NEIGHBORHOOD BUILT ENVIRONMENT CHARACTERISTICS AND COGNITION IN NON-DEMENTED OLDER ADULTS

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ABSTRACT

Lilah M. Besser: Neighborhood Built Environment Characteristics and Cognition in Non-Demented Older Adults
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Research suggests that neighborhood built environment (BE) characteristics consistent with increasing urban density may be associated with better cognition in older adults; however, few of these studies have been conducted to date. Focusing on older adults, my study aimed to: 1) systematically review studies on neighborhood social and BE and cognition; 2) examine whether social/walking destination density, intersection density, residential/retail land use, distance to nearest bus/train stop, or population density is associated with cognition; and 3) investigate if BE-cognition associations vary by individual-level characteristics (education, race/ethnicity, sex, apolipoprotein ε4 genotype [APOE; genetic risk factor for Alzheimer's disease], or sedentary behavior).

I used cross-sectional, Exam 5 data on 4,123 participants from the Multi-Ethnic Study of Atherosclerosis (MESA), a longitudinal study of subclinical cardiovascular disease that began in 2000. MESA recruited from six US regions (New York, Baltimore, Chicago, Los Angeles, Minneapolis-St. Paul, and Winston Salem) and oversampled minorities (Chinese, African American, and Hispanic).

The literature review suggested that BE features such as presence of a community center and transit stops, increased land use mix, and public spaces in better condition may be associated

with better cognition. Additionally, the literature suggested that lower neighborhood socioeconomic status (SES) is associated with worse cognition, independent of individual-level SES. Aim 2 analyses suggested that increasing population and intersection density are associated with worse cognition, whereas increased land dedicated to retail uses is associated with better cognition. Aim 3 analyses suggested that BE-cognition associations vary significantly by an individual's education, race/ethnicity, sex, APOE genotype, and sedentary behavior. BE characteristics consistent with increasing urban density were associated with worse cognition in Hispanics but not Whites and in APOE ε4 carriers but not APOE ε4 non-carriers.

Although an increase in neighborhood retail destinations was associated with better cognition in the overall sample, these results suggest that increasing urban density may have a disproportionately negative effect on cognition in racial/ethnic minorities and those with genetic susceptibility for Alzheimer's disease. Compact growth policies may not be beneficial to all, and thus, planners and public health researchers need to consider the BE's positive and negative effects on cognition in vulnerable populations.

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LIST OF ABBREVIATIONS AND SYMBOLS

ε4	Apolipoprotein epsilon 4 allele, Alzheimer's disease genetic risk factor
AD	Alzheimer's disease
APOE	Apolipoprotein E
BE	Built environment
CASI	Cognitive Abilities Screening Instrument
CES-D	Center for Epidemiologic Studies Depression Scale
COPD	Chronic obstructive pulmonary disease
DS	Digit Symbol
DSB	Digit Span Backward
DSF	Digit Span Forward
FDA	Federal Drug Administration
HIA	Health impact assessment
KM	Kilometer
MCI	Mild cognitive impairment
mmHg	Millimeter mercury
MESA	Multi-Ethnic Study of Atherosclerosis
MESA-SHARE	Single Nucleotide Polymorphism (SNP) Health Association Resource
MMSE	Mini Mental State Exam
MoCA	Montreal Cognitive Assessment
NETS	National Establishment Time-Series
NPH	Neighborhood psychosocial hazards

NSES	Neighborhood socioeconomic status
PA	Physical activity
PC1-PC3	Principle components number 1 through 3
QOL	Quality of life
SE	Social environment
SEM	Socioecological model
SES	Socioeconomic status
TICS	Telephone Interview for Cognitive Status
UK	United Kingdom
US	United States
WAIS	Wechsler Adult Intelligence Scale

I. INTRODUCTION

1.1. City planning, the built environment, and public health

Beyond exposures, characteristics, and risk factors measured at the level of the individual, contextual factors such as features of the community environment may have negative and positive effects on health. Increasingly, community level characteristics and exposures, such as the social and physical characteristics of a neighborhood, have been incorporated into public health research[1], thereby indirectly exploring the public health consequences of urban planning policies. For example, as a product of planning policies and infrastructure investment, the built environment (BE) has been associated with a range of health-related behaviors and outcomes such as physical activity, depression, and quality of life[2-5] in past studies, and thus, there is an intrinsic connection between planning and health.

Historically, city planning efforts were often based on concerns for public health and safety, although the planning and public health fields can seem disparate today.[6] For instance, zoning was originally based on the desire to reduce crowding and proximity of undesirable land uses and the associated health problems. Recently, planners have started incorporating considerations of health in local and regional planning projects, which hitherto were primarily focused on the more recognizable and immediate consequences of planning decisions, such as logistic and economic concerns. As an example, the Federal Highway Administration and US Department of Transportation recently published on “Statewide Transportation Planning for Healthy Communities”.[7] The paper outlines four strategic points along the transportation planning timeline in which considerations of health can be incorporated: 1) in providing motivation for planning efforts; 2) in developing partnerships with other agencies; 3) in setting up objectives, policies, and priorities that include health; and 4) in making structural changes to incorporate public health impacts during the decision making process. This latter strategy may include implementation of health impact assessments (HIA), tools that can be used to assess the potential health consequences of policies, projects, or programs. To date, HIAs have been used in a modest number of locales by planners in collaboration with public health professions.[8]

The academic literature suggests an increase in the amount of interdisciplinary research spanning the planning and health fields, although the differences in the technical vocabulary[9], methods, and priorities of the professionals in the two disciplines can be challenging. For instance, while transportation planners may be focused on predicting mode choice (automobile, transit, bicycle, or walking) for comprehensive plans, public health researchers may be concerned with whether walking or bicycling to places meets daily physical activity recommendations. The growing interest in examining the connection between urban planning and health relates to evidence that aspects of the BE are associated with health outcomes. For example, one literature review found sufficient evidence to promote physical activity by implementation of urban planning policies that increase population density, decrease distance to nonresidential places, and increase land use mix.[10] While research on the intersection between BE and health has increased in productivity over the years, much work is still needed, particularly with respect to understanding how the BE influences health in vulnerable populations such as children[11], minorities and the economically disadvantaged[12], and older adults.[13] Ultimately, urban planners and public health professionals need to collaborate to determine the BE features and health outcomes that will be the most fruitful to investigate, and planners are essential for determining the best means of measuring the BE and for providing their planning expertise to inform these types of studies from inception.

The impact of urban planning decisions on the health of older adults is a salient topic, with planning for aging recognized as an important issue by the American Planning Association[14] and with recent increases in US funding for aging and dementia research[15]. In 2013, the US population of adults aged 65 years and older was estimated at 45 million, representing 14% of the population.[16] Older adults are expected to grow to over 22% of the US population and their numbers will approximately double to over 83 million by 2050.[16,17] As a result of the projected increase in this population over the next 40 years, the prevalence of health problems associated with older adults can also be expected to greatly increase and pose a significant public health burden. In addition, approximately 80% of the US population lived in urban areas in 2010[18] and over 90% of older adults would like to age in place, staying in their homes and neighborhoods for as long as possible.[19] Therefore, urban planning and public health policies developed to preserve health among older adults and allow them to remain in their neighborhoods may help relieve the economic and public health burden associated with the increasingly aging nation.

1.2. The research problem

The neighborhood environment has been hypothesized to be related to health due to its impact on multiple factors such as opportunities to exercise, access to healthy food options, opportunities for social engagement, exposure to pollution, crime, and social deprivation, and access to green space. Studies on the neighborhood environment have suggested associations with health outcomes such as physical activity, blood pressure, obesity, depression and quality of life.[4,20-23] However, most of the previous studies have focused on younger or middle age adults, with limited research on older adults[24,25], although the impact of the neighborhood environment on older adults may be intensified by issues such as limited mobility, disability, lack of local social and family ties, cognitive impairment, and a heightened sense of a lack of safety. Given the expected rise in the population of older adults, better information is needed on the possibilities of aging in place and the neighborhood and BE factors that are associated with positive and negative health outcomes in this population.

The neighborhood increases in importance as older adults spend less time driving and experience shrinking social networks[26]. The life space of older adults, the area they conduct all of their activities, declines sharply upon driving cessation[27], with up to 33% spending little time outside of their neighborhood.[28] Some studies suggests that driving cessation is associated with depression and decreased time spent outside of the home, but the evidence to date is limited[27,29], and at least one study found that social engagement with neighbors did not decline after driving cessation.[30] Although some older adults will spend more time in the neighborhood and in their homes and less time driving due to cognitive or physical difficulties[31], the number of healthy older adults spending more of their time in the neighborhood will likely increase with the rising population living in urban areas and desiring to age in place.[32]

Two health behaviors that are directly influenced by the older adult's neighborhood environment are their walking and social interactions. Walking in older adults has been associated with proximity to destinations, street connectivity, and traffic and street conditions.[26] In addition, higher levels of social participation have been found among older adults who live closer in proximity to social destinations[33] and who live in neighborhoods with higher levels of mixed-used development and walkability[34]. Neighborhoods with higher levels of walkability are pedestrian friendly because they offer a variety of nearby places to walk including restaurants, banks, post offices, retail establishments, and parks; shorter distances to get to nearby destinations; safe walking environments including sidewalks, walking paths, sufficient lighting, and crosswalk signals; and elements of design that encourage walking such as building setbacks.

1.3. Cognition

The issue of cognitive impairment is of public health importance for a number of reasons, including the high prevalence of dementia (e.g., Alzheimer's disease dementia) and mild cognitive impairment (MCI) among older adults. Alzheimer's disease (AD), one of the major causes of dementia and MCI, affects approximately 5 million older adults in the US. Assuming no treatments have been found to reduce AD incidence, it is projected there will be 13.8 million Americans with AD by 2050.[35] Worldwide, approximately 47 million individuals were diagnosed with dementia in 2015, and that number is expected to rise to 132 million in 2050.[36] In addition, MCI is estimated to be present in ≥10% of older adults.[37] Before receiving a diagnosis of AD, many individuals are first diagnosed with mild cognitive impairment (MCI), which is characterized by cognitive symptoms that do not yet significantly affect activities of daily living such as balancing a checkbook or following a recipe.[38,39] MCI is often due to AD, but can also be caused by other neurodegenerative diseases or due to systemic illness, stroke, depression, or medications, among other causes.[37] Individuals with cognitive impairment not meeting the diagnostic criteria for dementia are at high risk for developing dementia in the future.[40] Consequently, interventions and public health prevention efforts that target the early stages that precede dementia are expected to have the best chance of reducing the incidence and prevalence of dementia.

No pharmaceutical treatments have been found to cure or delay AD, although studies suggest that non-pharmaceutical interventions or pharmaceutic interventions aimed at vascular comorbidities may help delay AD onset. The few FDA approved medications for AD have been shown to improve cognitive symptoms for a few years at most, sometimes offer no relief, and do not halt the progression of the disease pathology but instead simply treat the symptoms.[41] Much of the preventive research related to cognitive decline and dementia has been focused on studying the biological mechanisms that could be targeted via a pharmaceutical treatment. However, some studies have examined how cognition is affected by factors that may not be directly related to the primary pathological cause of the disease, but that may help via mechanisms related to improved vascular health or cognitive reserve. Examples include interventions such as treating hypertension or increasing physical activity.[41] Additionally, studies have found that years of education and a history of mentally demanding jobs were associated with lower risk of dementia or a delay in dementia onset, and that performing mentally demanding activities such as crossword puzzles was associated with better cognition and may be associated with reducing pathology associated with Alzheimer's disease dementia.[41-43] New studies are needed to determine whether other non-pharmaceutical mechanisms have some effect on the incidence of cognitive impairment or if they can delay onset.

Cognitive impairment can significantly impact the daily functioning and quality of life of the affected individuals, and the emotional and physical burden due to cognitive impairment can pose undue strain on family members and caregivers. Fifty-nine percent of AD patient caregivers have indicated that they have high emotional stress due to caregiving, and 38% report high physical stress due to caregiving.[35] Given the public health importance of cognitive impairment, additional research is needed to investigate how individual, interpersonal, and environmental factors such as the BE may be associated with cognitive functioning.

Urban planning may relate to cognition in older adults in a number of ways. The types of housing that is suitable and available for older adults affects whether they live in urban, suburban, or rural areas, and consequently, the incidence and prevalence of cognitive impairment and dementia may vary by neighborhood/area depending on the availability of housing. Similarly, neighborhoods that are more suitable for older adults (e.g., greater proportion of older adults, perceived as safer, less confusing) will likely retain individuals as they age and attract individuals to move there, thereby affecting area-level incidence and prevalence of cognitive impairment. Regions that plan for and accommodate older adults through urban planning policies and infrastructure investments can influence cognition by allowing individuals to age in place. Neighborhood factors that would encourage aging in place include environments that provide safe spaces for walking, that are easier to navigate, and that have suitable housing options. More specifically, urban planning policies may positively influence cognition when they foster the development of neighborhood environments that promote mental, physical and social activity. Examples of BE features that may improve cognition include presence of nearby social and walking destinations and green space. On the other hand, urban planning policies that promote driving may result in neighborhood environments that are not walkable or safe for older adults, and thus could be detrimental to their cognition.

1.4. Gaps in the literature

Studies to date suggest that the neighborhood environment affects health through a variety of mechanisms, including changing health behaviors such as physical activity. However, fewer of the published studies have focused on older adults, who are of increasing importance due to the projected increase in their population over the next few decades. Additionally, few studies have investigated if neighborhood social and BE characteristics are associated with cognition in older adults, although it seems likely that the neighborhood environment becomes increasingly important to the health of older adults because they drive less and spend more time closer to home as they age.

Some studies have found that the prevalence of dementia and cognitive impairment is higher in rural than urban regions.[44,45] Although education or other individual-level differences between urban and rural residents may help explain these findings, the regional differences also may relate to environmental or social factors that are better measured at the level of the neighborhood. For instance, a previous systematic review on community environment and cognition in older adults (n=14 published studies)[46] found that worse neighborhood socioeconomic status (SES) was associated with worse cognition after controlling for individual-level demographics and SES. Only one of the 14 studies examined BE characteristics[47], finding that living in neighborhoods with more institutional resources (e.g., libraries) was associated with better cognition.

Before 2005, little research was conducted on the neighborhood's influence on cognition in older adults (Figure 1.1), with the bulk of the work published in 2011 and 2012. Additionally, almost all of the research on the topic focused on neighborhood social characteristics. Thus, although it appears that the research interest in neighborhood environment and cognition in older adults in increasing, and previous studies suggests significant associations particularly between neighborhood SES and cognition, there is a large gap in the literature regarding the neighborhood BE and cognition. Therefore, much more work is needed in this growing field to determine the neighborhood BE characteristics that have the strongest influence on cognition in older adults, and the individual-level characteristics that may modify BE-cognition associations.

1.5. Dissertation study proposal

My dissertation study uses data from the Multi-Ethnic Study of Atherosclerosis (MESA)[48] to examine whether neighborhood BE characteristics are cross-sectionally associated with cognition in non-demented older adults. Additionally, I examine whether the BE-cognition associations vary by individual-level demographics, apolipoprotein E genotype, a genetic risk factor for developing Alzheimer's disease dementia, or sedentary behavior.

MESA is a population-based, longitudinal cohort study aimed at examining the characteristics and risk factors for progression of subclinical cardiovascular disease. Since 2000, six exams have been conducted on the 6,814 participants aged 45 to 84 year olds living in six US regions (New York, Baltimore, Chicago, Los Angeles, Minneapolis-St. Paul [Twin Cities henceforth], and Winston Salem). The study was designed to oversample minorities, resulting in 39% whites, 28% African Americans, 12% Chinese Americans, and 22% Hispanics at baseline. My analyses are restricted to Exam 5 (2010-2012), the most recent exam available to researchers that also has cognitive assessment data.

The findings of the study are written up as three publishable papers:

Paper 1. The first paper is a systematic review of published studies on the neighborhood social and BE and cognition in older adults. As the aim of Paper 1, a comprehensive literature review was not provided in the introduction section of my dissertation.

Paper 2. The second paper is focused on neighborhood BE characteristics and cognition among older adults, and effect modification of the BE-cognition associations by education and race/ethnicity. The first aim cross-sectionally examines whether multiple neighborhood BE characteristics are associated with cognition, with the hypothesis that BE characteristics consistent with increasing urban density will be associated with better cognition. The second aim investigates if the BE-cognition associations vary based on individual-level education or race/ethnicity. Few published studies can help inform hypotheses on effect modification by individual-level education or ethnicity; however, one study[47] found that cognition of non-white participants was negatively impacted by the presence of institutional resources, suggesting that we may find cognition of non-white participants and those of lower education may be affected differentially by the BE compared to participants of white race and higher education.

Paper 3. The third paper examines effect modification of the BE-cognition associations by individual-level sex, APOE genotype, or sedentary behavior. The first aim is to examine whether there are sex-based differences in the associations between neighborhood BE and cognition, with the hypothesis that the association between the BE and cognition will be stronger in women than men. The second aim assesses whether the associations between neighborhood BE and cognition varies by sedentary behavior. The hypothesis is that the BE-cognition associations will be stronger among those with lower levels of television watching in a typical week in the past month. Higher levels of television watching will serve as a proxy for decreased time exposed to the neighborhood environment during a typical week. The third aim investigates if the presence of at least one APOE ε4 allele modifies the association between neighborhood BE and cognition, with the hypothesis that the BE-cognition associations will be stronger among those with ≥1 APOE ε4 alleles.

The apolipoprotein E (APOE) gene has been found to be a risk factor for AD. Individuals with one copy of the APOE ε4 allele have a 4-fold increased risk of AD and those with two copies have a 12-fold increased risk.[49] Alleles are genes that are found in pairs in a given individual and in the case of the APOE gene, come in the ε2, ε3, and ε4 allele variants.

1.6. Conceptual framework

The conceptual framework guiding my dissertation work combines and builds upon previously proposed models. Many aspects of the BE may influence cognition and this may occur through one or more causal mechanisms, as outlined in my conceptual model in Figure 1.2.

The neighborhood BE factors proposed to influence cognition have been grouped into the following major categories: 1) street network, including factors such as intersection density and block size; 2) density, including factors such as population and housing density; 3) land use, including factors such as presence of social destinations and parks; 4) transport and access, including factors such as presence of sidewalks and bike paths; 5) design, including factors such as condition of sidewalks and aesthetics; 6) housing, including factors such as housing types and heights; and 7) environments conducive to traffic and noise, including factors such as tall buildings and proximity to major roadways.

The BE characteristics outlined above may relate to cognition through a number of causal mechanisms: 1) air pollution exposure; 2) quality of life; 4) cognitive mechanisms; 5) social mechanisms; and 6) health behaviors. Details about each causal mechanism are below.

Air pollution. Urban environments can be associated with increased exposure to vehicular pollutants due to decreased distances to busy roadways.[50] Airborne pollutants[51] have been associated with worse cognition in older adults, and therefore, the BE may be associated with cognition by increasing or decreasing risk of exposure to pollutants. If found to be a valid causal mechanism relating the BE and cognition, air pollutant exposures would mediate the association between BE and cognition.

Quality of life. Quality of life (QOL) is a sense of wellbeing, encompassing perceived physical health such as health status and mental health measures such as stress, anxiety, and depression. BE characteristics that improve QOL may in turn improve cognition. In past studies, land use mix, parking density, mass transit station density, population density, and neighborhood SES have been associated with differences in QOL[20,52-54]. In addition, neighborhoods with higher levels of walkability, greater access to transit, and greater density have been associated with lower levels of depression.[22,55,56] Traffic and other noise associated with an urban environment may be associated with greater levels of anxiety[57] and increased traffic volume has been associated with greater perceived stress.[58] Stress in late-life has been associated with worse baseline cognition and cognitive decline in older adults[59,60] and a decrease in stressors has been associated with improved cognition.[61] Thus, evidence suggests that the mental health aspect of QOL is a plausible causal mechanism relating the BE and cognition.

QOL research often measures QOL through a composite measure that incorporates multiple aspects of physical and mental health and wellbeing. These kinds of broader QOL measures have been understudied to date in relation to exposures that may impact cognition.[62] Although some studies have investigated changes in QOL in relation to cognitive functioning[63,64], few have examined how QOL affects cognition.[62] Similarly, no known studies have examined how the BE may influence cognition by way of improved or worsened QOL. Nonetheless, the complicated and multifaceted nature of the BE seems likely to be associated with QOL, and QOL is a plausible predictor of cognitive functioning. If found to be a valid causal mechanism, measures of QOL, such as anxiety, stress, depression, and composite QOL measures, would mediate the BE-cognition association.

Cognitive stimulation/overload. Exposure to various neighborhood BE features may serve as a passive source of cognitive stimulation, which can either improve cognition or cause cognitive overload that worsens cognition. Performance of cognitively stimulating activities, such as working on crossword puzzles, has been associated with improved cognition in older adults.[65,66] Similarly, living in a complex neighborhood environment in older age may help delay onset of cognitive impairment by requiring constant but passive adaptation that serves as a beneficial source of mental stimulation.[67] However, the neighborhood BE may serve as a source of cognitive overload[68,69] if the neighborhood environment becomes too complex to process and navigate by older adults. While there are no obvious mediators of the BE-cognition association assuming this causal mechanism, measures of brain activity could conceivably suggest that this mechanism is at work.

Social engagement/isolation. Some research suggests that staying social in older age can reduce the risk of dementia.[70,71] Neighborhoods with more social opportunities may improve social engagement and consequently maintain or improve cognition. On the other hand, neighborhood psychosocial disorder (e.g., crime, graffiti), fear of falls[72], and sensory overload (e.g., confusing spaces, noise, crowds)[73] may increase social isolation[74,75] if residents minimize neighborhood-based walking. Increased social isolation may then worsen cognition. Measures of social participation in the neighborhood would be an example of a mediator of the BE-cognition association based on this causal mechanism.

Health-related behaviors. The neighborhood BE may influence health behaviors such as PA or diet, thereby affecting cognition through changes in vascular and endocrine health. PA interventions have been associated with improved cognition in those with normal cognition, mild cognitive impairment, and dementia[76-78], and some evidence indicates that certain BE features may be associated with increases in overall PA.[20,79] Other health behaviors that may be affected by the BE and that may be associated with cognition include eating habits based on neighborhood food options and driving frequency. Greater availability of fast food options in the neighborhood has been associated with increased fast food consumption in younger adults.[80] In turn, diabetes, a diet-related health condition, has been associated with cognition and brain atrophy associated with cognitive impairment.[81] In addition, the choice of transport modes other than driving has been associated with increases in urban density and land use mix.[82,83] Decreases in driving may be associated with less sedentary behavior due to increased walking for transit, but it is also possible that the opposite occurs, in which older adults living in denser neighborhood environments travel less in general and this lack of cognitive stimulation is associated with worse cognition. Measures of the health behaviors, such as PA, diet, and driving, would be mediators of the BE-cognition association under this causal mechanism.

Cognition. The BE may affect an individual's overall cognitive functioning, or possibly only certain cognitive domains, depending on the causal mechanisms at work. Additional details about cognitive domains are discussed further below, but briefly, the domains include memory, attention, processing speed (efficiency of completing tasks), language (e.g., naming everyday objects), executive function (e.g., problem solving), and visual-spatial function. If a particular cognitive domain is affected, this may suggest a region of the brain that is affected by a given environmental exposure such as the BE. For instance, consider visuospatial function, which is one's ability to perceive and reconstruct the spatial relationship of objects. This cognitive domain seems likely to be affected by the BE, with greater time spent in the neighborhood possibly improving one's visuospatial abilities through practice of navigating the neighborhood.

Individual-level effect modifiers/moderators. Part of my conceptual model includes consideration of effect modifiers, which are factors that modify the BE-cognition association such that the associations vary by different levels of the effect modifier. For instance, the association between the condition of public spaces and cognition may be stronger with increasing age because younger older adults can more easily navigate around parts of the neighborhood that are in worse condition.

In determining plausible effect modifiers, it is useful to consider some of the previously outlined causal mechanisms relating the BE and cognition. For instance, if the BE-cognition association relates to air pollution exposure, effect modifiers could include time spent walking in the neighborhood, distance to the nearest busy road, and home ventilation. Individuals who walk more often in their neighborhoods may have the worst cognitive function because of increased exposure to the air pollution. If the BE-cognition association relates to QOL and mental health, a plausible effect modifier may include a genetic predisposition for depression. BEs that are associated with increases in depression may be associated with the worst cognitive functioning in those with genetic predisposition to depression. If the BE-cognition association relates to cognitive stimulation/overload, plausible effect modifiers include having a physical or mental disability that would increase the difficulty of navigating and processing the neighborhood environment. Thus, the association between the BE and cognition may be modified by individual-level characteristics (i.e., “Person-Environment” fit[84]) and may also depend on the specific BE characteristic being measured. For example, while the association between condition of public spaces and cognition may increase with age, the association between traffic and noise and cognition may be more consistent across age groups.

Neighborhood-level effect modifiers/moderators. In addition to individual-level effect modifiers (e.g., individual-level race/ethnicity), neighborhood-level characteristics may also moderate BE-cognition associations. For instance, neighborhood-level SES may modify the association between condition of public spaces and cognition such that condition of public spaces may be more strongly related to cognition in low versus high SES neighborhoods. In this case, living in neighborhoods in the worst conditions and with the lowest SES levels may be associated with the worse cognitive functioning. Among those in low SES neighborhoods, the presence of better neighborhood conditions may be associated with better cognition compared to those living in worse neighborhood conditions.

