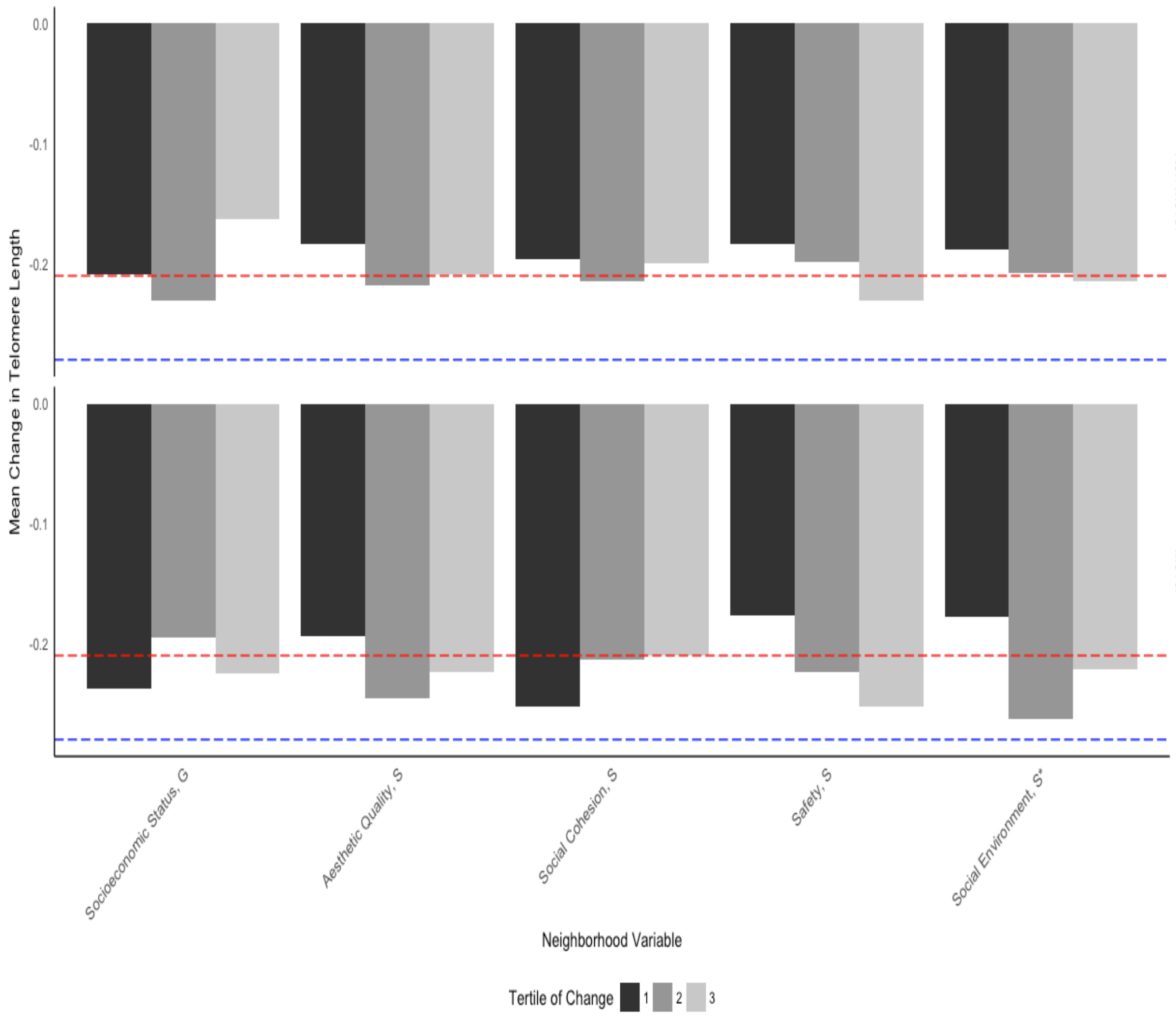

Figure 4.4 There were no statistically significant differences in mean change in telomere length (crude T/S) by tertile of change in each neighborhood characteristic and moving status. The red horizontal line indicates the overall mean change telomere length in the sample, -.21 (SD = .18). The blue horizontal line indicates the threshold for short telomere length for those in the lowest tertile of the distribution (T/S=-.28). Mean change in telomere length did not surpass the lowest tertile of the distribution (i.e., decrease in T/S ratio was among the highest in the study population) in any subgroup. There were 212 movers and 819 non-movers in the sample. *Notes*. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Statistical significance thresholds for the ANOVA tests were set at * for $p<.05$, ** for $p<.01$, and *** $p<.001$.