Comparison to other conceptual models. Various frameworks have been proposed to link BE exposures to health, including the frequently referenced socioecological model (SEM)[85]. The SEM is useful for considerations of multiple levels of influence on health outcomes, including the impact of urban planning policies and neighborhood characteristics. The SEM also conceptualizes how the associations between higher-level factors such as the neighborhood environment and cognition vary by individual-level factors. However the SEM does not provide specific causal mechanisms by which the BE relates to cognition.

Other useful frameworks that include more specific causal mechanisms include those by Wells et al[6] and Casserino & Setti[67]. The Wells et al model focuses on how specific planning decisions (i.e., nature and open space, urban form, food environment, housing) influence multiple health outcomes. In contrast, the model by Casserino & Setti[67] aims to explain potential associations between the physical environment and cognition, via the mechanisms of cognitive stimulation/overload, physical activity, and social engagement. Cassarino & Setti also specifically discuss potential effect modifiers of the association between the physical environment and cognition. Thus while the Wells et al model is oriented around planning decisions that influence various health outcomes, the Cassarino & Setti model is oriented around the causal mechanisms linking the environment and cognition.

My conceptual model combines concepts from the SEM and the frameworks by Wells et al and Casserino & Setti, but also adds a number of unique features. Firstly, my model is the only one focused specifically on the BE and cognition. The BE characteristics that are included are those that are hypothesized to be associated with cognition, and inclusion of the BE characteristics (e.g., land uses) and not planning decisions (e.g., zoning) orients the conceptual model around environmental exposures that are the result of planning decisions and policies but that can be more immediately measured by public health researchers. This kind of conceptual model can be used by both planners and public health researchers in considering the influence of the BE on cognition. Secondly, additional features are considered only in my conceptual model, such as environments promoting noise, design considerations such as aesthetics and condition of public spaces, and facilities for walking and bicycling. Thirdly, my model considers multiple aspects of cognition that may be affected by the BE, such as attention or visuospatial function. Fourthly, my model considers causal mechanisms beyond those included by Cassarino & Setti, specifically, air pollution exposure and quality of life. Lastly, my model denotes the importance of considering individual- and neighborhood-level effect modifiers of the BE-cognition association.

1.7. Neighborhood built environment measures

Neighborhood features can be divided into either physical or social characteristics. Social characteristics include measures such as neighborhood demographics (e.g., age, race/ethnicity, SES), social connectedness of neighborhood residents, violence, safety, crime, and social disorder (e.g., graffiti and broken windows). Physical characteristics can include measures such as features of the pedestrian environment, aesthetics, availability of healthy food options, land use, and population density.

The main exposure variables for my dissertation study are objective neighborhood BE measures surrounding the MESA participants' homes, which have been previously developed for use in other MESA neighborhood studies by Ana Diez Roux and colleagues. The measures include proportion land dedicated to retail uses, proportion land dedicated to residential uses, intersection density, population density, density of social and walking destinations, and distance to nearest to bus and train stop.

Population density. Population density was calculated for ¼-mile, ½-mile, and 1-mile as-the-crow-flies buffers around the participants' homes based on the 2000 and 2010 Census population density at the census block level. Assuming an equal distribution of the population per block, the population was calculated for each buffer zone. For my study, population density was measured as the number of persons per square kilometer in 2010 in a ½ mile radius around the participant's home. The ¼ and 1-mile buffers were used in sensitivity analyses.

Proportion of land dedicated to retail uses. I used the proportion of the ½ mile buffer around the participants' homes that is dedicated to retail. Land parcels for each of the study sites were classified as residential, retail, or commercial. Parcels dedicated to retail use were defined to include shopping centers, food stores, convenient stores, restaurants, bars/night clubs, clothing stores, mixed use buildings. The proportion of the area that is retail was calculated by dividing the retail area in meters square by the total area of the buffer in meters square. The ¼ and 1-mile buffers were used in sensitivity analyses. This measure was derived from administrative land use data at the city/county level.

Proportion land dedicated to residential uses. I used the proportion of the ½ mile buffer around the participants' homes that is dedicated to residences. Parcels dedicated to residential use were defined to include single family homes, duplexes, apartment complexes/condominiums, assisted living facilities, and rooming houses, including mixed-use parcels with some residential activity. The proportion of the area that is residential was calculated by dividing the residential area (in square meters) by the total area of the buffer (also in square meters). The ¼ and 1-mile buffers were used in sensitivity analyses. This measure was derived from administrative land use data at the city/county level. Because buildings can be more than one story, the area built may be greater than the buffer area and this measure can exceed 100%.

Distance to nearest bus line and train stop. The straight line distance to the nearest bus line and to the nearest train stop were calculated for MESA participants in which land use and public transit files were available.

Intersection density. Intersection density served as a measure of the connectivity of streets and was calculated by dividing intersection counts (all types [e.g., 3-way, 4-way] but excluding culs-de-sac and dead ends) in the buffer area by the total area of the buffer. The ½-mile buffer measure was used in the primary analysis and the ¼-mile and 1-mile buffers were used in sensitivity analyses. This measure was derived using StreetMap Premium 2012 data.

Density of social and walking destinations. The ½-mile density of social engagement destinations included the density per square mile of the following destinations divided by the buffer area: beauty shops and barbers, performance-based entertainment, participatory entertainment, sports entertainment, exercise facilities, coin-operated amusements, amusement parks, membership clubs, libraries, museums, zoos and aquariums, civil/social/political clubs, religious organizations, eating places, and night clubs. The ½-mile simple density of total walking destinations included the following: postal service, drug stores/pharmacies, banks, non-beverage food stores, non-beverage eating and dining places, non-alcoholic drinking places. The ¼-mile and 1-mile buffers were used in sensitivity analyses. These measures were derived using 2010 National Establishment Time Series (NETS) business data.

Neighborhood SES. Neighborhood SES has been shown in some studies to be related to worse cognition, and is likely related to the physical characteristics of the neighborhood; therefore it was controlled for in the analyses. A principal components analysis was conducted to derive a single measure of neighborhood SES, which was based on the percent of neighborhood residents with a bachelor's degree, a high school degree, a managerial occupation, and an annual household income >$50,000, as well as the median home value, median household value, and percent rental income of the neighborhood. The neighborhood SES measure was based on the participant's US census tract.

1.8. Cognitive measures

Neuropsychological tests are one means of evaluating cognitive functioning and decline, and are designed to measure global cognition as well as various cognitive domains. Neuropathology of the brain, which can cause mild cognitive impairment and dementia, has been associated with patterns of cognitive impairment as detected by neuropsychological tests[86], such as those used in MESA.

Measures of global cognition. Older adults receiving cognitive evaluations through their primary physicians generally receive a brief cognitive test such as the Mini Mental State Exam (MMSE). In addition, cohort and observational studies often use a brief cognitive assessment when cognition is just one component of a broader health evaluation. The sensitivity and specificity of the global cognition tests range depending on the test and the outcome of interest (e.g., mild cognitive impairment, dementia, cognitive decline). For example, the MMSE has a sensitivity range of 45-60% for MCI and specificity of 65-90%, whereas the Montreal Cognitive Assessment (MoCA; another screening test) has a sensitivity of 80-100% and a specificity of 50-76% for MCI.[37] Measures of global cognitive function are generally used for screening, such that if a subject scores lower than a pre-established cutpoint, the subject would undergo further cognitive testing of affected cognitive domains, in addition to a more thorough clinical evaluation.

Measuring cognitive domains. More detailed cognitive evaluations assess whether there are impairments in specific cognitive domains, such as memory, language, attention, executive function, and visuospatial function. Clinicians can use information on affected cognitive domains to try to understand the underlying etiology of the cognitive impairment. For instance, knowing that a subject is impaired in the language domain and has no impairment in any other domains may help the clinician diagnose Primary Progressive Aphasia.

Over the years numerous tests have been developed to detect cognitive impairment.[87] Typically, a subject's score on a neuropsychological test would be compared to norms, which are expected test scores for subjects with normal cognition that are derived from testing a large sample of cognitively normal individuals. However, some studies use neuropsychological test scores to characterize individuals with a particular clinical or neuropathological diagnoses, or to compare individuals who differ in some key characteristic, such as age, sex, race, or an environmental exposure (e.g., air pollution).

The MESA data set includes the Cognitive Abilities Screening Instrument (CASI, version 2)[88] total scores, Digit symbol coding test scores, and the Digit Span test scores, and these were the outcome variables in my study. The CASI is a global measure of cognitive function, which briefly assesses the following domains: attention, concentration, orientation, short-term memory, long-term memory, language, visual construction, verbal fluency, abstraction, and judgment. The Digit Symbol Test, which is a subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III)[89], is a measure of processing speed. The Digit Span Test, a subtest of WAIS-III),[89] is a measure of short term and working memory.

1.9. Contributions of dissertation study

As evidenced by the literature review by Wu et al, my dissertation study fills a large gap in the literature regarding associations between the neighborhood BE and cognition and whether the BE-cognition associations vary by individual-level factors. The Wu et al review article revealed only a single study by Clarke et al[47] that examined neighborhood BE and cognition in older adults. The Clarke et al study investigated whether the presence of recreational centers, institutions, and park area were associated with cognition as measured via the Modified Telephone Interview for Cognitive Status (TICS), a brief cognitive test. This same study examined whether the association between the presence of institutional resources and cognition varied by individual-level race. The first aim of my dissertation study was to conduct a systematic literature review to identify whether any additional studies beyond the Clarke et al article have examined the BE and cognition, as the BE was not a specific keyword searched in the Wu et al article. My literature review revealed five additional studies published on the neighborhood BE. In comparison to the six previously published studies, the second and third aims of my study examine associations between previously unexplored BE measures (i.e., intersection density, distance to the nearest bus/train stop, proportion land dedicated to retail or residential uses, social and walking destination density) and previously unexplored cognitive measures (i.e., CASI, Digit Span Forward and Backward, and Digit Symbol). In addition, my literature review revealed that one additional study by Magaziner et al examined effect modification of the BE-cognition association and found that the association between distance to community resources and cognition was not modified by living alone.[90] Therefore, the five effect modifiers in my study have not been assessed in previous studies. Considering the extant literature to date, my study will uniquely contribute to the newly burgeoning research on the neighborhood BE and cognition in older adults.

Compared to the few similar studies conducted to date, my dissertation study is unique in a number of other ways. I am using a sample of diverse races/ethnicities, which allows for the consideration of how the BE affects vulnerable populations with a sufficient sample size of non-white races/ethnicities to detect significant associations. The MESA data originate from six US geographic sites, which provides evidence that BE-cognition associations are observed outside of the regions included in previous studies of the BE and cognition. Additionally, the MESA sample was obtained using population-based methods, which improves generalizability.

This study has a number of other methodological strengths. It defines neighborhoods based on the area around the participant's home instead of using administrative boundaries as in past studies (e.g., US Census tracts). This is viewed as an advancement of previous methods because measures such as the ½ mile area around a participant's home may better reflect the nearby places an older adult would walk, compared to neighborhoods defined by administrative boundaries. Additionally, no composite measures of the BE are used. Although there is utility in measuring a complex characteristic of a neighborhood by developing a composite of multiple factors, effective interventions or policies to improve neighborhoods cannot be based on esoteric definitions (e.g., "walkability"). Therefore, in my dissertation study, each BE characteristic is examined separately, which allows for more specificity and clarity in the interpretation of the findings.

Figure 1.1. Trend in publications on neighborhood characteristics and cognition in older adults, 2001-2012

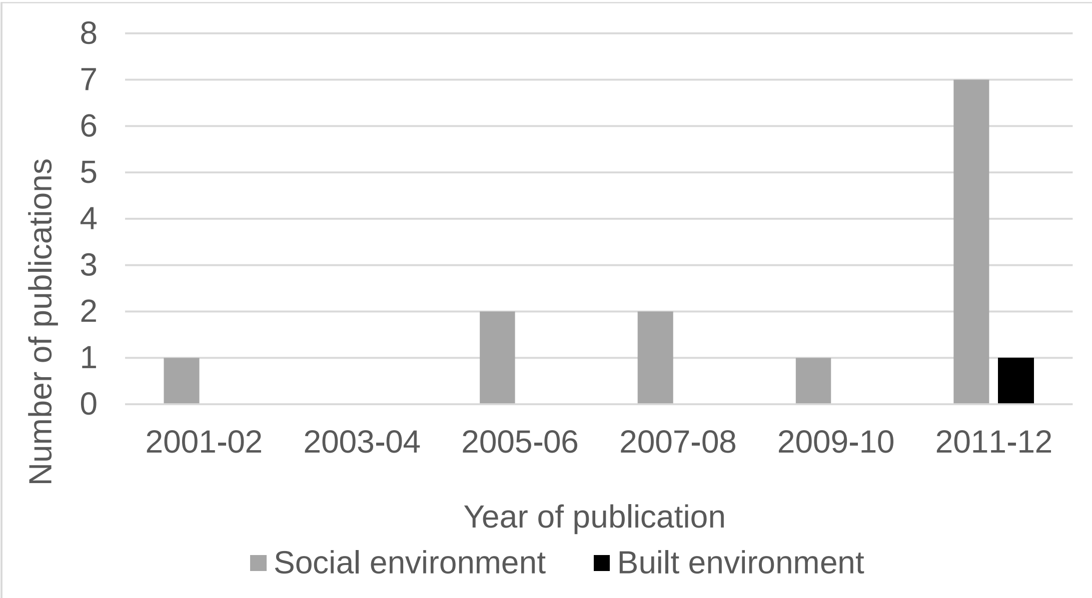
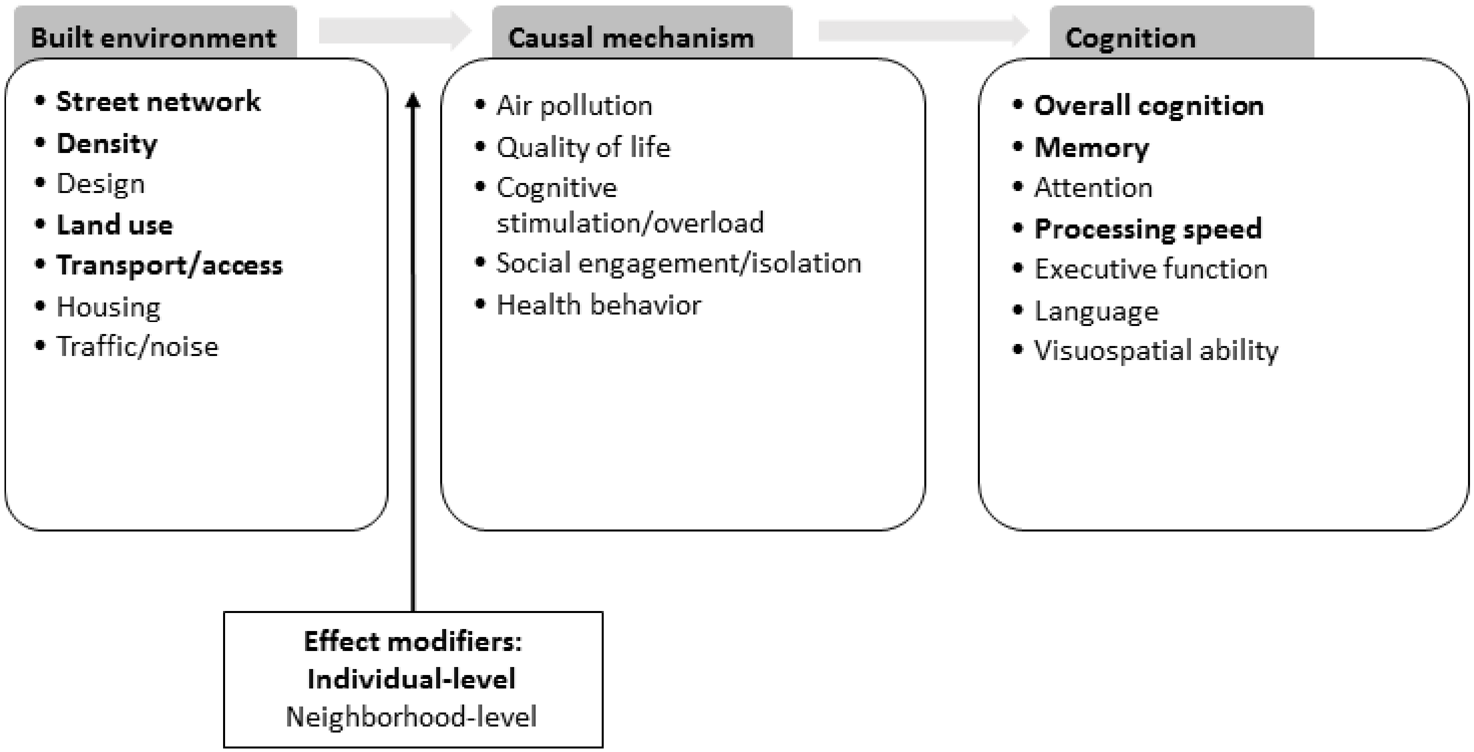


Figure 1.2. Conceptual model of the causal mechanisms linking the built environment and cognition



Bolded items are addressed in dissertation study

II. NEIGHBORHOOD ENVIRONMENT AND COGNITION IN OLDER ADULTS: A SYSTEMATIC REVIEW

2.1. Context

At least 10% of older adults (≥65 years) have mild cognitive impairment[37] and approximately 5 million Americans have Alzheimer's disease dementia (AD)[35], conditions that will increase in incidence with the projected rise in population of older adults.[16,17] To date, no effective treatments are available to ameliorate or cure AD, the most common neurodegenerative cause of cognitive impairment. However, some research suggests that treating vascular risk factors and performing cognitively-stimulating activities may delay the onset of cognitive impairment[41] and reduce AD pathology.[42] Exposure to complex, stimulating neighborhood environments may be one mechanism that delays cognitive impairment.[67]

Recently, studies have started examining how the neighborhood social environment (SE) and built environment (BE) may affect cognition in older adults. The BE encompasses the physical aspects of living and work environments, including the placement and configuration of roads, homes, commercial buildings, and public spaces; whereas, the SE includes human-centered characteristics, such as demographics, socioeconomic status (SES), social disorder, and social climate. A literature review of neighborhood environment and health in older adults[91] found that neighborhood SES (NSES) was more frequently associated with health than neighborhood BE measures, and the only study of cognition found that living in neighborhoods with less educated residents was associated with worse cognition.[92] In another systematic review focused on community environment and cognition in older adults[46], the authors also found that lower community SES was frequently associated with worse cognition.

The same mechanisms that link the neighborhood environment and physical activity, blood pressure, obesity, depression and quality of life[4,20-23] may explain associations between the neighborhood environment and cognition. The mechanisms may relate to the neighborhood's impact on personal mobility, one's sense of security and safety, potential for chance interactions, exercise and social engagement, access to healthy foods and green space, and exposure to pollution, crime, and social deprivation. For older adults, the neighborhood may become more important with increasingly less time in motorized transportation and more time in the neighborhood.[31] The neighborhood environment's impact on health may be intensified by physical disability or difficulty navigating and interacting in the neighborhood due to normal cognitive aging.[67] Additionally, the neighborhood may play a strong role in determining the social ties and social participation among older adults[74,75], which can affect psychological health and well-being.

Approximately 80% of the US population lived in urban areas in 2010[18] and over 90% of older adults would like to age in place, staying in their homes and neighborhoods for as long as possible.[19] Compared to the SE, the BE is more directly targeted by urban planning efforts and has been studied less in relation to cognition in older adults. Therefore, this study aimed to systematically review publications on the neighborhood SE and BE and cognition in older adults, with added emphasis on the BE and effect modification (e.g., differential impact on vulnerable populations), two areas that were mentioned only briefly in a 2014 review of community environment and cognition.

2.2. Evidence Acquisition

Neighborhoods were defined as geographic areas smaller than towns, cities, or counties and were delineated using administrative boundaries, circumscribed areas (e.g., ½-mile around home), or perceived geographic boundaries. The environment surrounding the home was chosen to represent the social and physical exposures likely to affect older adults frequently.

Neuropsychological tests are one means of evaluating cognitive functioning, and have been designed to measure global cognition as well as various cognitive domains (e.g., memory, language).[86] In this review, cognition could have been determined by a clinician or assessed using brief cognitive measures such as the Mini Mental State Exam (MMSE) or domain-specific neuropsychological tests.

2.2.1. Search Criteria

PubMed, Web of Science (all databases), and ProQuest Dissertation and Theses Global database were systematically reviewed for papers and dissertations published through March 5, 2016 (resulted in publications from February 1, 1989). The following keywords were searched: (built environment or neighborhood environment or neighborhood level or walkability) AND (cognition or cognitive function or cognitive decline or cognitive impairment or dementia or Alzheimer or Alzheimer's or demented or cognitive or memory). Given these search criteria, results were likely to include studies of the BE, SE, or both. Papers were excluded if they were: not in English, not quantitative, or not focused on community-dwelling adults aged ≥45 years, neighborhood-level characteristics, and the neighborhood–cognition association.

2.2.2. Methods

The SE findings were synthesized into four categories: SES (e.g., income), demographics (e.g., race/ethnicity), social disorder (e.g., crime), and social climate/social ties (e.g., social support). The BE findings were grouped according to the '5Ds' previously proposed to influence travel behavior[93]: Density (e.g., population density, density of social destinations), Diversity (e.g., land use mix), Design (e.g., intersection density, presence of sidewalks), Destination accessibility (e.g., distance to nearest store), and Distance to transit (e.g., nearest bus stop). The '5D' categories allow for a synthesis using terminology that is frequently used in neighborhood research and relatable to city planners. Data were synthesized between May 3, 2015 and October 7, 2016.

The studies were too disparate to evaluate whether they met the epidemiological criteria for causality. Instead, the risk of bias by participant selection, confounding of the neighborhood-cognition association, and missing data (all variables) was determined using the ROBINS-I tool[94-96], which helped assess the strength of evidence to date. Additionally, six criteria were developed to evaluate the neighborhood measures (1. Did not provide validity/reliability; 2. Used ≥1 perceived measure; 3. Used ≥1 composite measure) and cognitive measures (1. Did not provide validity/reliability; 2. Used ≥1 composite measure; 3. No longitudinal measure used). Bias can occur if perceived measures of the neighborhood relate to cognition[97] or if the neighborhood or cognitive measures are associated with measurement error[98,99] (e.g., invalid measures[100], composite measure[101]). Each domain (e.g., selection) was evaluated for risk of bias (Low=1, Moderate=2, Serious=3, Critical=4), and overall risk of bias was calculated by a simple average of the domain scores.

2.3. Evidence Synthesis

The final sample included 25 studies[47,74,90,92,102-122] (Figure 2.1). Six non-US studies were from the Netherlands, UK, Japan, and Singapore.[102,106,110,114,119,122] The majority focused on ≥65-

year-olds (36% included <65-year-olds) and 80% included minorities. Appendices 2.2–2.6 outline study details.

2.3.1. Research Methods

Sixty-eight percent of samples originated from cohort studies, with the remaining based on clinical trials or other observational studies. Seventy-six percent of samples were population-based or randomly sampled. Eleven[90,102,106,107,114,116,118-122] studies used the MMSE, five[47,74,92,109,112] used the Telephone Interview for Cognitive Status (TICS), five used domain-specific cognitive measures[108,111,113,117,120], and four used composite cognitive measures.[103-105,110] Eighty-four percent of studies used continuous measures of cognition instead of categorical/dichotomous measures, and 10 studies used longitudinal cognitive measures.[103,105,109,112-116,120,121]

Most studies focused on objective neighborhood measures, with only four[90,103,104,114] including perceived measures (i.e., neighborhood social disorder, neighborhood climate, number of friendly neighbors, neighborhood homogeneity, distance to community resources). Almost half of the studies (n=12) used US Census tracts to define neighborhoods, with the remaining using US Census block groups, neighborhood perceptions, alternative definitions such as city-defined boundaries, or other regional definitions (e.g., UK enumeration district).

2.3.2. Neighborhood Social Characteristics and Cognition

Twenty-two studies examined the association between neighborhood SE and cognition.[47,74,90,92,102-104,107-119,121,122]

Neighborhood SES. Eight of 15 studies found that lower NSES was associated with worse cognition (Table 2.1), with 78% of cross-sectional and 17% of longitudinal studies finding a significant association. The majority (n=13) of studies developed composite measures of NSES based on components such as the proportion with no high school degree or living in poverty. All SES measures were based on objective data sources such as the US Census.

Neighborhood demographics. Four of eight studies found that neighborhood demographics were associated with cognition (Table 2.1). Living in a neighborhood with a greater percent of 65+ year olds[47] and fewer Hispanics[107] or African Americans[112] was associated with better cognition. Conversely, a greater percent of Mexican-Americans was associated with decreased odds of cognitive decline.[116] Two[112,116] of four longitudinal studies of neighborhood race (African American, Hispanic, or minority) found a significant association with cognition. Perceived homogeneity of neighbor characteristics was not associated with cognitive decline in a Japanese sample.[114]

Psychosocial Disorder and Social Climate. Two[103,111] of five studies (one cross-sectional, one longitudinal) found that greater psychosocial disorder was associated with worse cognition (Table 2.1). In two cross-sectional studies on social climate, positive acts of neighboring was associated with better cognition[104], but perceptions of friendly neighbors or the number of children, relatives, and friends in the neighborhood was not associated with cognition.[90]

2.3.3. Neighborhood Built Environment and Cognition

Six studies examined neighborhood BE and cognition[47,90,105,112,120,122], using a wide variety of neighborhood definitions (i.e., city block, US Census tract, US Census block group, perceived neighborhood, ½ mile radius around home, UK Lower-layer Super Output Area) and data sources (i.e., block observations, city-based geographic data, audit, participant report, US Census, map data, United Kingdom neighborhood statistics).

Density. One[122] of three cross-sectional studies examining density found an association with cognition (Table 2.2). Neighborhood area dedicated to natural environment (hence lower population density) was associated with worse cognition in an English sample[122]; however, increased neighborhood park area was not associated with cognition in a US-based sample.[47] The single study examining population density and cognition found no association.[112]

Design. Both studies of neighborhood design found an association with longitudinal measures of cognition (Table 2.2). Neighborhoods in poor condition (deterioration of public spaces) but not those lacking pedestrian facilities were associated with accelerated cognitive decline.[105] Additionally, greater street connectivity was associated with faster cognitive decline using one measure (fewer turns needed to reach all other streets in network) but slower cognitive decline using another (greater paths/streets connected to each street).[120]

Destination accessibility. Three studies (two cross-sectional, one longitudinal) examined the association between neighborhood destination accessibility and cognition (Table 2.2). An increased distance to community resources[90] and presence of a community center[105], but not presence of recreational centers and institutions (e.g., schools)[47], were associated with better cognition.

Diversity of Land Uses and Distance to Transit. Neighborhood diversity of land uses was associated with lower odds of dementia[122], and the presence of a neighborhood transit stop was associated with slower cognitive decline[105] (Table 2.2).

2.3.4. Effect Modification of Neighborhood Environment-Cognition Association

Thirteen studies investigated effect modification[47,74,90,92,102-104,106,108-111,118] of the association between neighborhood characteristics and cognition.

Four of five cross-sectional studies found that individual-level SES modified the association between neighborhood SE and cognition.[74,92,102,106,118] Having low personal SES and living in a low SES neighborhood was associated with worse cognition in two studies.[74,92] In contrast, two studies found that the association between NSES and cognition was strongest when personal SES did not match NSES (i.e., low personal SES, high NSES; high personal SES, low NSES).[102,106] In addition, a higher percent of African Americans was cross-sectionally associated with worse cognition in those with lower education and better cognition in those with higher education.[74]

Three of six studies of the neighborhood SE and one study of the neighborhood BE found effect modification by individual-level demographics.[47,74,104,109,110,118] Individual-level race was not an effect modifier of the longitudinal association between neighborhood racial composition and cognition[109] or the cross-sectional association between NSES and cognition.[118] Sex did not modify the association between neighborhood social climate (e.g., social ties) and cognition.[104] However, higher NSES was associated with better cognition among younger participants[118] and in all but <70 year-old men[110] in two cross-sectional studies. Finally, the presence of institutional resources (e.g., community center) was cross-sectionally associated with better cognition among whites but worse cognition among African Americans.[47]

Both studies examining effect modification by apolipoprotein ε4 carrier status (APOE ε4; risk factor for AD) found significant associations.[103,111] The first found that while APOE ε4 genotype was associated with faster cognitive decline, the association was strongest when psychosocial disorder was low.[103] The second, cross-sectional study found that APOE ε4 carriers in the least psychosocially-hazardous neighborhoods had cognitive levels similar to APOE ε4 non-carriers, and APOE ε4 carriers in the most psychosocially hazardous neighborhoods had worse cognition compared to APOE ε4 non-carriers in neighborhoods with lower psychosocial hazards.[111]

Three studies examined effect modification by other individual-level factors.[47,90,108] Neighborhoods with a higher percent of older adults were associated with better cognition among those living 6-10 years in their neighborhood but worse cognition among those living >10 years in their neighborhood.[47] The association between community resources (e.g., number of children in neighborhood) and cognition did not differ among those who lived with others versus lived alone.[90] Finally, the association between higher tibia lead levels and worse cognition was stronger in those with higher versus lower neighborhood psychosocial disorder.[108]

2.3.5. Risk of bias

Selection bias. Eight studies used sampling weights or propensity scores to reduce the risk of selection bias[47,74,92,103,109-112], and 11 studies demonstrated a lack of overlap (by >2 years) between the dates in which the neighborhood and cognitive measures were collected.[74,92,103,105,107,108,110,112,115,116,121] Based on the ROBINS-I evaluation criteria, 19 studies had a moderate risk and 6 studies had a moderate to serious risk of selection bias (Table 2.3).

Confounding. Ten studies controlled for covariates (i.e., age, sex, race/ethnicity, income, education, married) hypothesized to be related to neighborhood characteristics and cognitive measures, and therefore were determined to have a moderate risk of residual confounding (Table 2.3).[47,74,92,105,109,111,112,116,118,119] The study with a critical risk for residual confounding did not adjust for any covariates, and the 14 remaining studies with moderate-serious to serious risk did not adjust for at least one covariate.

Missing data. Twenty studies failed to delineate missing data on the neighborhood characteristics, cognitive measures, or covariates, and therefore were not assessed for risk due to missing data. Five studies[92,102,116,118,121] used statistical methods or sensitivity analyses to account for missing data, and among these, one study had a low risk of bias due to missing data because few data were missing[102] (Table 2.3). Three studies were determined to have low-moderate risk because some evidence suggested that the results were not robust to missing data.[92,116,118] The fifth study showed that the results were not robust to missing data, and was categorized as moderate risk.[121]

Neighborhood measures. Eight studies met ≤1 of the criteria developed to evaluate the neighborhood measures (low risk of bias due to the neighborhood measure), 16 met two criteria (moderate risk), and one[90] met all three criteria (serious risk) (Table 2.3).

Cognitive measures. Eleven papers met ≤1 of the criteria developed to evaluate the cognitive measures (low risk of bias due to the cognition measure), 12 met two criteria (moderate risk), and two [110,111] met all three criteria (serious risk).

2.4. Discussion

Over half of the 25 reviewed studies found associations between neighborhood characteristics and cognition. The studies provided moderately strong evidence for an association between NSES and cognition and modest evidence for associations between neighborhood demographics, design, and destination accessibility and cognition. Similarly, most studies investigating effect modifiers found significant associations, with some evidence for effect modification of the association between NSES and cognition by individual-level SES. In addition, some evidence suggested that individual-level demographics and APOE ε4 genotype modify the association between the neighborhood SE and cognition. Although few studies examined effect modification, and the neighborhood measures and effect modifiers were too variable, the significant findings suggests that studies of effect modification may be a fruitful line of research. Considered together, no studies were found to have low risk of bias, the effect sizes were often small, and many of the studies tested multiple neighborhood-cognition associations that increased the chance of a statistically significant finding. Additionally, the combinations of neighborhood measures examined were inconsistent across the studies, and thus did not allow for a more thorough critique. Therefore, the evidence for an association between neighborhood characteristics and cognition is modest to date.

Lower NSES was associated with worse cognition after controlling for personal SES, a strong predictor of mortality and AD risk.[123,124] NSES has been associated with multiple health outcomes[125-127] and may be independently associated with cognition by affecting an individual's social interactions and level of social isolation[128,129], which indirectly affect health. Few longitudinal studies found significant associations; thus, it is possible that NSES is associated with life-long disparities in cognition but not late-life differences in cognitive decline. Nonetheless, social isolation is a plausible mechanism for the observed associations between lower NSES and worse cognition, and should be examined as a potential mediator in future studies.

Controlling for individual- and neighborhood-level SES and race may not fully account for the psychosocial impact of racism and segregation that can influence health.[74,130] Only 27% of the reviewed studies examining NSES controlled for neighborhood racial composition, and therefore, future studies will need to develop valid measures of and control for segregation, which may be independently associated with worse cognition.

Having lower personal SES and living in higher SES neighborhoods may cause social isolation, leading to poorer well-being and health consistent with the 'local social inequality model'[106,131]. In contrast, low SES individuals who have better cognition when living in higher SES neighborhoods are consistent with the 'collective resources model', in which they benefit from increased material and social resources.[131] Two studies supported the 'collective resources model'[74,92] and two supported the 'local social inequality model'[102,106]; thus, there is insufficient evidence to conclude if either of these models are at play, and additional research is needed on the interaction between individual- and neighborhood-level SES.

The reviewed studies demonstrated inconsistent associations between neighborhood psychosocial hazards and cognition. The only longitudinal study found a significant association with cognitive decline, but it used perceived measures to construct a composite measure of neighborhood psychosocial hazards. Perceived measures represent individual-based assessments that may be laden with other subjective influences, and composite measures can be associated with measurement error and lack specificity, which hinders the ability to pinpoint the causal mechanisms. The remaining studies were cross-sectional and used different objective measures of neighborhood psychosocial hazards. Overall, future studies of psychosocial hazards and cognition would benefit from using longitudinal measures of cognition and psychosocial hazard measures that are objective and measured individually. Additionally, future studies could examine potential mediators such as social engagement, isolation, well-being, and mental health, which would help support a mechanism by which any observed associations can be explained by social engagement/isolation.

A majority of the BE studies found significant associations. Cognition was associated with neighborhoods with a community center or transit stop, public spaces in poor condition, distance to community resources, street connectivity, land use mix, and area dedicated to the natural environment. Two studies examined potential modifiers of the BE-cognition association, finding that individual-level race modified the association between presence of institutional resources and cognition, but living alone did not modify the association between community resources and cognition. Overall, the BE studies to date provide suggestive evidence for an association between neighborhood design and destination accessibility and cognition. However, given this nascent field of research, new studies are needed to refine the BE and neighborhood measures, examine longitudinal measures of cognition, examine potential mediators and moderators, and elucidate the associated causal mechanisms.

2.4.1. Quality of studies

The majority of studies were at moderate to serious risk of bias due to selection, residual confounding, and missing data. New studies should use methods such as sampling weights or propensity scores to reduce selection bias and use techniques such as multiple imputation to address bias due to missing data. Additionally, future studies should effectively measure and control for individual characteristics that are likely associated with the neighborhood characteristics and cognition to reduce the possibility of residual confounding, which may help explain the studies finding associations in unexpected directions.

Most of the studies defined neighborhoods using administrative boundaries set by national or local governments (e.g., US Census tracts). Although this may allow for more consistent neighborhood definitions across studies, Census tracts are typically employed out of convenience, which ignores the potential that different neighborhood definitions may be more appropriate based on the neighborhood measure of interest and the proposed biological mechanism responsible for its association with cognition.[97] In addition, individuals living at the edge of a Census tract may be misclassified, if they typically walk in the neighboring Census tract. New studies can build upon the previous work, transitioning from using administrative boundaries to other measures such as of the ½ mile area around a participant's home, which may better reflect the nearby places and the distances an older adult would walk.

The employed neighborhood measures had a number of other weaknesses. Firstly, the characteristics measured to date may be only rough proxies of the neighborhood qualities associated with improved or worsened cognition. For example, population density could serve as a proxy for BE characteristics such as destination accessibility or SE characteristics such as chance social interactions. Secondly, 44% of the studies used neighborhood data collected at a different time than the cognitive data, which may result in bias related to measurement error. Lastly, all of the studies failed to account for longer-term neighborhood exposures that may be more important that late-life neighborhood exposures. For instance, if an individual lived for many years in a dense urban environment and recently moved to the suburbs, simply using measurements of the current suburban environment would inaccurately reflect life-long neighborhood exposures. Any association with cognition under these conditions would be hard to disentangle without additional information about residential history. Considering these weaknesses, much more work is needed to understand the neighborhood constructs that affect cognition, the ideal time points in which they should be measured, and the best ways to measure them.

The existing studies failed to address regional context, specifically the potential influence of nearby neighborhoods and the comparability of findings across regions. Neighborhoods that border a residence may influence study findings, if for instance, the affluence or disadvantage of surrounding neighborhoods decreases or increases accessibility to social destinations or community resources. Overall context of the town, city, or metropolitan area may be important to consider, as exemplified by a study finding that a neighborhood's regional location mattered more for neighborhood walking for commuting compared to the neighborhood's BE.[132] Additionally, the studies could have provided more thorough evaluations of the reasons why the neighborhood measures included may have limited external validity. For example, the variability of the neighborhood measures may not be comparable across cities, metropolitan regions, or countries, and certain neighborhood features (e.g., availability of walking paths) may have more influence than others based on regional cultural norms.

Most of the studies used brief cognitive tests (e.g., MMSE), which do not effectively measure particular cognitive domains that could assist in determining the biological mechanism by which the neighborhood environment relates to cognition. For example, if the neighborhood environment is hypothesized to influence cognition via the mechanism of social engagement, tests previously associated with social engagement (e.g., perceptual speed test[133]) would be preferred over non-specific screening instruments such as the MMSE.

2.4.2. Limitations of this Review

This review is not without limitations. It was difficult to assess the strength of the evidence and causality due to the limited studies to date, the variability of neighborhood and cognitive measures, and the cross-sectional study designs. Inconsistent findings may be due to the fact that no studies examined early-life neighborhood exposures, which have been associated with cognition.[134-137] Although the databases searched are comprehensive and cover a broad range of disciplines, this review may have missed some papers. In addition, the review could be affected by positive publication bias. Lastly, the method used to evaluate bias due to the neighborhood and cognitive measures has not been validated, but nonetheless provided a means of assessing the strength of the measures.

2.4.3. Future directions

Few studies have examined associations between cognition and the neighborhood SE and BE. A large majority of the reviewed studies found at least one significant association, suggesting that the neighborhood environment may be associated with cognition. While the published studies are a good starting point, future studies will need to use standardized BE measures; replicate and expand upon previous findings by including longitudinal measures of cognition; considering longer-term neighborhood exposures; considering the impact of moves, residential tenure, and time spent in and around the neighborhood; and considering the potential for individual-level effect modifiers and mediators. Finally, because the existing studies did not provide adequate evaluation or support for particular causal mechanisms, future studies are needed to tease apart and test the causal mechanisms by design.

Figure 2.1. Sample size flow diagram for Paper 1

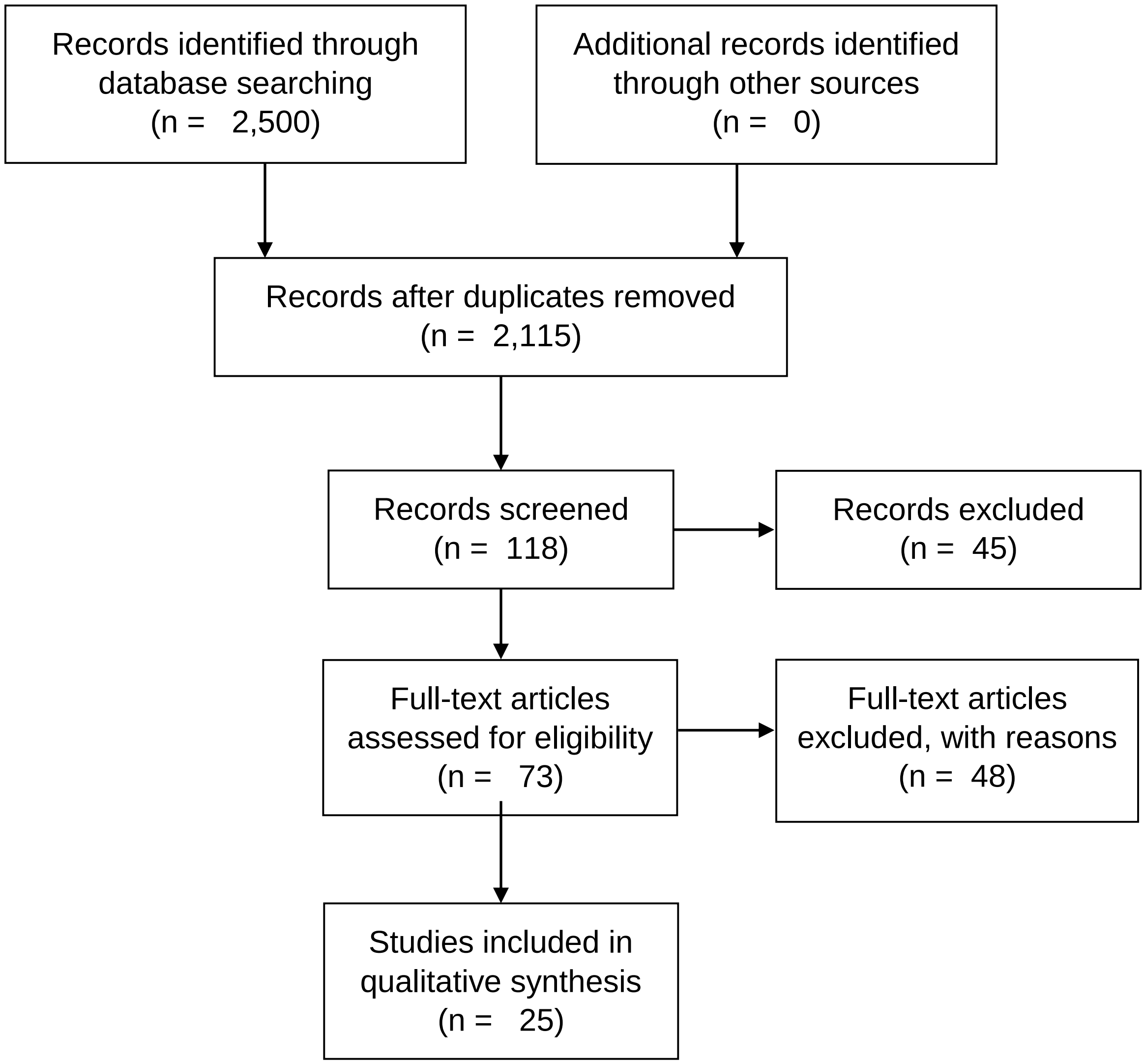


Table 2.1. Findings for Studies Examining Neighborhood Social Characteristics and Cognition among Older Adults

		Socioeconomic status (SES)[a]	Demographics[b]	Psychosocial disorder[c]	Social climate / social ties[d]
Author (year)	Study design	n = 15	n = 8	n = 5	n = 2
Aneshensel et al (2011)	Cross-sectional	+	NS		
Basta et al (2008)	Cross-sectional	+			
Boardman (2012)	Longitudinal	NS		+	
Brown (2009)	Cross-sectional				+
Clarke (2012)	Cross-sectional	+	+	NS	
Espino (2001)	Cross-sectional		+		
Glass (2009)	Cross-sectional			NS	
Kovalchik (2015)	Longitudinal		NS		
Lang (2008)	Cross-sectional	+			
Lee (2011)	Cross-sectional			+	
Magaziner (1989)	Cross-sectional				NS
Martinez (2007)	Longitudinal	NS	+		
Meyer (2015)	Longitudinal	NS	NS		
Murayama (2013)	Longitudinal		NS		
Rej (2015)	Longitudinal	NS			
Sheffield (2009)	Longitudinal	+	+		
Shih (2011)	Cross-sectional	NS			
Sisco (2012)	Cross-sectional	+			
Wee (2012)	Cross-sectional	+			
Wight (2006)	Cross-sectional	+			
Wu (2015)	Cross-sectional	NS		NS	
Zeki Al Hazzouri (2011)	Longitudinal	NS			
Total Significant Studies		8 of 15	4 of 8	2 of 5	1 of 2

Abbreviations: + At least one statistically significant association between neighborhood characteristic and cognition; NS = association between neighborhood characteristic and cognition was not statistically significant

[a] Includes composite measures of SES and measures of income or wealth, employment, and education

[b] Includes measures of age, race/ethnicity, and perceived homogeneity with neighbors

[c] Includes measures such as presence of graffiti and crime
[d] Includes measures of neighboring, social support/acts, and social ties in neighborhood (e.g., number of friends in neighborhood)

Table 2.2. Findings for Studies Examining Neighborhood Built Environment Characteristics and Cognition among Older Adults

		Built environment categories				
		Density	Design	Destination	Diversity	Distance to Transit
Author (year)	Study design	n = 3	n = 2	n = 3	n = 1	n = 1
Clarke (2012)	Cross-sectional	NS		NS		
Clarke (2015)	Longitudinal		+	+		+
Magaziner (1989)	Cross-sectional			+		
Martinez (2007)	Longitudinal	NS				
Watts (2015)	Longitudinal		+			
Wu (2015)	Cross-sectional	+			+	
Total Significant Studies		1 out of 3	2 out of 2	2 out of 3	1 out of 1	1 out of 1

Abbreviations: + At least one statistically significant association between neighborhood characteristic and cognition; NS = association between neighborhood characteristic and cognition was not statistically significant

[a] Density: e.g., population density, density of social destinations; Diversity: e.g., land use mix, business types in the neighborhood; Design: e.g., intersection density, presence of sidewalks; Destination accessibility: e.g., distance to nearest store; Distance to transit: e.g., distance to nearest bus stop

Table 2.3. Potential risk of bias in the 25 reviewed papers

Paper	Domains					Overall risk of bias[d]
	Selection[a]	Confounding[a]	Missing data[a]	Neighborhood measure(s)[b]	Cognitive measure(s)[c]	
Aneshensel et al[74]	Moderate	Moderate	NA	Moderate	Low	Moderate
Basta et al[102]	Moderate	Serious	Low	Moderate	Moderate	Moderate
Boardman et al[103]	Moderate	Serious	NA	Moderate	Moderate	Moderate
Brown et al[104]	Moderate	Serious	NA	Moderate	Moderate	Moderate
Clarke et al[47]	Moderate	Moderate	NA	Low	Moderate	Moderate
Clarke et al[105]	Moderate-serious	Moderate	NA	Low	Moderate	Moderate
Deeg et al[106]	Moderate	Serious	NA	Moderate	Moderate	Moderate
Espino et al[107]	Moderate-serious	Serious	NA	Moderate	Moderate	Moderate
Glass et al[108]	Moderate-serious	Serious	NA	Moderate	Moderate	Moderate
Kovalchik et al[109]	Moderate	Moderate	NA	Low	Low	Low-moderate
Lang et al[110]	Moderate	Serious	NA	Moderate	Serious	Moderate-serious
Lee et al[111]	Moderate	Moderate	NA	Moderate	Serious	Moderate
Magaziner et al[90]	Moderate	Serious	NA	Serious	Moderate	Moderate-serious
Martinez et al[112]	Moderate	Moderate	NA	Low	Low	Low-moderate
Meyer et al[113]	Moderate	Serious	NA	Moderate	Low	Moderate
Murayama et al[114]	Moderate	Moderate-serious	NA	Moderate	Low	Moderate
Rej et al[115]	Moderate-serious	Critical	NA	Low	NA	Moderate-serious
Sheffield et al[116]	Moderate-serious	Moderate	Low-moderate	Moderate	Low	Moderate
Shih et al[118]	Moderate	Moderate	Low-moderate	Moderate	Low	Moderate
Sisco et al[117]	Moderate	Serious	NA	Moderate	Moderate	Moderate
Watts et al[120]	Moderate	Serious	NA	Low	Low	Moderate
Wee et al[119]	Moderate	Moderate	NA	Moderate	Low	Moderate
Wight et al[92]	Moderate	Moderate	Low-moderate	Low	Low	Low-moderate

Wu et al[122]	Moderate	Moderate-serious	NA	Moderate	Moderate	Moderate
Zeki al Hazzouri et al[121]	Moderate-serious	Serious	Moderate	Low	Low	Moderate

[a] Determined using *ROBINS-I tool (Risk of Bias in Non-randomized Studies – Interventions)*[94,95]

[b] Three criteria were developed to evaluate neighborhood measures: 1) Did not provide validity/reliability; 2) Used ≥1 perceived neighborhood measure; 3) Used ≥1 composite neighborhood measure

[c] Three criteria were developed to evaluate cognitive measures: 1) Did not provide validity/reliability; 2) Used ≥1 composite measure of cognition; 3) Did not use longitudinal measure

[d] The overall risk of bias was calculated by a simple average of the scores for the specific domains (Low=1, Moderate=2, Serious=3, Critical=4)

III. NEIGHBORHOOD BUILT ENVIRONMENT AND COGNITION IN OLDER ADULTS: THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

3.1. Introduction

Cognitive impairment, which is present in ≥10% of older adults [37,138], is associated with lower quality of life [139] and increased risk of nursing home placement [140,141]. The impending rise in the population of older adults [16,17,36] calls for public health and regional planning strategies to address the economic, health, and social burden associated with the concurrent increased prevalence of cognitive impairment. Interventions focused on diet and vascular risk factors known to reduce vascular disease may simultaneously delay the onset of cognitive impairment [41,142]. Additionally, there is an emerging recognition that residential environments are important in shaping health behaviors and health outcomes [4,20-23]. For example, lower neighborhood socioeconomic status has been associated with worse cognition in older adults in multiple studies [47,74,119]. Older adults may be particularly vulnerable to the neighborhood environment since they tend to have a smaller range of routine travel and thus have increased exposure to proximal environments [27,91]. Policies that promote a safe and walkable neighborhood environment may help older adults age in place and delay the onset of cognitive impairment by providing an environment that is socially and mentally engaging [67] and supportive of an active lifestyle[47].

The mechanisms by which the neighborhood built environment (BE) affects cognition are likely complex and multifaceted. Firstly, urban environments may be associated with increased exposure to vehicular pollutants due to decreased distances to busy roadways[50]. Airborne pollutants [51] have been associated with worse cognition in older adults, and therefore, the BE may be associated with cognition by increasing or decreasing risk of exposure to pollutants. Secondly, exposure to various neighborhood BE features may serve as a passive source of cognitive stimulation, which can either improve cognition or cause cognitive overload that worsens cognition. Performance of cognitively stimulating activities, such as working on crossword puzzles, has been associated with improved cognition in older adults [65,66]. Similarly, living in a complex neighborhood environment in older age may help delay onset of cognitive impairment by requiring constant but passive adaptation that serves as a beneficial source of mental stimulation [67]. However, the neighborhood BE may serve as a source of cognitive overload [68,69] among those with physical or mental disabilities or cognitive impairment. Thirdly, neighborhoods with more social engagement opportunities may improve well-being and consequently improve cognition. On the other hand, neighborhood psychosocial disorder (e.g., crime, graffiti), fear of falls [72], and sensory overload (e.g., confusing spaces, noise, crowds) [73] may increase social isolation [74,75] if residents minimize neighborhood-based walking. Lastly, the neighborhood BE may influence neighborhood-based physical activity (PA), and the resulting increase or decrease in overall PA affects cognition through changes in vascular health. PA interventions have been associated with improved cognition in those with normal cognition, mild cognitive impairment, and dementia [76-78], and some evidence indicates that certain BE features may be associated with increases in overall PA [20,79].