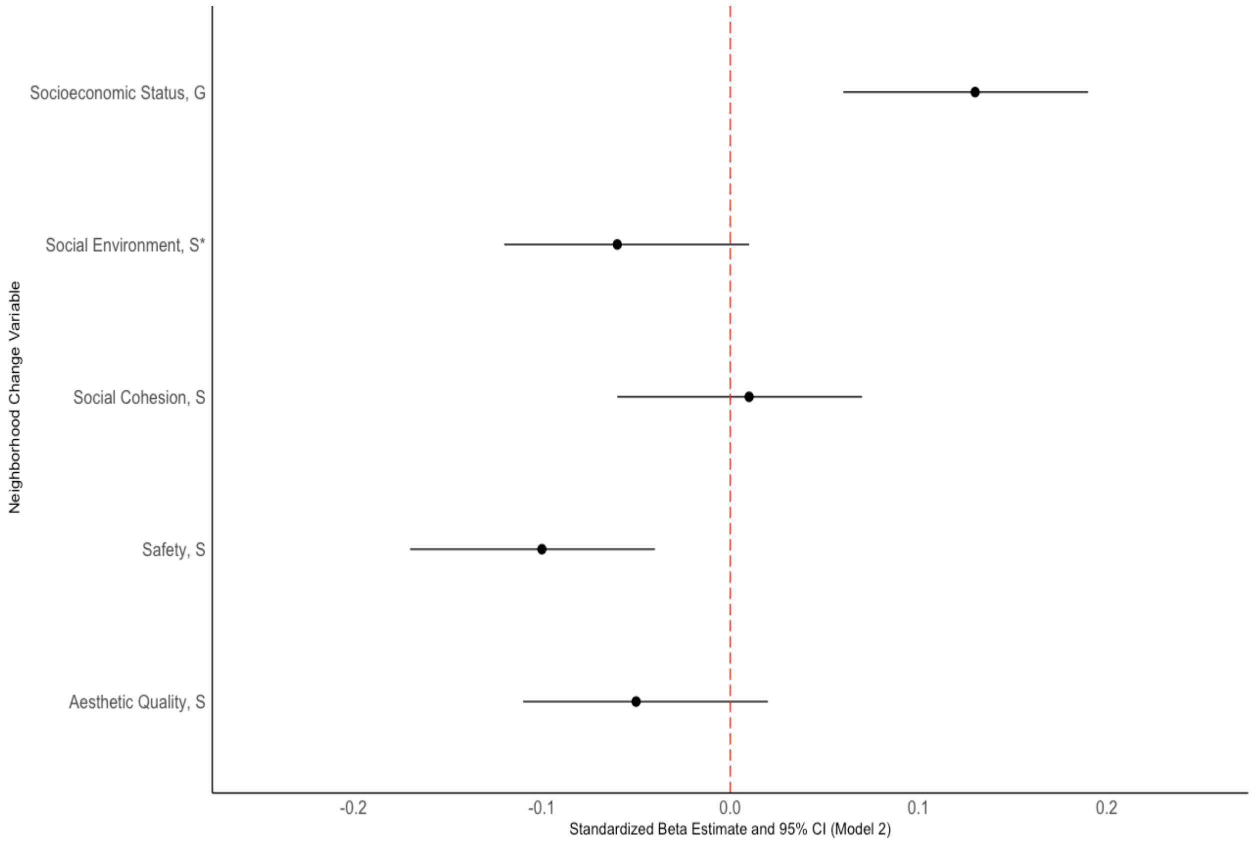

Figure 4.5 Summary of Associations of Change in Socioeconomic and Social Environment Features and Change in Telomere Length in MESA, 2000-2010 (N=1,031) *Notes*. Each linear mixed effect model included a random intercept for census tract. The models presented in this figure were adjusted for baseline measures of age, gender, race/ ethnicity, income, and education. Neighborhood change measures were grand mean centered and model estimates were standardized to 1 standard deviation unit. Neighborhood variables were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Statistical significance was set at *p*<.05 and the red vertical line indicates the null.