Few studies have examined the association between the BE and cognition in older adults [47,90,105,112,120,122] or have explored the potential causal mechanisms. The studies to date found associations between cognition and the presence of a community center or transit stop, condition of public spaces, distance to community resources, street connectivity, land use mix, and area dedicated to the natural environment. However, the types of BE and cognitive measures and methods of defining neighborhoods differed markedly in the studies, and additional work is needed to narrow down the BE features that may have the greatest influence on cognition, examine potential effect modifiers, and replicate findings in diverse samples. Considered the extant literature, some but not all of the studies suggest an association between increasing urban density and better cognition.

Therefore, we aimed to examine whether multiple neighborhood BE characteristics are associated with cognition in a diverse sample of older adults. We hypothesized that higher levels of the neighborhood BE measures consistent with increasing urban density, specifically social and walking destination density, intersection density, land dedicated to residences or retail, proximity to the nearest bus or train station, and population density, would be associated with better cognition. Additionally, we aimed to investigate if the associations between BE characteristics and cognition vary based on individual-level education or race/ethnicity, and explored potential mediators that may help elucidate the underlying causal mechanisms. The BE-cognition associations were expected to vary by education and race/ethnicity based on previous studies suggesting that these two individual-level characteristics moderate the association between neighborhood SES and cognition [92,102,143].

3.2. Methods

3.2.1. Sample

The analytic sample was derived from the 4,716 participants who completed Exam 5 (2010-2011) of the Multi-Ethnic Study of Atherosclerosis (MESA). MESA, a longitudinal, population-based cohort study of subclinical cardiovascular disease, has completed five exams to date starting in 2000. Participants aged 45- to 84-years-old were enrolled from six US regions (Forsyth County, North Carolina; New York, New York; Baltimore, Maryland; St. Paul, Minnesota; Chicago, Illinois; Los Angeles, California) with oversampling of African Americans, Chinese-Americans, and Hispanics. Details about MESA have been published previously[48]. The final sample was restricted to participants who: 1) had at least one non-missing cognitive test score; 2) one non-missing BE measure; 3) were not taking medications for Alzheimer's disease or Parkinson's disease; and 4) did not have a Cognitive Abilities Screening Instrument (CASI) score suggesting dementia (CASI<74)[144].

3.2.2. Cognitive and built environment measures

MESA's Exam 5 was the only available exam to include cognitive measures. The four cognitive tests included the CASI[88] (version 2), a brief cognitive test of global cognition; Digit Span Forward and Backward (DSF and DSB; subtests of Wechsler Adult Intelligence Scale [WAIS-III][89]), measures of short term and working memory, respectively; and Digit Symbol (DS; subtest of WAIS-III[89]), a measure of processing speed.

The neighborhood measures were originally developed as part of the MESA Neighborhood Study[145]. Population density (persons/km^2) was calculated for ¼-mile, ½-mile, and 1-mile as-the-crow-flies buffers around the participants' homes based on 2010 Census block population density estimates. Land parcels for each study site were classified as residential (e.g., family homes, apartment complexes/condominiums) or retail (e.g., shopping centers, bars, clothing stores), and the percent of the ¼-mile, ½-mile, and 1-mile buffers dedicated to residences or retail was calculated by dividing the residential/retail area by the total area of the buffer (m^2). The straight line distances to the nearest bus or train stop were calculated in meters and converted into kilometers. For the measures of land dedicated to retail and residences and distances to the nearest bus and train stop, approximately half of the source data on land parcels and public transit data were collected within one year of Exam 5, an additional 30% was collected within three years, and the remaining 20% was assessed four to six years prior to Exam 5.

Intersection density was determined by dividing intersection counts for the ¼-mile, ½-mile, and 1-mile buffer by the total area of the buffer, and was based on road data collected within two years of Exam 5. The simple densities of social engagement destinations (e.g., beauty shops/barbers, performance-based entertainment, libraries) and walking destinations (e.g., postal service, drug stores/pharmacies, non-beverage eating and dining places) per square mile were calculated for the ¼-mile, ½-mile, and 1-mile area around the home using National Establishment Time Series (NETS) business data collected within one year of Exam 5. The BE measures reported in the main analyses were based on ½-mile buffers around the participants' homes, hypothesized as the area most representative of the neighborhood for older adults. Finally, neighborhood SES was based on the participants' US Census tracts, and was previously developed using a principal components analysis to derive a measure based on the percent of the neighborhood residents with a bachelor's degree, a high school degree, a managerial occupation, and an annual household income >$50,000, as well as the median home value, median household income, and percent rental income of the neighborhood. The neighborhood SES variable is based on US Census American Community Survey (2007-2011).

3.2.3. Participant characteristics

Baseline characteristics included age, sex, education level, race/ethnicity, marital status, family income, and the presence of at least one apolipoprotein ε4 allele (APOE ε4), a genetic risk factor for Alzheimer's disease. Clinical characteristics included body mass index (BMI; kg/m^2), depression (Center for Epidemiologic Studies Depression Scale [CES-D] score$\geq$16), smoking status, amount of moderate to vigorous physical activity (PA) in a week, minutes spent walking to get places in a week, high systolic (>140mmHg) and diastolic (>90mmHg) blood pressure, self-reported diabetes and chronic obstructive pulmonary disease (COPD), and medication use for hypertension, hypercholesterolemia, and depression.

3.2.4. Statistical methods

The sample's demographics, clinical characteristics and APOE genotype were detailed using descriptive statistics. Mean scores (and standard deviations; SD) were calculated for each of the cognitive tests according to age group, sex, education level, race/ethnicity, family income, and APOE genotype. To describe the distribution of the BE measures, means and SDs, ranges, and the 25th, 50th, and 75th percentiles were calculated, and Pearson correlation coefficients were calculated to examine the correlation between the BE measures.

Unadjusted and adjusted linear regression models with generalized estimating equations (accounting for clustering by study site) were employed to examine the BE and cognition associations and effect modification. Thirty-two models were run to examine each BE measure (independent variable) and cognitive test (dependent variable) combination. Each BE measure was included in a separate model to eliminate multicollinearity due to including multiple BE measures in the same model and avoid using a composite variable that would reduce ease and specificity of interpretation and comparability with future studies. Both the BE and cognitive measures were treated as continuous variables in the models. The multivariable models adjusted for age, sex, race/ethnicity, income, marital status, neighborhood SES, and presence of APOE ε4 allele.

Interaction terms were entered into the multivariable models to test whether there was effect modification by education (≤12 years versus >12 years) or race/ethnicity (Chinese-American, African-American, and Hispanic, versus non-Hispanic white) (e.g., population density×education). For the analyses focused on effect modification, we focus most of the discussion on statistically significant interactions ($p<0.001$) with statistically significant ($p<0.001$) associations in at least one of the stratified groups (e.g., among Hispanics) to account for multiple testing and the exploratory nature of the analyses focused on effect modification.

Sensitivity analyses involved repeating the main effects analyses but using BE measures based on ¼- and 1-mile buffers around participants' homes. Additionally, the following variables were controlled for in the adjusted models in post-hoc sensitivity analyses: history of diabetes, cardiovascular disease (congestive heart failure, coronary heart disease, cardiac bypass, myocardial infarction, and/or cardiac arrest), cerebrovascular disease (stroke and/or transient ischemic attack), and body mass index.

Lastly, we explored whether self-reported measures of neighboring (people in the neighborhood are willing to help and can be trusted), depressive symptoms measured by the CES-D, or self-reported minutes spent per week walking to get places were mediators of the associations between the BE and cognition. These characteristics were hypothesized to be mediators through PA or social engagement/isolation mechanisms. Multivariable linear regression models, controlling for age, sex, race/ethnicity, income, marital status, presence of APOE ε4 allele, and neighborhood SES, investigated whether there were indirect effects through the mediators. Sobel tests [146] were conducted for each mediator separately to examine if the indirect effects were statistically significant.

3.3. Results

The final sample included 4,123 participants (Figure 3.1). The majority of the sample was between the ages of 55 and 84 years old, female, college educated, and married (Table 3.1). Forty-three percent were non-Hispanic whites, 12% Chinese-American, 26% African-American, and 19% Hispanic. Twenty-six percent were APOE ε4 carriers, and therefore at increased risk of developing Alzheimer's disease. Approximately 40% were overweight or obese, 14% had depression, and 32% had arthritis. The sample reported an average of five hours per week walking to get places.

Compared to the analytic sample, Exam 1 individuals who were excluded due to attrition or missing data were less educated and were less often married, less often non-Hispanic White, and of less often of higher family income (Appendix 3.3). Exam 5 participants who were excluded due to missing data lived in neighborhoods with higher walking destination densities, lower percent of land dedicated to residences and higher percent of land dedicated to retail, lower distances to train stop, and higher population densities than those in the analytic sample (Appendix 3.4).

The mean cognitive test scores were 89.2 for the CASI, 9.8 for the DSF, 5.8 for the DSB, and 52.3 for the DS (Table 3.2). The mean values for the neighborhood BE measures were 142.8 for social destination density, 65.8 for walking destination density, 0.78 for intersection density, 47% for land dedicated to residential, 4.7% for land dedicated to retail, 1,128 meters to the nearest bus stop, 5,223 meters to the nearest train stop, and 2,768 persons per square kilometer (Table 3.2; Appendix 3.5). The correlations between social and walking destination density ($\rho=0.92$; $p<0.0001$), walking destination density and population density ($\rho=0.91$; $p<0.0001$), and distance to nearest bus stop and to nearest train stop ($\rho=0.92$; $p<0.0001$) were very high (Appendix 3.6). In addition, the following were strongly correlated ($0.60<\rho<0.90$; $p<0.0001$): social and walking destination density, separately, with intersection density, proportion of land dedicated to retail uses, and population density; and distance to nearest bus stop with distance to nearest train stop.

In the unadjusted analyses focused on the ½-mile BE measures, social and walking destination density were associated with CASI (Appendix 3.7). No BE measures were associated with DSF; however, social and walking destination density, intersection density, and distances to the nearest bus and train stops were associated with DSB. Social and walking destination density and distances to the nearest bus and train stops were associated with DS.

In the adjusted analyses focused on the ½-mile BE measures, an increasing population density was associated with lower scores on the CASI (Table 3.3). Increasing distances to the nearest train stop and bus stop were associated with worse scores on the DSB, whereas increasing distance to the nearest train stop was associated with better scores on the DS. No other BE measures were statistically significantly associated with the cognitive measures.

Education was an effect modifier in eight of the 32 BE and cognition associations examined (Table 3.4). One interaction was statistically significant at $p<0.001$ and also demonstrated significant associations within the corresponding education strata. Increased distance to the nearest bus stop was associated with better DSF scores among those with low education but worse scores among those with higher education. Other notable interactions by education included effect modification of the associations between increased distance to nearest train stop and CASI and DS scores and between population density and DSB scores.

Race/ethnicity was an effect modifier in 20 of the 32 BE-cognition associations examined (Table 3.5). Nine interactions were statistically significant at $p<0.001$ and also demonstrated significant associations within the corresponding race/ethnicity strata. Compared to non-Hispanic whites who displayed no association between their neighborhood social destination density and DSB score, Chinese-Americans had worse DSB scores with increasing social destination density. Additionally, increasing social destinations was associated with worse DS scores among

Hispanics, an association not observed among non-Hispanic whites. Similarly, increasing walking destination density, increasing intersection density, increasing proportion land dedicated to retail uses, and increasing population density were associated with worse DS scores among Hispanics but were not associated with DS scores in non-Hispanic Whites. Additionally, more retail establishments in the neighborhood was associated with worse DSB scores among Chinese-Americans. An increased distance to the nearest bus stop was associated with better DSB scores among Chinese-Americans and non-Hispanics whites but worse DSB scores among African-Americans and Hispanics. When compared to non-Hispanic whites who had better DS scores with increasing distance to the nearest bus stop, African Americans showed no such association. Although both Chinese-Americans and non-Hispanic whites showed better DSF scores with increasing distance to the nearest train stop the effect such was much larger among Chinese-Americans.

In the sensitivity analyses focused on the ¼-mile BE measures, an increased intersection density and increased population density were associated with worse CASI scores, and an increased proportion land dedicated to retail uses was associated with better DSF and DS scores (Appendix 3.7). Similarly, focusing on the 1-mile surrounding the participant's home, an increased proportion land dedicated to retail uses was associated with better DSF and DS scores (Appendix 3.8). Additionally, increased population density was associated with better DSB scores and increased proportion land dedicated to residential uses was associated with better DS scores, when using the 1-mile BE measures. While the statistical significance of the findings differed when using the ¼-, ½-, and 1-mile BE measures, the estimates and direction of the associations remained relatively similar for most of the aforementioned associations. However, the association between population density and CASI scores was stronger for the ½- and 1-mile measures than the ¼-mile measures, the association between population density and DSB scores was stronger for the 1-mile measure than the ¼- and ½-mile measures, and the association between land dedicated to residences and DS scores was only found for the 1-mile measure. In the sensitivity analyses controlling for comorbidities (e.g., myocardial infarct), there was no meaningful change in the results (data not shown).

Finally, the presence of depressive symptoms (CES-D) and self-reporting that people in the neighborhood are willing to help were not statistically significant mediators (data not shown). However, minutes spent walking to get places was a partial mediator of the association between population density and cognition as measured by the CASI, in which increased population density was associated with increased time spent walking, and this was associated with worse CASI scores (Appendix 3.10). Additionally, self-reported trust in neighbors was a partial mediator of the association between land dedicated to retail and DSF score (Appendix 3.11). Curiously, increased retail establishments was associated with decreased trust in neighbors and decreased trust in neighbors was associated with better cognition; however, this indirect association had a small effect size.

3.4. Discussion

This study provides evidence for a cross-sectional association between the neighborhood BE and cognition in older adults independent of individual-level demographics and neighborhood-level SES. Increased population density and increased intersection density were associated with worse overall cognition (CASI), and increased percent of land dedicated to retail was associated with better short-term memory (DSF) and better processing speed (DS). While increased distances to the nearest bus and train stop were associated with worse working memory (DSB), increased population density was associated with better working memory. Finally, better processing speed was associated with increased proportion land dedicated to residential uses and increased distance to the nearest to the nearest train stop. More importantly, our study suggests that the associations between the BE and cognition vary significantly by individual-level education level and race/ethnicity and by the distances used to measure the BE surrounding the participants' homes. Low education was a significant effect modifier of the association between walking destination density, distance to nearest bus stop, distance to nearest train stop, and population density and cognition. However, the effect sizes for interaction by education were generally small, and race/ethnicity appeared to be a more consistent and clinically relevant effect modifier.

The BE characteristics that had strongest associations with cognition included intersection density, population density, and land dedicated to residences and retail establishments. In contrast, the effect sizes for distance to the nearest bus and train stops were extremely small. CASI test scores were 1.3 points lower in the highest versus the lowest population density neighborhoods (using ½-mile measure) and 5.2 points lower in the highest versus lowest intersection density neighborhoods (using ¼-mile measure). Focusing on the 1-mile BE measures, DS scores were 2.5 points higher in neighborhoods with the highest versus lowest number of residences, and 1.4 points higher in neighborhoods with the highest versus lowest number of retail establishments.

The only other known study to examine population density and cognition in older adults, as measured by the Mini Mental State Exam, found no association[112]. In our study, the CASI, which is a brief cognitive test similar to the MMSE, was associated with population density. If the association between population density and cognition were explained by improvements in vascular health due to increased PA, one would expect an improvement in cognition with increasing population density. However, our mediation analysis demonstrated that although increased population density was associated with increased minutes spent walking to get places, through the same indirect pathway, increased walking was associated with worse cognition. Some studies suggest that population density has a negative effect on quality of life[53,54]. Therefore, one possible explanation for the observed association between increased population density and worse cognition relates to potential negative impacts of walking in the urban environment, such as increased stress, decreased quality of life[53,54], or increased exposure to vehicular pollutants. BE characteristics that were thought to be more specific measures that may explain any observed association between population density and cognition, such as density of social and walking destinations, were not as strongly associated with cognition as population density. Thus, if our results are replicated in longitudinal studies, other yet unknown factors associated with population density may explain the observed association with cognition.

An increased percent of the neighborhood dedicated to retail also had a positive association with cognition. No other known studies have examined this particular measure in relation to cognition; however, one study found that increased land use mix, which indicates a greater percent of retail in the neighborhood, was associated with lower odds of dementia[122]. In contrast to our findings for land dedicated to retail, increased intersection density was also associated with worse cognition, and the reasons for this are unclear. Although we did not find that walking to get places was a mediator of the association between increased land dedicated to retail and cognition, the measure was self-reported and studies using a better PA measure may find significant mediation. Based on our findings, it is possible that the availability of more retail destinations specifically, and not compact and walkable neighborhoods generally, may promote increased physical or social activity that is then associated with improved cognition.

The negative association between intersection density and cognition may relate to the same factors that explain the observed association between increased population density and worse cognition.

An increased distance to transit was associated with cognition, but the direction of the associations depended on the cognitive test. The only previous study that examined the association between neighborhood transit availability and cognition[105] found that individuals living in neighborhood with at least one transit stop had slower cognitive decline. Their results were based on longitudinal data and a global composite measure of cognition and are thus not directly comparable to this study. However, it is plausible that increased availability of transit may be associated with improved cognition, and may be explained by increased PA through walking to transit or increased access to mentally stimulating or social activities. Future studies are needed to replicate the findings and also to investigate whether the measure of transit availability can be refined. For instance, a measure of the density of transit stops in the neighborhood, which has been associated with increased PA[147], may be a more specific measure and may have a stronger association with cognition.

The association between many of the BE measures and cognition varied by race/ethnicity. The greatest variation by race/ethnicity was observed for the associations between intersection density and DS scores and between land dedicated to retail and DSB and DS scores. The association between worse DS scores and increasing intersection density and increased land dedicated to retail was observed in Hispanics but not non-Hispanic Whites. This trend for Hispanics and non-Hispanic whites was also observed for the associations between walking destination density and DS scores and between population density and DS scores. At least one previous study had relevant findings, in that Mexican Americans living in barrios (typically higher density) had worse cognition compared to Hispanics living in suburban neighborhoods[148]. Similarly, increasing land dedicated to retail was associated with worse DSB scores in Chinese-Americans, and this association was not observed for non-Hispanic whites. These observed differences may be explained by the large proportion of the Hispanic and Chinese-American participants who were foreign born and whose primary language was not English (Appendix 3.12). Unlike the white participants who were almost all US born and whose primary language was English, almost all of the Chinese-Americans (95%) and 62% of Hispanics were foreign born. Consequently, among whites certain BE characteristics may be associated with improvements in cognition through mental stimulation and improvements in PA, whereas, among Chinese-Americans and Hispanics who were foreign born, a less familiar and compact BE may be associated with cognitive overload that is then associated with impaired cognition.

Digit symbol was associated with the neighborhood BE, in both the main effects analyses and the models examining effect modification by race/ethnicity. Typically, processing speed slows as one ages and has been found to be associated with decreases in white matter integrity[149]. In turn, white matter integrity has been shown to be better among older adults with higher levels of PA[150]. Therefore, the associations between the neighborhood BE and processing speed suggests a causal mechanism related to PA. Although our mediation analyses suggested that PA may not be a mediator, additional studies are needed that include longitudinal measure and objective-defined PA. Additionally, the evidence for an association between the BE and PA in other studies[3,20,99,151] suggests that PA is a plausible mediator in the association between BE and improved cognition.

The strengths of this study include the use a multi-ethnic, multi-site cohort recruited through population-based methods, which improves the generalizability of the findings.

Additionally, MESA provides a rich source of demographic, clinical, and neighborhood data that allowed for the control of important confounders. Also, when the ¼- and 1-mile BE measures were used instead of the ½-mile measures, the findings changed in some instances but were generally similar in effect size and in the direction of the association, suggesting that the findings are relatively robust to changes in the distances used to calculate the participants' neighborhood BE measures.

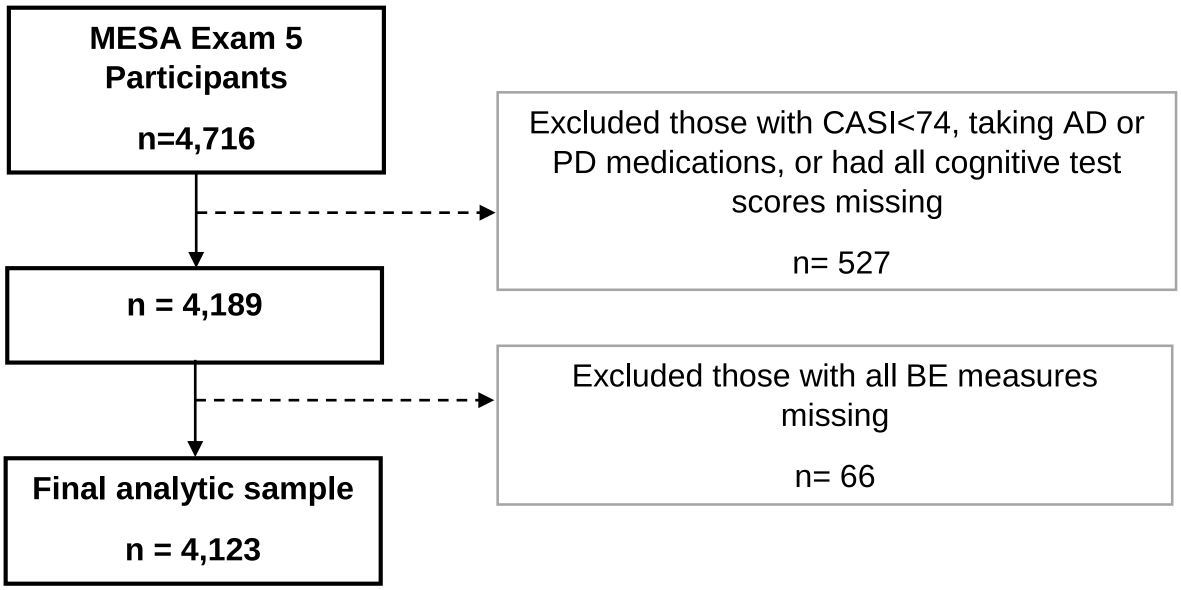
Nevertheless, this study has limitations, first and foremost that it is a cross-sectional study. Our results must be replicated in other cohorts and using methods that consider longitudinal measures of the BE and cognition to assess whether the association may be causal. The cross-sectional nature of the study also limits the ability to account for bias due to neighborhood self-selection, in which preferences for moving to a particular BE may also be related to an individual's cognition or factors associated with cognition[152]. However, the large majority of MESA participants did not move since their baseline exam[153] and almost half did not move during the 20 years preceding MESA enrollment[154], consistent with the expectation of decreased residential mobility with age[155]. There is some evidence that the MESA participants tended to move between neighborhoods with similar SES levels[154], and future research should examine whether this pattern can be extrapolated to neighborhood BE characteristics.

Subsequent studies should include a more rigorous analysis of the potential mediators to understand the underlying causal mechanisms for the observed associations. Although our mediation analysis is a reasonable starting point to examine potential mediators, the Sobel test can be conservative. Future analyses could improve upon this study by using better measures of potential mediators (e.g., objectively-measured PA) and by employing methods to examine the potential for parallel multiple mediators. In addition, other BE scales may be important to consider in tandem with the immediately surrounding neighborhood environment, such as the bordering neighborhoods and their availability of social or walking destinations or transit connections. New studies should take advantage of more expansive cognitive test batteries to further explore the cognitive domains that may be affected by the neighborhood BE exposures and to help address the limitations of using the CASI as a brief cognitive test. Finally, more work is needed to understand the complex relationships between race/ethnicity, the neighborhood BE, neighborhood racial composition, and cognition.

3.4.1. Conclusions

A number of neighborhood BE characteristics were cross-sectionally associated with cognition. Many of the BE-cognition associations varied by race/ethnicity, sometimes in opposite directions for non-Hispanic whites and Chinese-Americans or Hispanics, and our results for effect modification by race/ethnicity suggest that the associations between the BE and cognition are complex and vary based on individual-level characteristics. Future studies should investigate the BE-cognition association using longitudinal measures of the BE and cognition and additional cognitive measures that tap into other cognitive domains (e,g, executive function). Finally, additional mediation and moderation analyses are needed to elucidate the underlying mechanisms and other possible effect modifiers such as sex and physical disability.

Figure 3.1. Sample size flow diagram for Paper 2



Abbreviations: MESA = Multi-Ethnic Study of Atherosclerosis; CASI = cognitive Abilities Screening Instrument; AD = Alzheimer's disease; PD = Parkinson's disease; BE = built environment

Table 3.1. Demographics, APOE genotype, and health conditions (n=4,123)

Characteristic	
Age at exam 5, n (%)	
45-54	72 (1.8%)
55-64	1426 (34.6%)
65-74	1332 (32.3%)
75-84	1047 (25.4%)
85 and older	246 (6.0%)
Male, n (%)	1954 (47.4%)
Education, n (%)	
< High school degree	444 (10.8%)
High school degree	706 (17.2%)
Some college, no bachelor's degree	1239 (30.1%)
Bachelor's degree or higher	1728 (42.0%)
Married, n (%)	2649 (64.9%)
Race/ethnicity, n (%)	
White/Caucasian	1781 (43.2%)
Chinese-American	479 (11.6%)
Black/African American	1079 (26.2%)
Hispanic	784 (19.0%)
Family income ≥$30,000/year, n (%)	2785 (69.9%)
At least 1 APOE ε4 allele, n (%)	1021 (26.4%)
Depression (CES-D score ≥16), n (%)	556 (13.7%)
BMI (kg/m^2), n (%)	
≤24.9 kg/m2	1179 (28.6%)
25-29.9 kg/m2	1548 (37.6%)
≥30 kg/m2	1389 (33.8%)
Current smoker, n (%)	300 (7.4%)
Moderate-Vigorous PA (MET-min/week), mean (SD)	5149 (5905)
Minutes/week walking to get places, mean (SD)	308 (429)
Seated systolic BP>140 mmHg, n (%)	788 (19.1%)
Seated diastolic BP>90mmHg, n (%)	81 (2.0%)
Diabetes (self-reported), n (%)	427 (10.4%)
Hypertension (taking medication), n (%)	2260 (54.8%)
Hypercholesterolemia (taking medication), n (%)	1620 (39.3%)
Emphysema or COPD (self-reported), n (%)	83 (2.0%)
Arthritis (self-reported), n (%)	1288 (31.6%)
Taking depression medication, n (%)	575 (14.0%)
Cardiovascular disease, n (%)	318 (7.7%)
Cerebrovascular disease (TIA/stroke), n (%)	134 (3.3%)

Abbreviations: APOE = apolipoprotein E; CES-D = Center for Epidemiologic Studies Depression scale; BMI = body mass index; PA = physical activity; COPD = chronic obstructive pulmonary disease; BP = blood pressure
Number missing: APOE, n=255; income, n=138; education, n=6; CES-D, n=71; BMI, n=7; current smoker, n=60; MET minutes of PA and minutes walking, n=29; systolic and diastolic BP, n=2; emphysema, n = 19; diabetes, n=22; marital status, n =39; arthritis, n=49; cardiovascular disease, n=3; cerebrovascular disease, n=3

Table 3.2. Neighborhood characteristics and cognitive test scores

Characteristic	Mean (SD)
Cognitive test scores	
CASI	89.2 (6.4)
DSF	9.8 (2.7)
DSB	5.8 (2.3)
DS	52.3 (17.3)
BE measures	
Social destination density (1/2-mile)	142.8 (229.5)
Walking destination density (1/2-mile)	65.8 (104.3)
Intersection density (1/2-mile)	0.78 (0.52)
Proportion residential (1/2-mile)	0.47 (0.17)
Proportion retail (1/2-mile)	0.047 (0.051)
Distance to nearest bus stop (m)	1128 (8788)
Distance to nearest train stop (m)	5223 (12406)
Population density (1/2-mile) (persons/km^2)	6743 (9594)

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol
Number missing: proportion residential, n=275; proportion retail, n=275; distance to nearest bus stop, n=267; distance to nearest train stop, n=890

Table 3.3. Adjusted association between neighborhood built environment and cognitive test measures

	Adjusted estimate[c,d] (95% CI)			
BE measure (1/2 mile radius)	CASI	DSF	DSB	DS
Social destination density[a]	-0.0009 (-0.0021, 0.0003)	0.0002 (-0.0004, 0.0009)	-0.0002 (-0.0008, 0.0005)	0.0017 (-0.0021, 0.0055)
Walking destination density[a]	-0.0017 (-0.0034, 0.0000)	0.0008 (-0.0005, 0.0022)	-0.0005 (-0.0016, 0.0006)	0.0008 (-0.0024, 0.0040)
Intersection density[a]	-0.29 (-0.60, 0.01)	-0.01 (-0.14, 0.12)	-0.02 (-0.15, 0.10)	-0.76 (-1.72, 0.20)
Proportion residential[a,b]	0.35 (-0.63, 1.34)	-0.25 (-1.01, 0.51)	0.08 (-0.24, 0.40)	1.04 (-0.77, 2.85)
Proportion retail[a,b]	0.75 (-3.12, 4.62)	1.91 (-0.12, 3.95)	-0.25 (-1.26, 0.76)	4.38 (-0.16, 8.92)
Distance to nearest bus stop (km)	0.0068 (-0.0091, 0.0227)	-0.0004 (-0.0014, 0.0007)	**-0.0087***** (-0.0121, -0.0053)	0.0152 (-0.0050, 0.0353)
Distance to nearest train stop (km)	0.0060 (-0.0111, 0.0231)	0.0016 (-0.0002, 0.0035)	**-0.0065***** (-0.0088, -0.0042)	**0.0189**** (0.0065, 0.0314)
Population density[a] (1000 persons/km^2)	**-0.0229**** (-0.0393, -0.0064)	0.0049 (-0.0119, 0.0216)	0.0052 (-0.0026, 0.0130)	0.0062 (-0.0795, 0.0918)

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol

Boldface indicates statistical significance (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] e.g., if proportion residential = 0.37, percent of the neighborhood that is residential = 37%

[c] controlling for age, education, sex, race/ethnicity, income, married, presence of at least 1 APOE ε4 allele, and neighborhood SES

[d] provide up to 4 decimal values as needed

Table 3.4. Effect modification of association between built environment and cognition by education

BE measure	Cognitive test	Adjusted estimate (95% CI)[c]	Interaction p-value
Walking destination density[a]	DSF	L: -0.0003 (-0.0020, 0.0014)	p<0.001
		H: 0.0009 (-0.0009, 0.0027)	
	DSB	L: -0.0052 (-0.0244, 0.0139)	p<0.05
		H: 0.0090 (-0.0138, 0.0317)	
Distance to nearest bus stop (km)	DSF	**L: 0.0127 (0.0079, 0.0174)*** **	p<0.001
		H: -0.0073 (-0.0081, -0.0065)* **	
	DS	L: -0.0079 (-0.0230, 0.0072)	p<0.001
		H: 0.0264 (-0.0020, 0.0548)	
Distance to nearest train stop (km)	CASI	**L: -0.0117 (-0.0189, -0.0045)** **	p<0.05
		H: 0.0156 (-0.0139, 0.0452)	
	DS	L: 0.0004 (-0.0130, 0.0139)	p<0.05
		**H: 0.0283 (0.0054, 0.0511)* **	
Population density (1000 persons/km^2)	DSF	L: -0.0052 (-0.0244, 0.0139)	p<0.05
		H: 0.0090 (-0.0138, 0.0317)	
	DSB	**L: 0.0158 (0.0087, 0.0230)*** **	p<0.01
		H: -0.0007 (-0.0073, 0.0058)	

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; NC = not calculated; interaction was not statistically significant at p<0.05; L = ≤12 years of education; H: >12 years of education

Boldface indicates statistical significance for that particular education level (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, sex, race/ethnicity, income, married, presence of ≥1 APOE ε4 allele, and neighborhood SES

[c] provide up to 4 decimal values as needed

Table 3.5. Effect modification of association between built environment and cognition by race/ethnicity

BE measure	Cognitive test	Adjusted estimate (95% CI)	Interaction p-value
Social destination density[a]	DSF	**HS: 0.0018 (0.0015, 0.0021)*** **	HS vs W: p<0.05
		W: -0.0005 (-0.0008, -0.0001)*	
	DSB	**CA: -0.0026 (-0.0033, -0.0019)*** **	CA vs W: p<0.001
		W: -0.0004 (-0.0012, 0.0004)	
	DS	**HS: -0.0044 (-0.0058, -0.0030)*** **	HS vs W: p<0.001
		W: 0.0024 (-0.0025, 0.0073)	
Walking destination density[a]	DSF	**HS: 0.0031 (0.0027, 0.0035)*** **	HS vs W: p<0.05
		W: -0.0010 (-0.0022, 0.0003)	
	DS	**HS: -0.0181 (-0.0228, -0.0134)*** **	HS vs W: p<0.001
		W: 0.0040 (-0.0048, 0.0127)	
Intersection density[a]	CASI	CA: 0.39 (-0.39, 1.17)	CA vs W: p<0.001
		W: -0.20 (-0.43, 0.03)	
	DSB	CA: -0.20 (-0.47, 0.07)	CA vs W: p<0.001
		W: 0.02 (-0.17, 0.21)	
	DS	**HS: -4.02 (-5.01, -3.03)*** **	HS vs W: p<0.001
		W: -0.13 (-0.86, 0.60)	
Proportion residential[a]	DSF	CA: -0.43 (-1.17, 0.31)	CA vs W: p<0.001
		W: 0.37 (-0.22, 0.96)	
	DSB	**HS: 0.50 (0.21, 0.78)*** **	HS vs W: p<0.05
		W: 0.04 (-0.87, 0.95)	
Proportion retail[a]	DSB	**CA: -4.35 (-5.60, -3.11)*** **	CA vs W: p<0.001
		W: -0.60 (-2.47, 1.26)	
	DS	**HS: -26.54 (-42.72, -10.37)** **	HS vs W: p<0.001
		W: 9.73 (-5.77, 25.23)	
Distance to nearest bus stop (km)	CASI	**HS: 0.0148 (0.0138, 0.0158)*** **	HS vs W: p<0.05
		W: 0.0055 (-0.0107, 0.0217)	
	DSF	**CA: 0.0609 (0.0540, 0.0678)*** **	CA vs W: p<0.001
		AA: -0.0681 (-0.1062, -0.0300)* **	AA vs W: p<0.001
		HS: -0.0038 (-0.0071, -0.0004)*	HS vs W: p<0.01
		W: 0.0030 (0.0016, 0.0045)* **	

	DSB	**CA: -0.0140 (-0.0209, -0.0072)***** **HS: -0.0060 (-0.0079, -0.0041)***** **W: -0.0062 (-0.0073, -0.0051)*****	CA vs W: p<0.01 HS vs W: p<0.05
	DS	AA: -0.0902 (-0.2138, 0.0035) **W: 0.0362 (0.0076, 0.0649)***	AA vs W: p<0.001
Distance to nearest train stop (km)	DSF	**CA: 0.0348 (0.0296, 0.0400)***** **W: 0.0024 (0.0001, 0.0046)***	CA vs W: p<0.001
	DSB	CA: -0.0028 (-0.0121, 0.0066) **W: -0.0061 (-0.0077, -0.0044)*****	CA vs W: p<0.01
	DS	AA: -0.0738 (-0.2315, 0.0840) **W: 0.0399 (0.0140, 0.0659)****	AA vs W: p<0.05
Population density[a]	DS	CA: -0.1828 (-0.4864, -0.1209) **HS: -0.1369 (-0.1670, -0.1068)***** W: 0.0253 (-0.0969, 0.1476)	CA vs W: p<0.001 HS vs W: p<0.001

Abbreviations: BE = built environment; CASI=Cognitive Abilities Screening Instrument; DSF=Digit Span Forward; DSB=Digit Span Backward; DS=Digit Symbol; CA=Chinese American; AA=African American; HS=Hispanic; W=Non-Hispanic White

Boldface indicates statistical significance for that particular race/ethnicity (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, race/ethnicity, income, married, presence of $\geq$1 APOE ε4 allele, neighborhood SES, and top three principle components of ancestry

[c] provide up to 4 decimal values as needed

IV. MODERATION OF THE BUILT ENVIRONMENT AND COGNITION ASSOCIATION IN OLDER ADULTS BY INDIVIDUAL-LEVEL FACTORS: THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

4.1. Introduction

The health and economic burden of cognitive impairment due to neurodegenerative diseases, such as Alzheimer's disease (AD), is expected to increase with the imminent rise in the population of older adults[16,17,36] and the lack of preventative treatments. However, some evidence suggests that treatment of vascular risk factors[156] and health behaviors such as physical activity[157] and social[158,159] and mental activities[160,161] may help delay the onset of cognitive impairment. The neighborhood built environment (BE) has been associated with health outcomes such as physical activity, obesity, and mental health[2-5], and more recently with cognition in older adults.[47,90,105,112,120,122] Researchers have hypothesized that these observed associations are related to how the neighborhood affects factors such as utilitarian walking and exercise, nutrition, and social engagement or isolation.[6,67] Therefore, the neighborhood environment may help delay or accelerate the onset of cognitive impairment through some of the aforementioned mechanisms by serving as an upstream influence.

Although few studies have investigated the association between the neighborhood BE and cognition in older adults, the extant research has found that cognition is associated with a variety of neighborhood measures, including the availability of community resources and transit, places to socialize or walk, land use mix including amount of natural environment and retail, street connectivity, population density, and condition of public spaces.[47,90,105,112,120,122] These previous studies indicate that some but not all measures related to increased urban density may be associated with improved cognition, and in other cases, measures suggestive of decreased urban density are associated with better cognition. Yet, little overlap exists between the BE measures used in the studies, and additional research is need to ascertain the BE characteristics that have the strongest influence on cognition and to elucidate the underlying mechanisms.[67]

Importantly, past studies of the health of older adults suggest that the neighborhood may influence cognition differently depending on individual-level characteristics[47,74,92,102,103,106,108,110,111,118] For instance, studies have found that the association between neighborhood SES and cognition varies by individual-level SES[74,92,102,106] and age.[110,118] Also, Chapter III of my dissertation demonstrated that race/ethnicity and education may modify the association between various BE characteristics and cognition. Among the existing studies examining the association between the neighborhood and cognition, often effect modification and the associated stratum-specific estimates were significant more frequently than associations focused on the main effects (see Chapter II).

Thus, this study aims to examine whether the association between neighborhood BE characteristics and cognition varied by three characteristics hypothesized to be important modifiers: 1) sex; 2) apolipoprotein (APOE) ε4 genotype, a risk factor for Alzheimer's disease dementia; and 3) sedentary behavior. Consistent with the previous study examining the main effects in the same analytic sample used in Chapter III of my dissertation, we hypothesized that higher levels of the neighborhood BE measures indicative of increased urban density, specifically social and walking destination density, intersection density, land dedicated to residences or retail, distance to the nearest bus or train station, and population density, would be associated with better cognition. Additionally, we hypothesized that the association between the

BE and cognition would be stronger in women than men, stronger in those with at least one APOE ε4 allele versus no ε4 alleles, and stronger among those with lower levels of sedentary behavior, which may suggest less indoor time and increased exposure to the neighborhood environment.

The aims of this study are consistent with the socioecological model (SEM)[85], which asserts that multiple levels of influence have a cumulative impact on an individual's health and well-being, including individual, interpersonal, community (including neighborhood), organizational, and higher level policy/enabling factors. Examining the association between the BE and cognition is an example of studying whether a higher level factor, above and beyond individual-level characteristics, is associated with individual-level health. In addition, the SEM presumes that there is a differential impact of higher level factors depending on an individual's characteristics (e.g., individuals with physical disabilities will be particularly affected by poor sidewalk conditions). In other words, interaction between higher-level factors such as the BE and individual-level characteristics such as sex are likely.

The neighborhood environment may affect cognition differently in women and men by way of differences in neighborhood perceptions, which thereby influence mental health, social engagement in the neighborhood, and behaviors such as neighborhood-based exercise and walking[162] to local destinations and transit. For instance, perceived neighborhood safety has been associated with physical activity in women but not men.[163-165] Also in women, perceived social disorder such as vandalism, panhandling, and loitering has been associated with greater fear of neighborhood crime than in men.[166] This fear of crime may influence how often women walk and participate in social and physical activities in the neighborhood, which then may affect cognition. Elements of the neighborhood BE may influence cognition differently in women than men through a similar mechanism of perceived safety or through gender preferences for places to eat and shop, socialize, and exercise, as well as preferred transportation modes. For instance, increased park area has been associated with increased leisure time PA in women but not men.[167] Additionally, another study found that more nearby grocery stores was associated with higher body mass index only among women.[168] The only known study to examine effect modification of the association between neighborhood characteristics and cognition by sex found that among <70 year olds, the association between neighborhood deprivation and worse cognition was significant among women but not men.[110] Altogether, it is plausible that the association between the BE and cognition varies significantly between men and women.

Sedentary behavior increases with age, is highest in older adults[169], and is often measured as time spent watching television, sitting/driving, or using the computer.[170] Television watching, which is highly prevalent in older adults[171], has been correlated with objective accelerometer measures of sedentary behavior[172] and has been found to be self-reported fairly accurately.[173,174] In addition, time spent watching television has been associated with health outcomes such as depression[175,176] and physical strength.[177] Television watching may additionally serve as an effect modifier of the association between the BE and cognition, by serving as a proxy of the amount of time an individual has available to be exposed to the neighborhood environment.[178] For example, the neighborhood has been found to have stronger associations with health among those with restricted car access.[179] Individuals who rely on public transportation are more likely to walk for transportation and to public transit, and are thus more likely to be exposed to their neighborhood BE. We hypothesize that similar to those with restricted car access, those who are less sedentary and watch less television are more likely to walk in their neighborhoods and therefore more likely to be influenced by their neighborhood BE.

Gene-environment interactions[180] have been shown to be related to health behaviors such as smoking[181] and alcohol consumption[182] and health outcomes such as depression.[183] It has been argued that genetic factors may be associated with residential location (e.g., ethnic groups tend to settle in certain neighborhoods and cities) and may moderate how environments impact health behaviors and outcomes.[184] Relevant to this current study, the associations between neighborhood deprivation and cross-sectional and longitudinal measures of cognition have been found to be modified by APOE ε4 genotype.[103,111] Specifically, one study found that the association between APOE ε4 genotype and cognitive decline was stronger when neighborhood psychosocial hazards (NPH) was low[103] and a different study found that APOE ε4 carriers in the most psychosocially hazardous neighborhoods had worse cognition compared to non-carriers in neighborhoods with lower psychosocial hazards.[111] The authors of the latter study proposed that APOE ε4 genotype may interact with stress induced by NPH, resulting in worse cognition than associated with APOE ε4 genotype or NPH alone. In contrast, the authors of the former study postulated that environments characterized by disadvantage may have a strong impact on health outcomes such as cognition, to the point that it overpowers any weaker associations with genetic factors, except in conditions where the neighborhood disadvantage is low. Thus, the authors of the former study proposes that among those living in low NPH environments, APOE ε4 genotype would have a stronger association with cognition than among those living in high NPH environments. Similarly, the association between neighborhood BE characteristics and cognition may also be modified by APOE ε4 genotype, and therefore, we hypothesize an additive interaction in which the BE-cognition associations will be stronger among APOE ε4 carriers than non-carriers.

To investigate our aims that the associations between neighborhood BE characteristics and cognition in older adults vary by sex, APOE genotype, and sedentary behavior, we used data on 4,123 participants from the Multi-Ethnic Study of Atherosclerosis (MESA). Only two known studies has examined effect modification of the BE-cognition associations, finding that living alone does not modify the association between community resources and cognition[90] and that multiple BE-cognition associations vary by education and race/ethnicity (see Chapter III). Thus, this study contributes to the emerging body of literature surrounding the BE and cognition.

4.2. Material and Methods

4.2.1. Sample

The analytic sample was derived from the 4,651 participants who completed Exam 5 (2010-2011) of the MESA, the only exam in which cognitive tests were conducted. MESA is a longitudinal cohort study of subclinical cardiovascular disease among 45- to 84-year-olds, which began in 2000 and consists of five exams to date. Participants were enrolled from six US regions (Forsyth County, North Carolina; New York, New York; Baltimore, Maryland; St. Paul, Minnesota; Chicago, Illinois; Los Angeles, California) with oversampling of African Americans, Chinese-Americans, and Hispanics. Details about MESA have been published previously.[48] The final sample consisted of participants who: 1) had at least one non-missing cognitive test score; 2) one non-missing built environment measure; 3) were not taking medications for Alzheimer's disease or Parkinson's disease; and 4) did not have a Cognitive Abilities Screening Instrument (CASI) score suggesting dementia (CASI<74).[144]

4.2.2. Cognitive and built environment measures

MESA exam 5 participants received four cognitive tests: the CASI[88] (version 2), a brief cognitive test of global cognition; Digit Span Forward and Backward (DSF and DSB; subtests of

Wechsler Adult Intelligence Scale [WAIS-III][89]), measures of short term and working memory, respectively; and Digit Symbol (DS; subtest of WAIS-III[89]), a measure of processing speed.

The neighborhood measures were previously developed as part of the MESA Neighborhood Study.[145] Population density was calculated for ¼-mile, ½-mile, and 1-mile as-the-crow-flies buffers around the participants' homes based on the 2010 Census block population density estimates. Land parcels for each study site were classified as residential (e.g., family homes, apartment complexes/condominiums, assisted living facilities) or retail (e.g., shopping centers, bars, clothing stores), and the percent of the ¼-mile, ½-mile, and 1-mile buffers dedicated to residences or retail was calculated by dividing the residential/retail area by the total area of the buffer (m^2). The straight line distances to the nearest bus or train stop were calculated in meters. Intersection density was determined by dividing intersection counts for the ¼-mile, ½-mile, and 1-mile buffer by the total area of the buffer. The simple densities of social engagement destinations (e.g., beauty shops/barbers, performance-based entertainment libraries) and walking destinations (e.g., postal service, drug stores/pharmacies, non-beverage eating and dining places) per square mile were calculated for the ¼-mile, ½-mile, and 1-mile area around the home. Finally, neighborhood SES was based on the participants' US Census tracts, and was developed using a principal components analysis to derive a single measure based on the percent of neighborhood residents with no vehicle, with owner-occupied housing, living in poverty, and who were unemployed. The large majority of the data used to create the neighborhood BE measures were collected within three years of Exam 5; however, in some instances, data were collected up to six years preceding the exam depending on the data available on the participant's locale.

4.2.3. Participant characteristics

Baseline characteristics included age, sex, education level, race/ethnicity, marital status, family income, and the number of participants with at least apolipoprotein ε4 allele (APOE ε4; genetic risk factor for AD). Clinical characteristics included depression (CES-D score≥16), smoking status, minutes of weekly moderate to vigorous physical activity (PA), minutes walking to get places in a week, high systolic (>140mmHg) and diastolic (>90mmHg) blood pressure, self-reported diabetes and chronic obstructive pulmonary disease (COPD), and medication use for hypertension, hypercholesterolemia, and depression. Additionally, because one of our aims was to examine effect modification by APOE genotype, the first three principal components of ancestry[185], which were previously computed by the MESA-SHARE study to account for population stratification (systematic genetic differences in populations) and admixture (interbreeding of groups who were previously genetically isolated), were included as covariates. Sedentary behavior was measured as the minutes that the participant self-reported watching television per week.

4.2.4. Methods

The sample's demographics, clinical characteristics and APOE genotype were detailed using descriptive statistics. Mean values (and standard deviations; SD) of the BE characteristics and cognitive test scores were stratified by sex, APOE ε4 genotype, and sedentary behavior. To assess whether the first three principle components of ancestry were potential confounders of the BE and cognition association, we examined their unadjusted associations with the BE measures and with the cognitive test scores.

To examine effect modification of the BE and cognition associations, we used unadjusted and adjusted linear regression models with generalized estimating equations to account for clustering by study site. The BE measures reported in the main analyses were based on ½-mile buffers around the participants' homes, an area hypothesized to be most representative of the neighborhood for older adults. Thirty-two models were run to examine each BE measure (independent variable) and cognitive test (dependent variable) combination, which eliminated the possibility of multicollinearity by including multiple BE measures in the same model and avoided the creation of a composite variable that would reduce ease of interpretation and comparability with future studies. Both the BE and cognitive measures were treated as continuous variables in the models. The unadjusted models simply stratified the BE-cognition associations by the effect modifiers, and then interaction terms between each BE measure and the potential effect modifiers were included in the adjusted models to test whether effect modification was statistically significant. The multivariable models adjusted for age, sex, race/ethnicity, income, marital status, neighborhood SES, presence of APOE ε4 allele, and the first three principal components of ancestry. For ease of interpretation, the potential effect modifiers were dichotomized (APOE genotype: ≥1 APOE ε4 alleles versus none; low versus high sedentary behavior: ≤900 minutes watching television a week versus >900 minutes). Sensitivity analyses involved repeating the adjusted analyses using BE measures based on the ¼- and 1-mile buffers surrounding the participants' homes, given the lack of a standardized method of perceiving or measuring neighborhood boundaries.[186] Only statistically significant interactions ($p<0.05$) are summarized, and in these instances, the results are presented by stratifying the BE-cognition associations by the dichotomized effect modifier.

4.3. Results

The final sample included 4,123 participants who were a mean age of 69 years old. The majority of the sample was female (53%), college educated (72%), and married (65%) (Table

4.1). Twenty-six percent were APOE ε4 carriers, and therefore at increased risk of developing Alzheimer's disease. Approximately 34% were obese (see Chapter III), 14% had depression, 32% had arthritis, and 55% had hypertension. Fifty-two percent of the sample had lower levels of sedentary behavior (<900 minutes per week). Data on how the analytic sample compared to the excluded participants from the original MESA sample can be seen in Chapter III.

The mean values of the BE measures differed significantly by sex for all except the distances to the nearest bus and train stop (Table 4.2). On average, women lived in more urban environments, with higher densities of social and walking destinations, intersection densities, proportion land dedicated to retail uses, and population densities. When stratified by APOE ε4 genotype and sedentary behavior, the only significant differences were that the distance to the nearest train stop was greater for APOE ε4 non-carriers versus APOE ε4 carriers, and population density was higher for those with higher sedentary behavior.