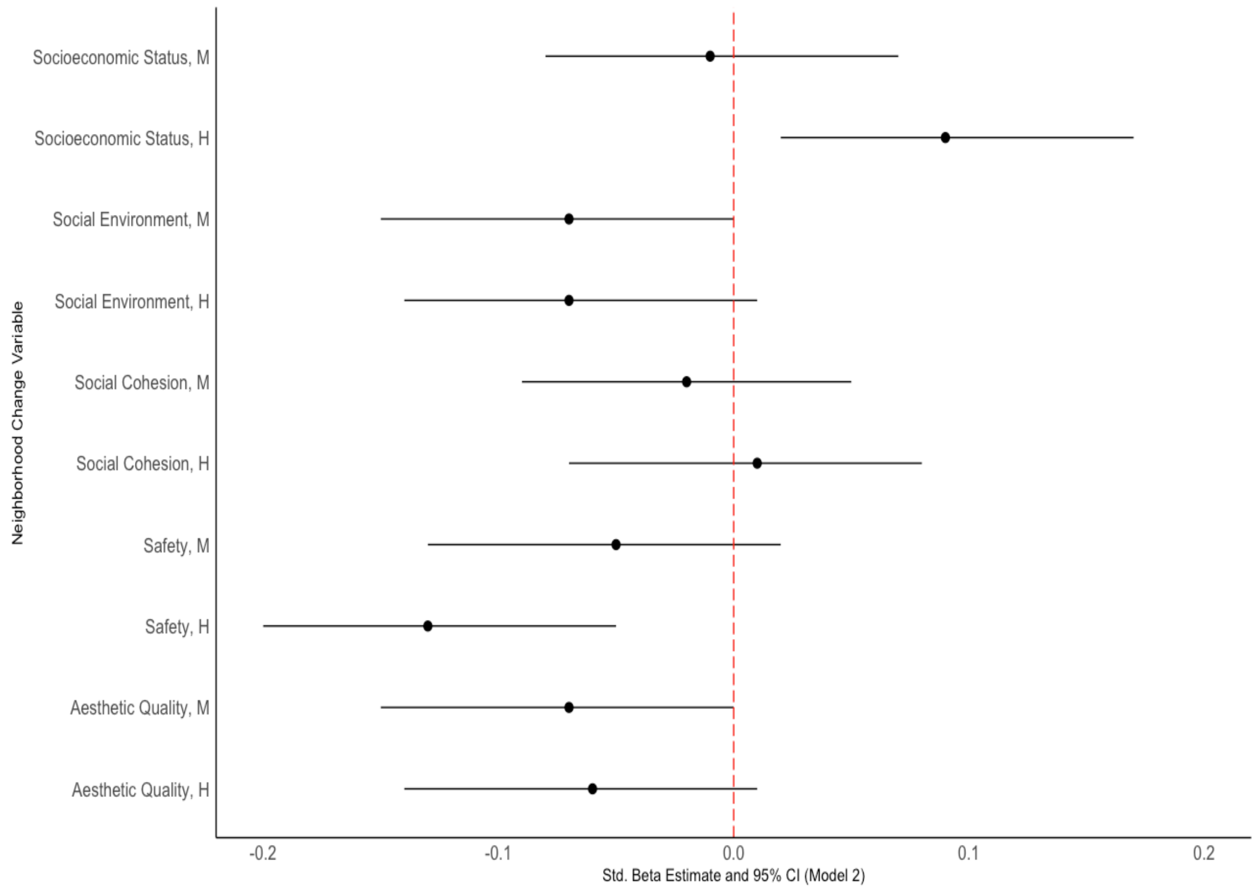

Figure 4.6 Summary of Associations of Tertile of Change in Socioeconomic and Social Environment Features and Change in Telomere Length in MESA, 2000-2010 (N=747) *Notes*. Each linear mixed effect model included a random intercept for census tract. The models in this figure were adjusted for age, gender, race/ ethnicity, income, and education. All measures were grand mean centered and model estimates were standardized to 1 standard deviation unit. Study measures were described using the following indicators: G = GIS-based measure, S = Survey-based measure, GS = Combined GIS- and survey-based measure, and *= Composite measure. Tertiles were defined as H for high and M for middle. The reference category was the low tertile of the distribution of each physical environment variable. Statistical significance was set at p<.05 and the red vertical line indicates the null.