Compared to men, on average women had worse DSF scores but better DS scores (Table 4.3). Additionally, APOE ε4 carriers had worse mean CASI and DSF scores than non-carriers, and those with low sedentary behavior had better mean scores on all four of the cognitive tests compared to those with high sedentary behavior.

In the unadjusted analyses, the associations between many of the BE measures and cognitive test scores were significant for men and women (Appendix 4.2). The only BE measure not associated with cognition in women or men was proportion land dedicated to residential uses. Similarly, in the unadjusted analyses stratified by APOE ε4 genotype and sedentary behavior, all measures except proportion land dedicated to residential uses were associated with cognition in APOE ε4 carriers and non-carriers (Appendix 4.3), and all measures except proportion land dedicated to retail uses among those with low and high sedentary behavior (Appendix 4.4).

The principal components of ancestry were associated with all of the cognitive test measures, with the exception that the first and second principal components (PC1, PC2) were not associated with DSF (Appendix 4.5). However, only the third principal component (PC3) was associated with the BE measures (Appendix 4.6). Taken together, these findings suggested that these principal components should be controlled for in the multivariable analyses.

4.3.1. Main analyses

Fourteen of the adjusted associations were modified by sex at $p<0.05$ and seven of these associations were modified by sex at $p<0.001$ (consistent with a Bonferroni adjustment for multiple comparisons) (Table 4.4). However, only four associations demonstrated significant effect modification by sex and were statistically significant in men and/or women. An increased distance to the nearest bus stop was associated with worse DSF and DSB scores among women but was not associated with either test among men. In addition, an increased distance to the nearest bus stop was associated with better DS scores among men but was not associated with DS scores among women. Finally, increased distance to the nearest train stop was associated with worse DSB scores among women, an association not observed among men.

Seven of the adjusted associations were significantly modified by APOE ε4 genotype at $p<0.05$, four of which were significant at $p<0.001$ (Table 4.5). Among the associations that also demonstrated significant associations in APOE ε4 carriers and/or non-carriers, we found that ε4 carriers demonstrated significantly worse CASI scores with an increase in social and walking destinations and with an increase in population density, associations not observed among non-carriers. Additionally, while both APOE ε4 carriers and non-carriers demonstrated worse DSB scores with increasing distance to the nearest bus stop, the association was stronger among ε4 carriers.

Sedentary behavior was a significant effect modifier of 10 adjusted associations at $p<0.05$, three of which were significant at $p<0.001$ and six of which were statistically significant in those with low and/or high sedentary behavior (Table 4.6). An increased distance to the nearest bus stop was associated with better CASI and DSF scores in those with low sedentary behavior, worse DSF and DSB scores in those with high sedentary behavior, and worse DSB scores in those with low sedentary behavior. An increased distance to the nearest train stop was associated with better DSF scores but worse DSB scores among those with low sedentary behavior, and worse DSB scores among those with high sedentary behavior. Lastly, an increased population density was associated with worse CASI scores among those with low sedentary behavior, with no association among those with high sedentary behavior. Moreover, the associations between increasing distance to nearest bus or train stop and worse DSB scores were stronger for those with high sedentary behavior versus low sedentary behavior.

4.3.2. Sensitivity analyses for effect modification by sex

Beyond what was found using the ½-mile BE measures, sex was an effect modifier of the association between multiple BE characteristics (social destination density, walking destination density, intersection density, proportion land dedicated to residential uses, and population density) and new cognitive measures using the ¼-mile and 1-mile buffers (Appendix 4.7). For example, focused on social destination density, sex only modified the association between the ½-mile measure and DS scores, but additionally modified the association between the ¼-mile measure and DSF scores and between the 1-mile measure and CASI and DSF scores. Overall, many of the statistically significant interactions with sex were not observed consistently across the ¼-mile, ½-mile, and 1-mile measures or across the cognitive tests, and while the interaction may have been significant, the sex-specific associations between the BE characteristics and cognitive test scores were often not statistically significant.

Among the statistically significant sex-specific associations, the ¼-mile measure of intersection density was associated with worse CASI scores in women but not men and with worse DSF scores among men but not women. In addition, the 1-mile measures of social destination density, walking destination density, intersection density, and population density were associated with worse CASI scores among women but not men. The 1-mile measure of proportion land dedicated to residential uses was associated with worse DSB scores among men but better scores among women. Finally, the ¼-mile measure of proportion land dedicated to retail uses was associated with better cognition in men and women, with a stronger association among men than women.

4.3.3. Sensitivity analyses for effect modification by APOE genotype

When using the ¼-mile and 1-mile BE measures, additional associations were modified by APOE genotype beyond what was found using the ¼-mile measures (Appendix 4.8). APOE genotype modified the association between the ½-mile and 1-mile measures (but not the ½-mile measures) of intersection density and proportion retail and cognition. Additionally, APOE genotype modified the association between the ¼-mile and 1-mile BE measures and additional cognitive test scores outside of what was found using the ½-mile measures. For instance, whereas the association between the ½-mile measure of social destination density and cognition was modified by APOE genotype only when focused on the CASI scores, APOE genotype additionally modified the association between the 1-mile measure of social destination density and DSF scores.

Compared to the findings for the ½-mile measures, new statistically significant findings included the association between the 1-mile measure of walking destination density and better DSF scores among APOE ε4 non-carriers but not among ε4 carriers. The ¼-mile and 1-mile measures of intersection density were associated with worse DSF scores among APOE ε4 carriers, associations not observed in the non-carriers. The 1-mile measures of proportion land dedicated to residential and retail uses were associated with better CASI and DSF scores among non-carriers, respectively, with no association among APOE ε4 carriers. Finally, the 1-mile measure of population density was associated with worse DS scores among APOE ε4 carriers but was not associated with scores among non-carriers. Irrespective of whether the ¼-mile, ½-mile, or 1-mile buffer was used for the social and walking destination density or population density measures, they were associated with worse CASI scores among APOE ε4 carriers but not among non-carriers.

4.3.4. Sensitivity analyses for effect modification by sedentary behavior

A few associations were found to be modified by sedentary behavior when using the ¼-mile BE measures but not the ½-mile or 1-mile measures, including those between ¼-mile social destination density and DSF scores, ¼-mile walking destination density and DSB scores, and ¼-mile proportion land dedicated to retail uses and DSB scores (Appendix 4.9).

When the results were stratified by sedentary behavior, the ¼-mile measure of social destination density was associated with better DSF scores among those with low sedentary behavior but was not associated with scores among those with high sedentary behavior. Regardless of whether the ¼-mile, ½-mile, or 1-mile buffer was used for the population density measure, it was associated with worse CASI scores among those with low sedentary behavior and was not associated with CASI scores among those with high sedentary behavior.

4.4. Conclusions

The results from this study suggest that the cross-sectional associations between multiple BE characteristics and cognition vary by sex, APOE genotype, and sedentary behavior. However, the directions of the effect modification and the stratum-specific associations were not always consistent with our hypotheses. Focused on the results based the ½-mile BE measures, we found that increased distances to bus and train stops were generally associated with worse cognition among women but not men. Additionally, increased social and walking destination density and population density were associated with worse cognition among APOE ε4 carriers but were not found to be associated with cognition in non-carriers, and the association between increased distance to the nearest bus stop and worse cognition was stronger among ε4 carriers than non-carriers. While the associations between increased distance to the nearest bus and train stop and cognition varied by sedentary behavior, the direction of the association for those with low and high sedentary behavior changed depending on the cognitive test. Lastly, in those with low sedentary behavior, increased population density was associated with worse cognition, with no such association among those with high sedentary behavior. The most consistent associations observed regardless of whether the ¼-mile, ½-mile, or 1-mile buffers were used were between increased social and walking destination density and increased population density and worse cognition among APOE ε4 carriers; and between increased population density and worse cognition among those with low sedentary behavior.

A greater distance from a transit stop was typically associated with worse cognition in women but not men. Nevertheless, the effect size was extremely small. For instance an increase of up to 2 miles to a bus stop was in women associated with 0.03 and 0.07 point lower scores on the DSF and DSB tests, respectively. The small but statistically significant difference between women and men may be explained by higher rates of driving cessation in older women than men.[187] Less access to other forms of transportation may have a negative impact on cognition by affecting women's ability to participate in activities and obtain services outside of the immediate neighborhood. Another possibility is that greater distance to the nearest transit stop is associated with a greater decrease in overall PA among women compared to men, which thereby worsens cognition in women through vascular mechanisms.

A number of other associations varied significantly by sex, but the sex-specific associations between the BE and cognition were not statistically significant when using the ½-mile BE measures. However, effect modification of the association between the ¼-mile measure of percent of land dedicated to retail and DS scores is of note. When comparing individuals living in the neighborhoods with the highest versus the lowest percent of land dedicated to retail, men had an estimated 4.7 point higher DS score whereas women had a 2.3 point higher DS score. In a previously published paper of this sample, which focused on the main associations between the BE and cognition measures, the ¼-mile measure of proportion land dedicated to retail uses was also strongly associated with DS score. It is not immediately clear why the association is stronger in men than women, but may have to do with differences in driving habits. Retail establishments within a ¼ mile of the home may induce men more than women to walk more often than drive and may thus have a greater positive benefit to men than women. Nonetheless, this is speculative and will need to be examined further in future studies.

Consistent with our hypotheses, associations between the BE and cognition were stronger in APOE ε4 carriers, but the associations indicated a negative relationship in which increased density was associated with worse cognition in ε4 carriers. Compared to individuals living in the lowest social destination, walking destination, and population densities, APOE ε4 carriers living in the highest densities scored 2.7, 3.1, and 3.2 points lower on the CASI, respectively. It is possible that the stress associated with higher density environments overshadows any potentially positive cognitive benefits of living in urban environments among APOE ε4 carriers. Although not statistically significant among APOE ε4 non-carriers, the associations were similarly in the negative direction, with increasing densities associated with worse cognition. In addition, the association between increasing distance to the nearest bus stop and worse cognition was stronger in APOE ε4 carriers than non-carriers, but the effect sizes were very small. This observed association in APOE ε4 carriers demonstrates the potential additive and detrimental impact on cognition of having both lower accessibility to transit and the APOE ε4 genotype.

Those with lower sedentary behavior experienced worse cognition with increased population density and these associations were not observed among those with high sedentary behavior. However, based on our a priori hypotheses, we expected that increased population density would be associated with improved cognition. As a proxy of exposure to the neighborhood environment, these findings may suggest that increased time exposed to higher population densities may have a negative effect on cognition by way of increased stress.[188] Stress in late-life has been associated with worse baseline cognition and cognitive decline in older adults[59,60] and a decrease in stressors has been associated with improved cognition.[61] On the other hand, increased social destination density measured in the ¼-mile surrounding the home was associated with better cognition in those with low sedentary behavior, but not in those with high sedentary behavior. Comparing individuals living in neighborhoods with the highest to lowest social destination density (¼-mile measure), individuals with low sedentary behavior scored 1.8 points better on the DSF. It is possible that spending less time in sedentary behavior, and thus more opportunity for neighborhood exposure, is most pertinent and is associated with better cognition when there are increased opportunities for social engagement in the neighborhood. Finally, the direction of the association between distance to nearest transit stop and cognition by sedentary behavior differed based on the cognitive test, and thus is difficult to interpret. Better measures of transit availability in the neighborhood (e.g., density of transit stops) or improved measures of time exposed to the neighborhood environment may clarify these relationships.

Our results did not reveal the most pertinent measure of cognition for studies focused on BE-cognition associations, as the four measures of overall cognition, working and short-term memory, and processing speed were associated with at least one neighborhood BE measure. Similarly, depending on the buffer size used to measure the BE, each of the BE measures were associated with at least one cognitive test. Taken together, these results suggest that multiple aspects of the BE may affect multiple cognitive domains; although it is also possible that some of the observed associations may have been observed by chance due to testing multiple associations. Each of the cognitive domains measured by MESA could plausibly be affected by the BE through mechanisms related to PA, social support and engagement, or cognitively stimulating activities.[133,158,159] For instance, processing speed may be affected if the BE influences PA levels or the need for an individual to more quickly process the ever shifting neighborhood social environment when walking, and working memory may be influenced if the BE induces more social engagement or social support. Each of the BE measures studied could plausible influence cognition by way of the aforesaid mechanisms.

Our study has limitations including its cross-sectional nature. Future studies will need to include longitudinal measures of the BE and cognition to provide some indication for a causal association between the BE and cognition. Although the current study suggests that BE-cognition associations vary by individual-level characteristics, the effect modification and the main associations between the BE and cognition may be explained by residual confounding by unknown factors. Additionally, a lifecourse approach would help discern whether late-life cognition is associated with longer-term exposures to the neighborhood environment, or whether late-life cognitive differences are really lifelong differences that are associated with differences in socioeconomic status and related factors from early life. Sedentary behavior, which was used a proxy measure of exposure to the neighborhood BE, may be best measured using other factors in addition to time spent watching television. Finally, results from Chapter III suggested that utilitarian walking and neighboring acts were partial mediators of two BE-cognition associations, additional research is needed to investigate the underlying causal mechanisms for the BE-cognition associations and whether they differ by individual-level characteristics.

In conclusion, we found that sex, APOE genotype, and sedentary behavior modified the cross-sectional association between the neighborhood BE and cognition in older adults. In addition, we found that some associations were significant regardless of whether the ¼-mile, ½-mile, or 1-mile buffers were used to measure the BE characteristics. However, in other cases, the associations were only statistically significant when using the ¼-mile and 1-mile buffers instead of the ½-mile buffers used in our main analyses. Therefore, our study demonstrates that the manner in which the neighborhood is defined (e.g., ¼-mile, ½-mile, or 1-mile surrounding the participant’s home) and the specific BE characteristics examined may greatly affect the findings of a study focused on the BE and cognition. Additional work is needed to clarify the underlying mechanisms that explain how the BE is associated with cognition and the individual-level factors that render an individual more or less susceptible to the influence of the BE.

Table 4.1. Demographics, APOE genotype, and health conditions (n=4,123)

Characteristic	
Age at exam 5, mean (SD)	69.3 (9.3)
Women, n (%)	2169 (52.6%)
Education, n (%)	
< High school degree	444 (10.8%)
High school degree	706 (17.2%)
Some college, no bachelor's degree	1239 (30.1%)
Bachelor's degree or higher	1728 (42.0%)
Married, n (%)	2649 (64.9%)
Race/ethnicity, n (%)	
White/Caucasian	1781 (43.2%)
Chinese-American	479 (11.6%)
Black/African American	1079 (26.2%)
Hispanic	784 (19.0%)
Family income ≥$30,000/year, n (%)	2785 (69.9%)
At least 1 APOE ε4 allele, n (%)	1021 (26.4%)
Depression (CES-D score ≥16), n (%)	556 (13.7%)
Current smoker, n (%)	300 (7.4%)
Moderate-Vigorous PA (MET-min/week), mean (SD)	5149 (5905)
Minutes/week walking to get places, mean (SD)	308 (429)
Seated systolic blood pressure >140 mmHg, n (%)	788 (19.1%)
Seated diastolic blood pressure >90mmHg, n (%)	81 (2.0%)
Diabetes (self-reported), n (%)	427 (10.4%)
Hypertension (taking medication), n (%)	2260 (54.8%)
Hypercholesterolemia (taking medication), n (%)	1620 (39.3%)
Emphysema or COPD (self-reported), n (%)	83 (2.0%)
Taking depression medication, n (%)	575 (14.0%)
Arthritis (self-reported), n (%)	1288 (31.6%)
Lower level of sedentary behavior[a], n (%)	2144 (52.4%)

Abbreviations: APOE = apolipoprotein E; CES-D = Center for Epidemiologic Studies Depression scale; PA = physical activity; COPD = chronic obstructive pulmonary disease

Missing data: APOE, n=255; income, n=138; education, n=6; CES-D, n=71; current smoker, n=60; MET minutes of PA and minutes walking, n=29; systolic and diastolic BP, n=2; emphysema, n = 19; diabetes, n=22; marital status, n =39

[a] <900 minutes of television watching per week

Table 4.2. Mean values for built environment measures by sex, APOE ε4 genotype, and sedentary behavior

	Mean (SD)					
BE characteristic	Men	Women	APOE ε4+	APOE ε4-	Low sedentary behavior	High sedentary behavior
Social dest. density[a]	**132.0 (222.4)***	**152.6 (235.4)***	140.7 (217.3)	139.4 (231.9)	144.5 (236.2)	139.9 (219.9)
Walking dest. density[a]	**59.5 (99.0)***	**71.6 (108.5)***	64.8 (101.4)	63.9 (103.9)	63.7 (101.1)	67.8 (107.0)
Intersection density[a]	**0.76 (0.52)***	**0.80 (0.52)***	0.78 (0.55)	0.77 (0.51)	0.79 (0.55)	0.76 (0.49)
Proportion residential[a]	**0.48 (0.17)***	**0.47 (0.16)***	0.48 (0.17)	0.47 (0.17)	0.47 (0.17)	0.47 (0.16)
Proportion retail[a]	**0.045 (0.051)***	**0.049 (0.051)***	0.048 (0.052)	0.045 (0.050)	0.047 (0.51)	0.046 (0.050)
Nearest bus stop (m)	1334 (10600)	945 (6768)	718 (5113)	1346 (10121)	1028 (8628)	1248 (9017)
Nearest train stop (m)	5655 (14293)	4833 (10402)	**4279 (8216)***	**5780 (13962)***	5123 (12011)	5372 (12918)
Population density[a,b]	**6110 (8984)***	**7314 (10080)***	6722 (9355)	6453 (9423)	**6334 (8975)***	**7181 (10216)***

Abbreviations: BE = built environment; SD = standard deviation; dest = destinations; m = meter

Boldface indicates statistically significant difference by sex/ APOE ε4 genotype/sedentary behavior (*p<0.05)

[a] Measured by ½ mile radius of participant's home

[b] persons/kilometer^2

Table 4.3. Mean values for cognitive test measures by sex, APOE ε4 genotype, and sedentary behavior

	Mean (SD)					
Cognitive test	Men	Women	APOE ε4+	APOE ε4-	Low sedentary behavior	High sedentary behavior
CASI	89.4 (6.3)	89.1 (6.4)	**88.9 (6.6)***	**89.4 (6.3)***	**89.7 (6.4)***	**88.7 (6.3)***
DSF	**10.0 (2.8)***	**9.7 (2.7)***	**9.6 (2.7)***	**9.9 (2.8)***	**10.0 (2.8)***	**9.6 (2.6)***
DSB	5.8 (2.3)	5.8 (2.3)	5.7 (2.3)	5.8 (2.3)	**6.0 (2.4)***	**5.6 (2.2)***
DS	**51.0 (16.8)***	**53.4 (17.6)***	51.6 (17.5)	52.6 (17.2)	**54.6 (17.5)***	**49.8 (16.6)***

Abbreviations: CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; SD = standard deviation; APOE ε4+ = apolipoprotein ε4 positive; APOE ε4- = apolipoprotein ε4 negative
Boldface indicates statistically significant difference by sex/ APOE ε4 genotype/sedentary behavior (* $p<0.05$)

Table 4.4. Effect modification of adjusted association between built environment and cognition by sex

BE measure	Cognitive test	Adjusted estimate (95% CI)[b,c]	M vs W: Interaction p-value
Social destination density[a]	DS	M: 0.0033 (-0.0022, 0.0088) F: 0.0010 (-0.0015, 0.0034)	<0.001
Walking destination density[a]	DSF	M: 0.0002 (-0.0011, 0.0016) F: 0.0014 (-0.0003, 0.0032)	<0.01
	DS	M: 0.0063 (-0.0021, 0.0147) F: -0.0021 (-0.0064, 0.0022)	<0.001
Intersection density[a]	DS	M: -0.28 (-1.67, 1.11) F: -1.08 (-2.61, 0.45)	<0.001
Proportion residential[a]	DSB	M: -0.15 (-0.45, 0.14) F: 0.36 (-0.17, 0.89)	<0.05
Proportion retail[a]	CASI	M: 4.29 (-0.23, 8.81) F: -3.60 (-8.50, 1.31)	<0.05
	DSB	M: 0.60 (-0.70, 1.90) F: -1.22 (-3.60, 1.16)	<0.01
	DS	M: 8.17 (-0.20, 16.54) F: 1.45 (-6.90, 9.81)	<0.001
Distance to nearest bus stop (km)	DSF	M: 0.0026 (-0.0000, 0.0053) **F: -0.0081 (-0.0118, -0.0044)*** **	<0.01
	DSB	M: -0.0032 (-0.0066, 0.0003) **F: -0.0224 (-0.0253, -0.0195)*** **	<0.001
	DS	**M: 0.0271 (0.0031, 0.0511)* ** F: -0.0323 (-0.0655, 0.0010)	<0.001
Distance to nearest train stop (km)	DSB	M: -0.0029 (-0.0063, 0.0006) **F: -0.0147 (-0.0167, -0.0127)*** **	<0.05
Population density[a]	DSF	M: -0.0092 (-0.0221, 0.0037) F: 0.0182 (-0.0077, 0.0440)	<0.01
	DS	M: 0.0438 (-0.0908, 0.1783) F: -0.0259 (-0.0975, 0.0457)	<0.001

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; NC = not calculated; interaction was not statistically significant at p<0.05

Boldface indicates statistical significance for that particular sex (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, race/ethnicity, income, married, presence of ≥1 APOE ε4 allele, neighborhood SES, and top three principle components of ancestry

[c] provide up to 4 decimal values as needed

Table 4.5. Effect modification of adjusted association between built environment and cognition by apolipoprotein ε4 genotype

BE measure	Cognitive test	Adjusted estimate (95% CI)[b,c]	APOE ε4+ vs APOE ε4-: Interaction p-value
Social destination density[a]	CASI	ε4+**: -0.0016 (-0.0026, -0.0005)****	<0.01
		ε4-: -0.0007 (-0.0017, 0.0003)	
Walking destination density[a]	CASI	ε4+**: -0.0043 (-0.0054, -0.0031)*****	<0.001
		ε4-: -0.0005 (-0.0023, 0.0013)	
Proportion residential[a]	DSF	ε4+: 0.26 (-0.46, 0.99)	<0.001
		ε4-: -0.38 (-1.16, 0.41)	
Distance to nearest bus stop (km)	CASI	ε4+: -0.0292 (-0.0592, 0.0007)	<0.05
		ε4-: 0.0111 (-0.0071, 0.0293)	
	DSB	ε4+**: -0.0168 (-0.0226, -0.0111)*****	<0.001
		ε4**-: -0.0081 (-0.0103, -0.0058)*****	
Population density[a]	CASI	ε4+**: -0.0583 (-0.0805, -0.360)*****	<0.01
		ε4-: -0.0041 (-0.0189, 0.0107)	
	DS	ε4+: -0.0865 (-0.2156, 0.0426)	<0.001
		ε4-: 0.0235 (-0.0551, 0.1022)	

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; NC = not calculated; interaction was not statistically significant at p<0.05

Boldface indicates statistical significance for that particular APOE genotype (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, race/ethnicity, income, married, presence of ≥1 APOE ε4 allele, neighborhood SES, and top three principle components of ancestry

[c] provide up to 4 decimal values as needed

Table 4.6. Effect modification of adjusted association between built environment and cognition by sedentary behavior

BE measure	Cognitive test	Adjusted estimate (95% CI)[b,c]	L vs H: Interaction p-value
Social destination density[a]	DSB	L: 0.0003 (-0.0003, 0.0009) H: -0.0005 (-0.0013, 0.0003)	<0.01
	DS	L: 0.0035 (-0.0023, 0.0094) H: -0.0009 (-0.0030, 0.0012)	<0.0001
Walking destination density[a]	DS	L: 0.0039 (-0.0015, 0.0092) H: -0.0018 (-0.0061, 0.0025)	<0.05
Distance to nearest bus stop (km)	CASI	**L: 0.0173 (0.0077, 0.0268)***** H: -0.0030 (-0.0229, 0.0169)	<0.05
	DSF	**L: 0.0074 (0.0061, 0.0087)***** **H: -0.0058 (-0.0083, -0.0033)*****	<0.0001
	DSB	**L: -0.0054 (-0.0100, -0.0008)*** **H: -0.0113 (-0.0139, -0.0086)*****	<0.01
Distance to nearest train stop (km)	DSF	**L: 0.0098 (0.0075, 0.0122)***** H: -0.0036 (-0.0053, -0.0019)***	<0.05
	DSB	**L: -0.0035 (-0.0070, -0.0001)*** **H: -0.0092 (-0.0129, -0.0055)*****	<0.0001
Population density[a]	CASI	**L: -0.0338 (-0.0526, -0.0150)***** H: -0.0047 (-0.0281, 0.0187)	<0.01
	DS	L: 0.0184 (-0.0921, 0.1290) H: -0.0277 (-0.1144, 0.0591)	<0.05

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; NC = not calculated; interaction was not statistically significant at p<0.05

Boldface indicates statistical significance for that particular sex (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, race/ethnicity, income, married, presence of ≥1 APOE ε4 allele, neighborhood SES, and top three principle components of ancestry

[c] provide up to 4 decimal values as needed

V. OVERALL SUMMARY AND CONCLUSIONS

5.1. Summary of findings

My dissertation study was organized around three publishable papers: 1) a systematic literature review of studies published on the neighborhood social and built environment and cognition in older adults; 2) an analysis examining whether social and walking destination density, intersection density, proportion of land dedicated to residential or retail uses, distance to the nearest bus or train stop, or population density are associated with cognition in older adults, and whether individual-level education or race/ethnicity modify these associations; and 3) an analysis investigating if individual-level sex, APOE genotype, or sedentary behavior modify the BE-cognition associations.

The literature review revealed that while over twenty published studies have examined associations between neighborhood characteristics and cognition in older adults, most have focused on social versus BE characteristics of the neighborhood. Based on those previous studies, there is some evidence that lower neighborhood SES is associated with worse cognition independent of individual-level demographics and SES. Additionally, there is also modest evidence that certain features of the BE such as presence of a community center and transit availability are associated with better cognition, but more research is needed to investigate how the BE is associated with cognition. The review also suggested that future studies may be more fruitful in examining effect modification of the BE-cognition association. For instance, the BE may differentially impact cognition among vulnerable populations.

The dissertation study analyses served to fill some of the gaps that have not yet been investigated in the studies conducted to date. Specifically, no known studies have examined the association between social destination density, walking destination density, proportion land dedicated to residential uses, or proportion land dedicated to retail uses and cognition, or effect modification of the BE-cognition associations by education, race/ethnicity, sex, APOE genotype, or sedentary behavior. In the main effects analyses, increased intersection density and population density were found to be associated with worse cognition, whereas increased land dedicated to retail establishments was associated with better cognition. Education was an effect modifier but the effect size was small, whereas race/ethnicity, sex, APOE genotype, and sedentary behavior were significant effect modifiers of multiple BE-cognition associations.

The findings for intersection and population density generally were not consistent with the a priori hypotheses that changes in BE measures consistent with increased urban density would be associated with better cognition. Specifically, increasing intersection and population density was associated with worse cognition in the main effect analyses and when stratified by race/ethnicity, sex, APOE ε4 genotype, and sedentary behavior, but not by education. Although the reasons for this inconsistency are not known, it is possible that at least a couple of underlying mechanisms are at work. Certain aspects associated with increased urban density may be associated with increased stress from noise, traffic, or increased interactions with strangers and decreased meaningful social engagement in the neighborhood, which may lead to worse cognition. Additionally, it is possible that increased urban density is associated with increased air pollution exposures by way of increased utilitarian walking in the neighborhood, as air pollution exposure has been associated with worse cognition in at least a few studies.[51,189]

In this study's preliminary mediation analysis, the association between increased population density and worse cognition was found to be partially mediated by increased utilitarian walking, although much of the negative association between population density and cognition was not mediated by time spent walking to get places. This suggests that, in future studies, a more rigorous method of examining simultaneous/parallel mediation by utilitarian PA, stress/cognitive overload, social engagement, and air pollution is needed to elucidate all of the underlying causal mechanisms. In addition, care must be taken to accurately measure these potentially mediators in future studies. For instance, in the MESA sample, time spent walking to get places was not validated and may have been over-reported.

In contrast to my finding of a negative association between neighborhood population density and cognition, the study by Martinez et al[112] found no association between these two variables. The reasons for this could relate to the differences in our neighborhood definitions, as their study was based on US Census tracts instead of a given distance around the participant's home. Another possibility is that the mechanism between population density and worse cognition relates in part to the race/ethnicity of the sample. The paper by Martinez et al. restricted to Whites and African Americans, and therefore did not examine the association among Hispanics or Chinese Americans. In my study, the negative association between these two variables was only found for Hispanics (statistically significant) and Chinese-Americans (not statistically significant), and in contrast, there was a positive association between population density and cognition among non-Hispanic Whites. Therefore, it seems that differences in the race/ethnicity of the samples may help to explain differences in findings across the two studies.

The negative association between intersection density and baseline cognition was also observed using one measure of street connectivity (integration: more turns needed to reach all other streets in network) employed in the Watts et al[120] study; however, their other measure of street connectivity (greater paths/streets connected to each street) demonstrated a positive association with cognition. The authors speculated that greater integration (less navigational turns to reach a given destination) may create cognitive overload among older adults because of the greater number of initial choices, and additionally, increased integration and the associated increase in traffic may be associated with stress when walking. The authors posited that the other street connectivity measure was associated with maintained cognition because it was indicative of increased accessibility or availability of walking or social destinations. The three similar measures used in the Watts et al paper and my study aim to quantify similar constructs of increased accessibility to destinations. One possible explanation for the conflicting results relates to the smaller sample size in the Watts paper (n=64) and the lack of control for potentially important confounders such as marital status and income. However, taken together, the Watts study and my study provide some limited evidence for a negative cross-sectional association between increasing accessibility and worse cognition.

Unlike the findings for intersection density and population density, increases in the proportion of land dedicated to retail uses was associated with better cognition in the overall sample. Although the presence of more retail establishments is another sign of increased urban density, the results suggest it is associated with improved cognition and in particular, better processing speed. None of the systematically reviewed papers on the BE and cognition in older adults specifically examined proportion of land dedicated to retail uses. However, Wu et al[122] found that increased land use mix was associated with decreased odds of dementia, which is consistent with my findings. Perhaps unlike the other measures of increased urban density, an increase in retail destinations in the neighborhood serves as an overall positive source of cognitive stimulation. This association may be partially explained by the increased opportunities for cognitive stimulation, social engagement, or utilitarian PA afforded by increased retail establishments in the neighborhood.

Although the effect sizes were small, my study also found that increased distances to the nearest bus and train stop were associated with cognition, but the direction of the association depended on the cognitive test measure. My observation of a positive association between increased distance to transit and DSB score is consistent with a previous study by Clarke et al[105] in which they found that older adults living in neighborhoods with a transit stop had slower cognitive decline. In contrast, I found that increased distances to transit was associated with better DS scores. The difference in findings may suggest that accessibility to transit has differential effects on cognition depending on the cognitive domain, and correspondingly the cognitive measure used. Alternatively, different measures of transit availability may be needed to better examine these relationships. For instance, a measure of the density of transit stops in the neighborhood, which has been associated with increased PA[147], may be a more specific measure and may have a stronger association with cognition. Additionally, my findings for the variation of the association between distance to nearest transit stop and cognition by education, race/ethnicity, sex, APOE ε4 genotype, and sedentary behavior, demonstrate the complexity of the association.

Each of the five potential moderators examined in this study were found to be statistically significant modifiers of the BE-cognition associations, and the variation in the direction of the effect modification and the stratum-specific estimates provide further evidence for the complex relationship between the BE and cognition. The more notable of the observed effect modification associations will be mentioned here. The most consistent associations when stratifying by race/ethnicity were found for Hispanics, of which a majority was born outside of the US and a large proportion spoke Spanish as their primary language. Increased urban density, as measured via social and walking destination density, intersection density, proportion land dedicated to retail uses, and population density, was associated with worse processing speed among Hispanics after controlling for neighborhood SES. Therefore, the results suggested that increased urban density may be associated with cognitive overload in Hispanics, particularly when they are foreign-born and do not speak English as their primary language.

Additionally, when focused on effect modification by sex, the association between the proportion land dedicated to retail uses and better cognition was stronger for men than women, suggested that the availability of more retail establishments in the neighborhood has a greater cognitive benefit to men than women. And finally, among APOE ε4 carriers and those with lower levels of sedentary behavior, there was a negative association between urban density and cognition, suggesting that these individuals may be more vulnerable to potential stress and cognitive overload associated with increased urban density.

While the preliminary mediation analyses suggested neighborhood social conditions (i.e., trust) and PA may partially explain the associations between the BE and cognition in older adults, they were only minor, partial mediators. Moreover, the BE was associated with each of the four cognitive measures employed in MESA and therefore it was not possible to discern a more specific biological pathway, by observing whether the BE differentially affected overall cognition, working memory, short-term memory, or processing speed. It is possible that the BE affects more than one cognitive domain, and biological markers such as structural MRI studies may be useful in determining the most affected regions of the brain. In addition, future studies should employ a more thorough cognitive battery of tests to examine the full range of cognitive domains that may be affected by the BE, such as episodic memory, executive function, and visuospatial function. Overall, based on the findings of this study and the limited studies on this topic to date, the potential causal mechanisms outlined proposed in Figure 1.2 remain plausible and new studies such as those involving more advanced mediation analyses will be needed to separate out the causal and biological mechanisms linking the BE and cognition.

Overall, when comparing my study to the six previously published studies on the BE and cognition in older adults, I found a few consistent findings but mostly novel findings. Consistent with the Watts et al[120] study, increased intersection density as a measure of accessibility was associated with worse baseline cognition in older adults. Consistent with the Wu et al[122] study, my study found that an increase in the proportion of land dedicated to retail uses was associated with better cognition. Also, consistent with the Clarke et al[105] study, increased distance to the nearest bus stop was associated with improved cognition as measured by the DSB test. However, compared to the three previous studies mentioned, my study used different measures of street connectivity, retail land use, and transit availability, and thus, is unique in that it corroborated results using alternative but similar BE measures.

The remaining findings in my study are novel as the specific BE measures or effect modifiers have not been investigated to date or because the findings are contradictory with past studies. Unlike the paper by Martinez et al[112], generally I found a significantly negative association between population density and cognition. No previous studies have examined whether neighborhood social or walking destination densities are associated with cognition in older adults, and in the overall sample, there were no significant associations using the four cognitive measures or the ¼-mile, ½-mile, or 1-mile social and walking destination density measures. Additionally, in the overall sample, proportion of land dedicated to residential uses was generally not associated with cognition. The exception was the significant and positive association between the 1-mile measure of proportion of land dedicated to residential uses and DS score. Two known studies examined effect modification of the BE-cognition association, finding that the association between increased distance to community resources and cognition was not modified by living alone[90] but that presence of institutional resources was associated with better cognition among whites but worse cognition among African Americans.[47] Therefore, the findings for effect modification of the BE-cognition association by individual-level education, race/ethnicity, sex, APOE ε4 genotype, and sedentary behavior had been previously unexplored in the literature and represent the most intriguing and unique findings from my study.

Though this study was not specifically designed to address the methodological concerns surrounding the definition of neighborhoods and the measurement of the BE, because it involved the secondary use of data, these considerations are important for the design of future studies of the same topic. A few BE-cognition associations were statistically significant and consistently in the same direction regardless of whether the neighborhood was defined as ¼-mile, ½-mile, or 1-mile surrounding the participant's home. Yet, frequently the statistical significance of the associations varied depending on whether the neighborhood was defined using the ¼-, ½-, or 1-mile measure. Therefore, as noted by other researchers[97,186], studies must be careful in how the neighborhood is defined and until a sufficient number of studies have been conducted to suggest the best neighborhood definitions for a given BE characteristic, research studies should continue to perform sensitivity analyses using multiple definitions. Only when there is a body of evidence from multiple studies and cohorts can there be some recommendation on the best methods to define neighborhoods.

Likewise, it is not clear that the BE features that are frequently associated with PA, as an example, are the same as are linked to cognition. Often, new studies of the BE are based on BE measures that have been be associated with health outcomes in the extant literature. However, some BE features may be related to PA or other health outcomes but not cognition, and vice versa. Thus, more work is needed to investigate the aspects of the BE that have the most impact on cognition in older adults, and among those, the most valid and reliable ways of measuring the BE characteristics. For example, studies have found that greater availability of green and open spaces are associated with increases in PA among older adults.[190,191] However, studies aimed at the BE-cognition association may ultimately be targeting a different causal mechanism than the mechanism relating BE and PA. Although the association between BE and cognition may in part relate to PA changes, it may also related to changes in stress or social engagement. Therefore, the association between neighborhood park space and PA may relate more specifically to park space with PA options such as walking trails. In contrast, the association between neighborhood park space and cognition may relate more specifically to the dispersion of green space throughout the neighborhood, which may decrease stress. Continuing with this example, the method of measuring greenspace and park space in the neighborhood would need to be more specific to the outcome of interest.

5.2. Study Limitations

A number of weaknesses of this study must be noted. The first is the cross-sectional nature of the analysis. Longitudinal cognitive measures were not available, and in their absence, this study was not able to provide evidence for a causal association between the BE and condition. Also, the MESA data were not collected to study the BE and cognition specifically, and therefore, the pre-existing BE and cognitive measures may not be ideally suited for that particular purpose. In addition to the measures of PA and trust of neighbors, future studies should investigate whether factors such as air pollution and stress are mediators of the BE-cognition associations. Furthermore, longitudinal and lifecourse measures of the BE will be needed to assess whether early-life, mid-life, late-life BE exposures, or a combination of the three, are the most important to consider in relation to cognition in older adults. Lifelong residential mobility but also residential moves at older ages will be important to consider in future studies, particularly if individuals move between substantially different BEs over time. Although the neighborhood BE was hypothesized to be the most pertinent environment to examine with regards to older adults, because they are typically retired and spend more time closer to home, other environments may also be important to consider. For instance, it may be important to examine the environment surrounding workplaces among older adults who continue to work or volunteer, but also neighborhoods adjacent to home neighborhoods (e.g., if a low SES neighborhood is surrounded by many high or low SES neighborhoods).

It is possible that my results were biased due to sample selection, self-selection into neighborhoods, or misclassification. The MESA sample was derived from population-based methods, which is a strength, but the six US sites may represent different BEs than other regions of the US; thus, threatening external validity. Sample selection of the analytic sample may have also biased the results, if characteristics of the excluded individuals are associated with both the BE and cognitive measures. The Exam 1 participants that were excluded had lower levels of education, were less often married, were more often of non-white race, and had lower family income, and therefore, excluding these participants may have biased the results. While the possibility of self-selection into neighborhoods is frequently mentioned as a weakness of many BE and health studies, there is some evidence that this may not cause significant bias[152], although this should be examined specifically for studies of the BE and cognition. Finally, if the BE or cognitive measures did not accurately measure the desired constructs, then the results may have been affected by misclassification bias. For example, this would have occurred if the measure of distance to nearest train stop did not accurately and reliably measure transit accessibility or if the DS test was not a valid and reliable measure of processing speed.

5.3. Future studies

In my study, I examine a small portion of the potential associations between the BE and cognition, as outlined in my conceptual model (Figure 1.2). Although I included measures of accessibility, land use, transit availability, and population density, there are many other measures that could be explored in future studies, including measures of park and green space, housing, and design (e.g., condition of public spaces). In addition, future studies could investigate the association between cognition and additional measures of accessibility, land use (e.g., entropy), transportation features (e.g., sidewalk availability), and density (e.g., housing density). The cognitive measures used in this study included a brief cognitive measure, and measures of short-term and working memory and processing speed. Future studies would benefit by examining better overall cognitive measures compared to the CASI, as well as measures of other cognitive domains that may be differentially affected by BE exposures, such as memory, executive function, and visual-spatial function.

Similarly, future studies could explore additional moderators and mediators of the BE-cognition association. Plausible moderators that were not examined in my study include age, time living in the neighborhood, and physical, cognitive, and health status (e.g., disability). Certain aspects of the BE may have a stronger influence on cognition among individuals who are older, who have lived less or more time in the neighborhood, or who have certain physical or health conditions. For example, older individuals and individuals with physical disabilities may be more affected by neighborhood sidewalks in poor condition. It is possible that in addition to individual-level moderators, two or more neighborhood-level characteristics have additive or multiplicative effects when an individual is exposed to them. For instance, individuals living in neighborhoods of with high population density and with higher levels of psychosocial hazards (e.g., graffiti, broken windows, loitering) may have worse cognition than individuals living in neighborhoods with none or only one of these characteristics. This dissertation study was not aimed at assessing mediators, and therefore, there are numerous potential mediators that future studies can investigate including air pollution exposures; quality of life measures; mental health measures of stress, anxiety, and depression; social measures of engagement, isolation, neighboring support, and trust in neighbors; and health-related behaviors including leisure-time and utilitarian PA, diet, and health care access.

New studies can build upon the methods in this study by using longitudinal BE and cognitive measures, to provide evidence for a causal association.[192] In particular, lifecourse approaches would help tease apart whether, in addition to early- or mid-life exposures and risk factors that are unrelated to the BE, long-term BE exposures are associated with differences in cognition in older adults. Studies are also needed to evaluate the objective and perceived neighborhood boundaries among older adults, and whether these definitions differ based on the BE and cognitive measures being examined. For instance, land use mix may be most important in the area immediately surrounding an individual's home, whereas the availability of green space could be important up to one mile from the home. A comparison of various definitions of the same BE features may help to clarify and expand upon some of the observed relationships in this study. As an example, future studies could investigate how different measures of transit accessibility (density of transit stops, distance to nearest stops, and accessibility of transit stops to the rest of the region) are associated with cognition in older adults.

5.4. Implications for urban planning

Although the results from my study are preliminary and only suggestive of an association between the BE and cognition, assuming my results are corroborated in future studies, there are a number of implications for urban planning. Firstly, although urban planning often includes a focus on issues of equity and vulnerable populations, additional attention is needed on older adults. A number of tools and resources[193] are available for planners to incorporate considerations of older adults in their planning decisions, such as American Planning Association's guide on multigenerational planning[194]. As the authors of this APA guide suggest, considerations of older adults need to be "deliberately" included in the planning process.

At least five parts of the comprehensive planning process may be informed by the results from my study: 1) Identifying problems, issues, and concerns; 2) visioning; 3) designing; 4) implementing; and 5) evaluating the implemented plan. The comprehensive planning process is used here for illustrative purposes because it is still used frequently in the US.

Identifying problems, issues, and concerns. The health and transportation, housing, and neighborhood needs of older adults, including minorities, needs to be incorporated into the planning process from inception. My study demonstrated that in the overall sample, the availability of increased retail use in the neighborhood may be important for maintaining cognition in older adults, and this information could be incorporated into the assessment of the evidence to date on the impact of the neighborhood BE on health of older adults. However, if my results are replicated, many BE factors associated with increased urban density may increase cognitive impairment among disadvantages populations through mechanisms such as stress, and thus, these issues will need to be weighed against the positives of increasing urban density such as increased PA levels. Given the rising population of older adults and the expected increase in prevalence of cognitive impairment, considerations of health outcomes such as cognition could be incorporated into urban planning decisions to help plan for the transportation and housing needs of the ever growing population of older adults. In addition, many communities face a growing population of minorities and immigrants, and thus, will need to consider how to plan for these unique populations. The results from my study suggest that increased urban density may be associated with worse cognition in immigrant populations, and thus planners will need to evaluate whether other environments or services can be provided to help counteract the potential negative impact or increased density on their cognition. Considerations of the increasing population of older adults and the projected public health and economic burden of cognitive impairment and dementia should be added to this stage of the planning process.

Visioning. Visioning is an opportunity for planners and politicians to work with the stakeholders and residents of a community to lay out a vision for the future, which could include comprehensive planning considerations including transportation, housing, businesses, and natural resources. Through increased involvement of older adults and immigrant populations in the visioning process, planners could get a sense of the types of neighborhoods and built environments that may encourage healthy behaviors and provide a perceived sense of safety and decreased stress, which may help inform planners on the types of BEs that influence cognition and health. Therefore, studies such as this may serve as inspiration to assess the perceptions of neighborhoods and BEs among older adults and minorities to inform the common vision.

Designing and setting goals, objectives, and policies. At the design phase, urban planners must take into consideration multiple needs and stakeholders, including older adults and minorities. The community residents may be involved during the design phase as well, in activities such as design charettes. Here too, urban planners can obtain a sense of and incorporate the types of environments that are desired by older adults, with the aim of reducing potential negative impacts and enhancing positive impacts of neighborhood BEs on cognition and other health outcomes. The types of neighborhood environments that are conducive to maintaining the cognition and health of older adults should also be included in the goals, objectives, and policy recommendations of the comprehensive plan. For example, a policy may emphasize the need for an increased number of retail establishments in the ½-mile immediately surrounding retirement housing.

Other programs could be planned to counteract some of the potentially negative impacts of the BE on the cognition and health of older adults, beyond potential changes to zoning and the physical environment. One such example is the “Village” model[195], in which grassroot organizations provide and connect older adults to transportation, social, housekeeping, and other community resources. Coupled with living in BEs that promote certain health behaviors and outcomes, provision of these types of services may help overcome any detrimental effect of increased urban density on cognition in older adults and minorities.

Implementing. As part of implementing a comprehensive plan, zoning laws may need to be amended to be consistent with the plan. Zoning is one mechanism to promote policies that allow aging in place and neighborhood BEs that would be beneficial to cognition and health of older adults. Additionally, as mentioned above, alternative mechanisms could be implemented, such as community programs like the “Village” model.

Evaluating. In evaluating whether the implemented plan addresses the needs of older adults, planners could work with public health professionals to determine if the resulting neighborhood BE is associated with cognition and health in ways consistent with the results of my study and similar studies. This evaluation would in turn inform future comprehensive plans, and future studies of the BE and cognition and health.

Overall, my results have some implications for the frequently advocated compact growth principles, which are aimed at reducing urban sprawl and are outlined as a major recommendation included in APA's Multigenerational Planning guide.[194] Although the extant literature provides evidence that increasing urban density is associated with positive health behaviors such as PA, my study suggests that a positive relationship is not necessarily present when focused on cognition. In particular, negative associations between increasing urban density (measured via multiple BE characteristics) and cognition were observed among Hispanic-Americans, who were primarily foreign born or did not speak English as their primary language. This suggests that current compact growth principles may have detrimental effects on the cognition of immigrant population and/or minorities, and that planners and public health professionals will need to consider issues of equity and the differential impact of the BE and planning policies on vulnerable populations in the future.[196] In addition, future comprehensive plans will need to consider these more complex implications to diverse populations and ultimately weigh the positive and negative effects of planning policies on health.

5.5. Conclusion

Overall, this study provides cross-sectional evidence for an association between the BE and cognition in older adults and for effect modification by multiple individual-level characteristics. Some of this study's central findings include the association between BE measures consistent with increasing urban density and worse cognition among Hispanics but not non-Hispanic whites and among APOE ε4 carriers but not non-carriers. My findings suggest that immigrant populations and individuals with a particular genetic susceptibility, specifically APOE ε4 carriers who are at higher risk of developing Alzheimer's disease, are more vulnerable to the potentially negative effect of increasing urban density. Additionally, when considering the overall sample, this study suggests that an increased number of retail establishments in the neighborhood are associated with better cognition, and the association is stronger for men than women. The BE and cognition relationship is extremely complex, and likely varies by multiple individual-level characteristics simultaneously and is associated with multiple biological/psychosocial mechanisms. Much more work is needed to provide evidence for a causal association between the BE and cognition[192], including providing evidence for a temporal ordering between BE exposures and cognition, reproducibility of findings across multiple studies, and evidence for plausible mechanisms. Nonetheless, this study provides a useful starting point to help guide future studies that will employ longitudinal and life course methods to determine the BE characteristics that are most strongly associated with cognition in older adults. The major implication for urban planning involves issues of equity, as this study suggests that increasing urban density may have a disproportionately negative effect on minorities. In the future, urban planners and public health professionals should evaluate how dense urban environments are associated with positive and negative health outcomes in diverse populations.

APPENDIX 2.1: PAPER 1 ABSTRACT

Context: Some evidence suggests that treating vascular risk factors and performing mentally stimulating activities may delay the onset of cognitive impairment in older adults. Exposure to a complex neighborhood environment may be one such mechanism to help delay cognitive decline.

Evidence acquisition: Pubmed, Web of Science, and Proquest Dissertation and Theses Global database were systematically reviewed, identifying 25 studies published from February 1, 1989-March 5, 2016 (data synthesized: May 3, 2015-October 7, 2016). The review restricted to quantitative studies focused on: 1) neighborhood social and built environment and cognition, and 2) ≥45-year old community-dwelling adults.

Evidence synthesis: The majority of studies were cross-sectional, US-based, and found at least one significant association. The diversity of measures and neighborhood definitions limited the synthesis of findings in many instances. Evidence was moderately strong for an association between neighborhood socioeconomic status (SES) and cognition and modest for associations between neighborhood demographics, design, and destination accessibility and cognition. Most studies examining effect modification found significant associations, with some evidence for effect modification of the neighborhood SES-cognition association by individual-level SES. No studies had low risk of bias and many tested multiple associations that increased the chance of a statistically significant finding. Considering the studies to date, the evidence for an association between neighborhood characteristics and cognition is modest.

Conclusions: Future studies should include longitudinal measures of the neighborhood characteristics and cognition, examine potential effect modifiers such as sex and disability, and

study mediators that may help elucidate the biological mechanisms linking neighborhood environment and cognition.