Chapter 5 Conclusion

5.1 Summary of findings

The three chapters of this dissertation examined how specific features of residential built, social, and socioeconomic environments were associated with 10-year changes in telomere length. The principal hypothesis of this work was that improvements in neighborhood context would slow telomere shortening.

Chapter 2 presented cross-sectional findings on the association between physical environment characteristics and leukocyte telomere length. Better physical activity and food environments were associated with shorter telomeres. Specifically, walking environments, physical activity resources, and favorable food stores were associated with telomere length, but not in the expected direction.

Chapter 3 examined how changes in features of the physical environment were associated with the change in leukocyte telomere length after 10 years. The results highlighted that improved availability of physical activity resources was associated with telomere maintenance. Also, better perceptions of walking environments and availability of healthy foods slowed telomere shortening. These findings did not differ by moving status.

Chapter 4 explored whether changes in neighborhood socioeconomic and social environments were associated with the change in leukocyte telomere length. The findings suggested that improved neighborhood socioeconomic status was associated with a 10-year maintenance in telomere length; whereas, improved perceived neighborhood safety was associated with less telomere attrition than expected. There were no statistically significant differences by moving status.

5.2 Limitations

No study is without limitation, and each chapter thoroughly addressed the inherent challenges of this research. Still, some overarching themes remained salient. Social selection and effect modification by moving status were two lingering concerns.

First, race/ ethnicity, individual-level socioeconomic status, and neighborhood indicators are deeply connected in the United States. From a statistical perspective, this poses some challenges in trying to isolate the association between neighborhood measures and changes in immune cell aging. The analyses addressed social selection bias by adjusting for individual-level socioeconomic status in adulthood and other individual factors in order to estimate the independent association between each neighborhood feature and the measures of immune cell aging. Thus, if people are clustered in certain neighborhoods because of race/ ethnicity or socioeconomic status, then adjusting for these factors in the analytic phase separated their association from the association that can be explained only by neighborhood exposures. In addition, competing hypotheses were explored by additionally adjusting for lifestyle factors and neighborhood socioeconomic status (or change in neighborhood socioeconomic status for the longitudinal analyses). Despite evidence in the literature, diet and exercise were not associated with telomere length or change in length in these data. Thus, including them in the models did not attenuate any of the measures of association. Future research should consider dietary choices that have exhibited associations with telomere length, such as the Mediterranean diet score. Similarly, physical activity was not associated with telomere length in cross-sectional or longitudinal analyses. As discussed, it might be prudent to examine engagement with physical activity resources in both the neighborhood of residence and in adjacent areas. Finally, neighborhood socioeconomic status was included in the models to account for structural confounding due to heterogeneity across built and social contexts. However, neighborhood components do not change in a vacuum and analyses of neighborhood change may benefit from a multisystem neighborhood composite measure or from racially- and ethnically-specific indices of neighborhood socioeconomic status. Social selection remains a concern, and future research should fully explore methods that are amenable to limiting this source of bias.

Another issue related to neighborhood analyses is that over time residential areas can change due to forces such as divestment or gentrification, which in essence also changes the composition of individuals living in those neighborhoods. Another angle of this problem is that the population in the neighborhood changes due an influx or efflux of residents and as a result the neighborhood characteristics change (e.g., median household income). These analyses attempted to capture the chronicity of neighborhood exposure using a difference-in-differences estimator of moving status. However, the change telomere length among those who moved did not differ significantly from those who stayed in a similar context. Also, there was low residential mobility among movers; thus, despite an acute change in context, there was little gain in neighborhood improvement. Thus, the influence of moving could not be explored fully given the study sample. These and other considerations represent efforts to carefully disentangle significant social forces and their relationship to changes in immune cell aging.

5.3 Conclusion

Leukocyte telomere length changes over time, and these changes are associated with features of built, social, and socioeconomic contexts. This dissertation identified that improvements in the availability of physical activity resources, perceptions of the walking environment, the availability of healthy foods, safety, and neighborhood socioeconomic status were associated with less telomere shortening than expected, or telomere length maintenance, after 10 years. To the extent that residential areas are amenable to modifications, then policy interventions should focus on enhancing features of the neighborhood environment to improve aging trajectories among residents. Telomere length is not a perfect indicator of biological aging, but these analyses exhibited that the measure is associated with multi-level risk mechanisms.

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