APPENDIX 2.2. CHARACTERISTICS OF THE 25 REVIEWED STUDIES

Paper	Sample characteristics			
	Age	Sex	Race/ethnicity	Sample (location)
Aneshensel et al[74]	55 to 65 years	Both	African American, Hispanic, Other, White	Health and Retirement Survey; (US, national study)
Basta et al[102]	65+ years	Both	Not provided	Cognitive Function and Ageing Study; (England and Wales, UK)
Boardman et al[103]	65+ years	Both	African American, White	Chicago Health and Aging Project; (Chicago, Illinois, US)
Brown et al[104]	70+ years	Both	Hispanics	Hispanic Elders' Behavioral Health Study (Miami, Florida, US)
Clarke et al[47]	50+ years	Both	African American, Hispanic, Other race/ethnicity, White	Chicago Community Adult Health Study (Chicago, Illinois, US)
Clarke et al[105]	65+ years	Both	African American, Other race, White	Chicago Health and Aging Project (Chicago, Illinois, US)
Deeg et al[106]	55-85 years	Both	Not provided	Longitudinal Aging Study Amsterdam (The Netherlands)
Espino et al[107]	65+ years	Both	Mexican Americans, European Americans	San Antonio Longitudinal Study of Aging (San Antonio, Texas, US)
Glass et al[108]	50-70 years	Both	Non-white race (including African American), White	Baltimore Memory Study (Baltimore, Maryland, US)
Kovalchik et al[109]	50+ years	Both	African American, Hispanic, Caucasian	Health and Retirement Study (US, national study)
Lang et al[110]	50+ years	Both	Unknown	English Longitudinal Study of Aging (England, UK)
Lee et al[111]	50-70 years	Both	African American/mixed, White	Baltimore Memory Study (Baltimore, Maryland, US)
Magaziner et al[90]	65+ years	Women	Not provided (mostly white)	Community sample (Baltimore, Maryland, US)

Martinez et al[112]	70+ years	Both	African American, White	Asset and Health Dynamics Among the Oldest Old Study (US, national study)
Meyer et al[113]	65+ years	Both	African American, White	Advanced Cognitive Training for Independent and Vital Elderly Study (Baltimore, Maryland; Birmingham, Alabama; Boston, Massachusetts; Detroit, Michigan; Indianapolis, Indiana; central Pennsylvania, US)
Murayama et al[114]	65+ years	Both	Asian	Community sample (Hatoyama, Saitama, Japan)
Rej et al[115]	65+ years	Both	African American, White	Maintenance Treatment in Late-life Depression III Study (Pittsburgh, Pennsylvania, US)
Sheffield et al[116]	65+ years	Both	Hispanics	Hispanic Established Populations for Epidemiologic Studies of the Elderly (Southwest US)
Shih et al[118]	65+ years	Women	African American, Hispanic, Other race, White	Women's Health Initiative Memory Study (US, national study)
Sisco et al[117]	65+ years	Both	African American, Other race, White	Advanced Cognitive Training for Independent and Vita Elderly Study (Baltimore, Maryland; Birmingham, Alabama; Boston, Massachusetts; Detroit, Michigan; Indianapolis, Indiana; central Pennsylvania, US)
Watts et al[120]	Mean of 75 years*	Both	Non-white, White	University of Kansas Medical Center sample (Kansas, US)
Wee et al[119]	60+ years	Both	Malay, Chinese, Indian, Other ethnicity	Community sample (Singapore)

Wight et al[92]	70+ years	Both	African American, Hispanic, Other race, White	Study of Assets and Health Dynamics Among the Oldest Old (US, national study)
Wu et al[122]	65+ years	Both	Not provided	Medical Research Council Function and Ageing Study (England, UK)
Zeki al Hazzouri et al[121]	60+ years	Both	Hispanics	Sacramento Area Latino Study (Sacramento, California, US)

Abbreviations: SES = socioeconomic status; TICS = Telephone Interview for Cognitive Status; UK = United Kingdom
* Did not provide age range

APPENDIX 2.3. RESEARCH METHODS OF THE 25 REVIEWED STUDIES

Reference	Sample size	Study type	Cognitive measure	Statistical method	Covariates
Aneshensel et al[74]	4,525	Cohort (P)	Continuous	Hierarchical linear regression	sex, age, married, employed, disabled, race/ethnicity, education, household wealth, household income, social integration, health conditions
Basta et al[102]	13,004	Cohort (P)	Categorical	Hierarchical logistic regression	age, sex, center, individual-level education, individual-level social class
Boardman et al[103]	1,655	Cohort (P)	Continuous	Multilevel linear regression	baseline cognition, race, education, age, sex, residential tenure, follow-up time, apolipoprotein E genotype
Brown et al[104]	273	Cohort (P)	Continuous	Structural Equation Modeling	age, education, income
Clarke et al[47]	949	Cohort (P)	Continuous	Multilevel linear regression	Age, gender, marital status, race/ethnicity, employment status, education, income, health status (index of health problems)
Clarke et al[105]	6,518	Cohort (P)	Continuous	Linear mixed model (growth curve)	sex, race, education, baseline income, years living in residence, individual's self-reported tendency to drive places, time-varying health status, physical activity, married, social support
Deeg et al[106]	2,540	Cohort (P)	Continuous	Linear regression	sex, age
Espino et al[107]	827	Cohort (P)	Categorical	Logistic regression	sex, age
Glass et al[108]	1,001	Cohort (P)	Continuous	Multilevel linear regression	age, sex, race/ethnicity, education, testing technician, testing in the evening

Kovalchik et al[109]	6,150	Cohort (P)	Continuous	Linear mixed model	age, sex, race/ethnicity, retired, education, wealth/total assets, married, body mass index, health behaviors (e.g., smoking, physical activity), health status, depressive symptoms, health conditions, number of living children, number of children living with participant
Lang et al[110]	7,126	Cohort (P)	Continuous	Linear regression	age, sex, smoking, alcohol use, diabetes, other vascular problems, visual problems, hearing loss, health problems, depression (CESD)
Lee et al[111]	1,140	Cohort (P)	Continuous	Linear regression with generalized estimating equations	age, sex, race/ethnicity, education, household wealth, testing technician
Magaziner et al[90]	702	Cross-sectional random sample (P)	Continuous	Linear regression	age, education, time in neighborhood, functional ability
Martinez et al[112]	2,580	Cohort (P)	Continuous	Hierarchical linear regression	age, gender, race, education, marital status, income, wealth, health, baseline cognitive impairment, and imputed cognition.
Meyer et al[113]	2,438	Clinical trial	Continuous	Linear mixed model	black race, age, sex, education, intervention, living in major city, depression, baseline health
Murayama et al[114]	681	Cohort (P)	Categorical	Logistic regression	age, sex, married, socioeconomic status, lifestyle factors and comorbidities, functional capacity
Rej et al[115]	130	Clinical trial	Continuous	Cox proportional hazards model	none
Sheffield et al[116]	3,050	Cohort (P)	Both	Hierarchical linear and logistic regression	education, age, sex, married, US born, income, occupation, depression (CESD), diabetes, stroke

Shih et al[118]	6,137	Clinical trial	Continuous	Linear mixed model	age, race/ethnicity, education, household income, married hysterectomy, vascular factors, health behaviors, psychosocial factors
Sisco et al[117]	2,521	Clinical trial	Continuous	Structural Equation Modeling	age, education, sex, race
Watts et al[120]	64	Longitudinal convenience sample	Continuous	Linear regression	age, sex, education, baseline cognition, amount of walking
Wee et al[119]	909	Cross-sectional convenience sample	Both	Hierarchical linear and logistic regression	age, Chinese ethnicity, sex, married, education, larger social network, hearing impairment, fall in past year, level of independence, depression
Wight et al[92]	3,442	Cross-sectional random sample (P)	Continuous	Hierarchical linear regression	age, sex, education, married, race/ethnicity, household wealth and income, assistance with activities of daily living, depressive symptoms, psychiatric problems, health conditions
Wu et al[122]	2,424	Cohort (P)	Categorical	Multilevel logistic regression	age, gender, education, social class, chronic illnesses, and area deprivation
Zeki al Hazzouri et al[121]	1,789	Cohort (P)	Continuous	Hierarchical linear regression	age, sex, born in Mexico, education, income, diabetes, stroke, depression

Abbreviations: P = Random sample/population-based4

APPENDIX 2.4. STUDIES EXAMINING ASSOCIATIONS BETWEEN NEIGHBORHOOD SOCIAL CHARACTERISTICS AND COGNITION

Reference	Cognitive measure (cognitive domain)	Neighborhood measure (neighborhood definition)	Results
Aneshensel et al[74] (CS)	Telephone Interview for Cognitive Status (TICS) (brief cognitive test)	1) neighborhood disadvantage (O,C); 2) percent African American (O,S); 3) percent Hispanic) (O,S) (all based on US Census tract)	Neighborhood disadvantage and racial segregation were not associated with cognition when included in model together; neighborhood disadvantage was associated with cognition when included alone in model (data not shown)
Basta et al[102] (CS)	Mini Mental State Exam (MMSE) (brief cognitive test)	1) community-based Townsend deprivation score (O,C) (UK Enumeration district)	Increased neighborhood deprivation associated with increased odds of being cognitively impaired
Boardman et al[103] (L)	Cognitive function score derived from 4 separate tests; standardized z-scores (global cognition)	1) neighborhood social disorder (P,C) (neighbors' perceptions); 2) neighborhood disadvantage (O,C) (US Census tract)	Neighborhood social disorder associated with greater decline in cognition over time
Brown et al[104] (CS)	Cognitive function score derived from 3 separate tests (global cognition)	1) neighborhood climate scale (P,C) (participant perceptions)	Better neighborhood climate associated with better cognitive functioning
Clarke et al[47] (CS)	Modified TICS (brief cognitive test)	1) percent ≥65 years old (O,S); 2) neighborhood affluence (O,C); 3) socioeconomic disadvantage (O,C); 4) neighborhood disorder (O,C) (all based on US Census tract)	Neighborhood affluence and age structure associated with better cognition
Espino et al[107] (CS)	MMSE (brief cognitive test)	1) neighborhood type (barrio, transitional, suburb) (O,C) (researcher-defined neighborhood)	Living in a suburb was associated with better cognition

Glass et al[108] (CS)	Derived 7 cognitive domain scores based on 20 tests (language, processing speed, eye-hand coordination, executive functioning, verbal memory/learning, visual memory, visuospatial construction)	1) psychosocial hazards (12-item scale) (O,C) (community-defined neighborhood)	No association between neighborhood psychosocial hazards and cognition
Kovalchik et al[109] (L)	Modified TICS (brief cognitive test)	1) percent African American (O,S); 2) percent Hispanic (O,S) (both based on US Census tract)	Higher neighborhood Hispanic composition association with better cognition at baseline, but was not associated with change in cognition over time Neighborhood African American composition not associated with cognition at baseline or change in cognition over time
Lang et al[110] (CS)	Cognitive function score derived from 6 tests (global cognition)	1) Index of Multiple Deprivation, measuring 7 dimensions (e.g., employment deprivation, crime) (O,C) (UK Super Output Area Level)	Top 3 quintiles of neighborhood deprivation associated with worse cognition
Lee et al[111] (CS)	Derived 7 cognitive domain scores based on 20 tests (language, processing speed, eye-hand coordination, executive functioning, verbal memory/learning, visual memory, visuospatial construction)	1) psychosocial hazards (12-item scale) (O,C) (community-defined neighborhood)	Neighborhood psychosocial hazards associated with eye hand coordination
Magaziner et al[90] (CS)	MMSE (brief cognitive test)	1) number of children in neighborhood (O,S); 2) number of relatives in neighborhood (O,S); 3) number of friends in neighborhood (O,S); 4) number of friendly neighbors (P,S) (all based on participant perceptions)	No association between number of children, relatives, and friends in neighborhood and friendly neighbors and cognition.

Martinez et al[112] (L)	TICS (brief cognitive measure)	1) percent African American (O,S); 2) percent with less than high school education (O,S); 3) percent unemployed (O,S); 4) percent on public assistance (O,S); 5) percent under poverty level (O,S); 6) percent ≥65 years old (O,S); 7) socioeconomic disadvantage (O,C) (all based on US Census tract)	An increased neighborhood percent of African Americans associated with worse cognition
Meyer et al[113] (L)	Derived 4 domain scores based on 11 tests (memory, reasoning, processing speed, everyday cognition)	1) socioeconomic position (SEP) (O,C); 2) percent minority (O,S) (both based on US Census tract)	Neighborhood SEP and percent minority were not associated with baseline memory, reasoning, or speed scores or changes over time.
Murayama et al[114] (L)	MMSE (brief cognitive test)	1) Homogeneity (similar age, SES, gender) (P,S) (participant perceptions)	No association between perceived neighborhood homogeneity and cognition
Rej et al[115] (L)	Conversion to MCI or dementia (no domain assessed)	1) median household income (O,S) (US Census tract)	No association between neighborhood median household income and conversion to MCI//dementia
Sheffield et al[116] (L)	MMSE (brief cognitive test)	1) economic status (O,C); 2) social disadvantage (O,C); 3) percent Mexican Americans (O,S) (all based on US Census tract)	Higher economic disadvantage associated with faster rate of cognitive decline over time; increased percent of Mexican Americans associated with lower odds of cognitive decline
Shih et al[116] (CS)	3MSE (modified MMSE) (brief cognitive test)	1) SES (O, C) (US Census tract)	No association between neighborhood SES and cognition at $p<0.05$
Sisco et al[117] (CS)	Derived 4 domain scores based on 11 tests (memory, reasoning, processing speed, everyday cognition); Vocabulary test (vocabulary)	Neighborhood socioeconomic position (SEP) (O,C) (US Census tract)	Neighborhood SEP predicted better cognition (vocabulary)
Wee et al[119] (CS)	MMSE (brief cognitive test)	1) neighborhood disadvantage (O,C); 2) neighborhood unemployment (O,C) (both based on Singapore block level)	Living in neighborhood with greater disadvantage was associated with worse cognition, but neighborhood unemployment rate was not associated with cognition

Wight et al[92] (CS)	TICS (brief cognitive test)	1) percent without high school degree (O,S); median income (O,S) (both based on US Census tract)	A greater neighborhood percent with no high school degree was associated with worse cognition
Wu et al[122] (CS)	Cognitive impairment (MMSE≤25) (brief cognitive test); dementia based on Geriatric Mental Status and an algorithm of Automatic Geriatric Examination (no cognitive domain)	1) deprivation (O,C); 2) crime (O,C) (both based on UK Lower-layer Super Output Area)	Neighborhood deprivation and crime were not associated with cognition
Zeki Al Hazzouri et al[122] (L)	3MSE (brief cognitive test)	1) SEP (O,C) (US Census tract)	No association between neighborhood SEP and baseline cognition or cognitive decline at $p<0.05$ after adjusting for all covariates

Abbreviations: CS = cross-sectional; L = Longitudinal; O = Objective measure; P = perceived measure; C = composite measure; S = non-composite, single measure; MMSE = Mini Mental State Exam; TICS = Telephone Interview for Cognitive Status; SEP = socioeconomic position; UK = United Kingdom

APPENDIX 2.5. STUDIES EXAMINING ASSOCIATIONS BETWEEN NEIGHBORHOOD BUILT ENVIRONMENT CHARACTERISTICS AND COGNITION

Reference	Cognitive measure (cognitive domain)	Neighborhood measure	5Ds[a]	Results
Clarke et al[47] (CS)	Modified Telephone Interview for Cognitive Status (TICS) (brief cognitive test)	1) presence of recreational center (O,S,A); 2) presence of institutions (O,S,A); 3) park area (O,S,G) (all based on US Census tract)	Destination; Density	No association between neighborhood measures (as main effects) and cognition
Clarke et al[105] (L)	Cognitive function score derived from 4 separate tests (global cognition)	1) presence of community center (O,S,A); 2) access to transit (O,S,A); 3) presence of pedestrian facilities (O,S,A); 4) discontinuous sidewalks (O,S,A); 5) public spaces in poor condition (O,S,A) (all based on US Census block group)	Destination; Distance to transit; Design	Individuals in neighborhoods with a community center or transit stop or in neighborhoods in better condition had slower cognitive decline; neighborhoods with crosswalks or discontinuous sidewalks were not associated with cognition
Magaziner et al (CS)[90]	Mini Mental State Exam (MMSE) (brief cognitive test)	1) distance to community resources (i.e., averaged 6 distances to: convenience/grocery stores, supermarket, pharmacy, public sitting areas, bus stop, medical facility/bank) (P,C,SR) (participant perceptions)	Destination	Increased number of blocks to community resources associated with better cognition
Martinez et al[112] (L)	TICS (brief cognitive test)	1) population density (O,S,G) (US Census tract)	Density	Neighborhood population density was not associated with cognition
Watts et al[120] (L)	MMSE (brief cognitive test); 2 domain scores based on 6 tests (verbal memory, attention)	1) street connectivity (O,S,G); 2) integration (O,S,G) (both based on ½ mile radius around participant's home)	Design	Higher neighborhood integration was associated with poorer baseline cognition and greater cognitive decline over 2 years; lower street connectivity was associated with poorer baseline cognition and higher street connectivity was associated with slower cognitive decline over 2 years

Wu et al[122] (CS)	Cognitive impairment (MMSE≤25) (brief cognitive test); dementia based on Geriatric Mental Status and an algorithm of Automatic Geriatric Examination (no domain)	1) land use entropy (O,S,G); 2) natural environment (O,S,G) (both based on UK Lower-layer Super Output Area)	Diversity; Density	Higher land use mix associated with decreased odds of dementia; higher percent of natural environment associated with increased odds of dementia and cognitive impairment

Abbreviations: CS = cross-sectional; L = Longitudinal; O = Objective measure; P = perceived measure; C = composite measure; S = non-composite, single measure; A = data from observation/audit; G = government records / local administrative data; SR = self-reported by participants; MMSE = Mini Mental State Exam; TICS = Telephone Interview for Cognitive Status; UK = United Kingdom

APPENDIX 2.6. STUDIES EXAMINING EFFECT MODIFICATION BETWEEN NEIGHBORHOOD SOCIAL AND BUILT ENVIRONMENT CHARACTERISTICS AND COGNITION

Reference	Cognitive measure (cognitive domain)	Neighborhood measure (neighborhood definition)[a]	Potential effect modifier	Results
Aneshensel et al[74] (CS)	Telephone Interview for Cognitive Status (TICS) (brief cognitive test)	1) neighborhood disadvantage (O,C); 2) percent African American (O,S); 3) percent Hispanic (O,S) (all based on US Census tract)	Individual-level: wealth, education, race	Neighborhood disadvantage associated with worse cognition among those with little personal wealth, no effect on those with higher personal wealth. Percent of African Americans in neighborhood was associated with slight decline in cognition among those with little education and was associated with improved cognition among those with higher education.
Basta et al[102] (CS)	Mini Mental State Exam (MMSE) (brief cognitive test)	1) community-based Townsend deprivation score (O,C) (UK Enumeration district)	Individual-level: education, social class	Increasing area deprivation was associated with greater cognitive impairment, but this association was weaker among those with lower education
Boardman et al[103] (L)	Cognitive function score derived from 4 separate tests; standardized z-scores (global cognition)	1) neighborhood social disorder (P,C) (neighbors' perceptions) (US Census tract)	Individual-level: apolipoprotein E (APOE) ε4 carrier status	APOE ε4 effect on cognition strongest in neighborhoods with low social disorder
Brown et al[104] (CS)	Cognitive function score derived from 3 separate tests (global cognition)	1) neighborhood climate scale (P,C) (participant perceptions)	Individual-level: sex	No difference in the relationship between neighborhood climate and cognition by sex

Clarke et al[47] (CS)	Modified TICS (brief cognitive test)	1) percent ≥65 years old (O,S); 2) presence of institutions (O,S) (both based on US Census tract)	Individual-level: time living in neighborhood, race/ethnicity	Residents in neighborhoods with more older adults had better cognition among those living in the neighborhood 6-10 years and worse cognition among those living in a neighborhood 10 or more years; living in a neighborhood with a high density of institutional resources was associated with better cognition among whites, and increased institutional resources had negative impact on cognition among blacks
Deeg et al[106] (CS)	MMSE (brief cognitive test)	1) income (O,C)	Individual-level: income	Among older adults living in high income neighborhoods, those with lower individual incomes had worse cognition than those with higher incomes. Among older adults with higher personal income, those living in lower income neighborhoods had worse cognition compared to those in high income neighborhoods.
Glass et al[108] (CS)	Derived 7 cognitive domain scores based on 20 tests (language, processing speed, eye-hand coordination, executive functioning, verbal memory/learning, visual memory, visuospatial construction)	1) psychosocial hazards (12-item scale) (O,C) (community-defined neighborhood)	Individual-level: tibia lead level	Individuals with higher neighborhood psychosocial hazards and increased lead levels had worse cognition in the language, processing speed, and executive functioning domains.
Kovalchik et al[109] (L)	Modified TICS (brief cognitive test)	1) percent African American (O,S); 2) percent Hispanic (O,S) (both based on US Census tract)	Individual-level: race/ethnicity	No effect modification of the association between neighborhood racial composition and cognition by individual-level race/ethnicity.

Lang et al[110] (CS)	Cognitive function score derived from 6 tests (global cognition)	1) Index of Multiple Deprivation, measuring 7 dimensions (e.g., employment deprivation, crime) (O,C) (UK Super Output Area Level)	Individual-level: sex	Neighborhood deprivation was not associated with cognition in men <70 years old, but was among men ≥70 years and women <70 and ≥70 years old
Lee et al[111] (CS)	Derived 7 cognitive domain scores based on 20 tests (language, processing speed, eye-hand coordination, executive functioning, verbal memory/learning, visual memory, visuospatial construction)	1) psychosocial hazards (12-item scale) (O,C) (community-defined neighborhood)	Individual-level: APOE ε4 carrier status	APOE ε4 carriers in most psychosocially hazardous neighborhoods had significantly worse cognition than ε4 non-carriers in lower 3 quartiles of neighborhood level of psychosocial hazards
Magaziner et al[90] (CS)	MMSE (brief cognitive test)	1) number of children in neighborhood (O,S); 2) number of relatives in neighborhood (O,S); 3) number of friends in neighborhood (O,S); 4) number of friendly neighbors (P,S) (all based on participant perceptions)	Individual-level: Living alone	No effect modification of the association between community resources and cognition by living alone
Shih et al[116] (CS)	3MSE (modified MMSE) (brief cognitive test)	1) SES (O, C) (US Census tract)	Individual level: age, race, education; Household level: income	Neighborhood SES was associated with better cognition among younger participants
Wight et al[92] (CS)	TICS (brief cognitive test)	1) percent without high school degree (O,S) (US Census tract)	Individual level: education	Cognition was worse among individuals with lowest education and the lowest neighborhood education level

Abbreviations: CS = cross-sectional; L = Longitudinal; SES = socioeconomic status; O = Objective measure; P = perceived measure; C = composite measure; S = non-composite, single measure; MMSE = Mini Mental State Exam; TICS = Telephone Interview for Cognitive Status; UK = United Kingdom

APPENDIX 3.1. PAPER 2 ABSTRACT

Background: Cognitive impairment, present in ≥10% of older adults, is associated with lower quality of life and increased risk of nursing home placement. Studies suggest that neighborhoods can shape health behaviors and outcomes, such as cognition and behaviors like physical activity that impact cognition. Older adults may be particularly vulnerable to the neighborhood environment because they may have a smaller range of routine travel and thus an increased exposure to proximal environments.

Objectives: We aimed to examine whether multiple neighborhood built environment (BE) characteristics are cross-sectionally associated with cognition in a diverse sample of older adults, and whether the associations between BE characteristics and cognition vary by individual-level education or race/ethnicity.

Methods: The sample included 4,123 Exam 5 participants (2010-2012) of the population-based Multi-Ethnic Study of Atherosclerosis (MESA). Multivariable linear regression with generalized estimating equations was used to examine the BE and cognition associations and effect modification. The four cognitive measures included: Cognitive Abilities Screening Instrument (CASI), a brief cognitive test; Digit Span Forward and Backward (DSF, DSB), measures of short term and working memory, and Digit Symbol (DS), a measure of processing speed.

Results: Increased distance to bus and train stations were associated with worse cognition, although the effect sizes were very small. While increased intersection and population density were associated with worse cognition, increased land dedicated to retail establishments was associated with better cognition. Education was an effect modifier but the effect size was small. On the other hand, race/ethnicity was a significant effect modifier of multiple BE-cognition associations.

Conclusions: A number of neighborhood BE characteristics were cross-sectionally associated with cognition. Future studies should investigate the BE-cognition association using longitudinal BE and cognitive measures as well as measures that evaluate other cognitive domains (e,g, executive function). Additional mediation and moderation analyses are needed to elucidate the underlying mechanisms and other possible effect modifiers, such as sex and physical disability.

APPENDIX 3.2. NEUROPSYCHOLOGICAL TEST SCORES AT EXAM 5

	CASI		DSF		DSB		DS	
Characteristic	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Age at exam 5								
45-54	72	91.2 (5.6)	72	10.2 (2.6)	72	6.2 (2.6)	66	63.2 (12.8)
55-64	1426	90.7 (6.0)	1421	10.1 (2.8)	1421	6.1 (2.5)	1308	59.6 (17.2)
65-74	1332	89.4 (6.3)	1329	9.8 (2.7)	1329	5.8 (2.4)	1228	52.4 (15.5)
75-84	1047	87.7 (6.2)	1044	9.6 (2.6)	1044	5.5 (2.1)	945	44.5 (15.0)
85 and older	246	85.7 (6.3)	244	9.2 (2.6)	244	5.3 (2.0)	217	38.2 (13.5)
Sex								
Male	1954	89.4 (6.3)	1949	10.0 (2.8)	1949	5.8 (2.3)	1778	51.0 (16.8)
Female	2169	89.1 (6.4)	2161	9.7 (2.7)	2161	5.8 (2.3)	1986	53.4 (17.6)
Education								
< High school degree	444	83.2 (5.5)	442	8.5 (3.1)	442	4.2 (1.8)	414	35.2 (14.0)
High school degree	706	87.3 (5.9)	702	9.4 (2.6)	702	5.2 (2.0)	653	47.6 (15.6)
Some college	1239	89.3 (6.0)	1235	9.8 (2.6)	1235	5.7 (2.2)	1117	52.8 (16.1)
Bachelor’s degree or higher	1728	91.5 (5.7)	1725	10.3 (2.6)	1725	6.5 (2.4)	1575	58.4 (15.9)
Race/ethnicity								
Non-Hispanic white	1781	91.8 (5.7)	1773	10.0 (2.4)	1773	6.5 (2.3)	1597	57.1 (15.9)
Non-white/Hispanic	2342	87.3 (6.1)	2337	9.6 (3.0)	2337	5.2 (2.2)	2167	48.8 (17.4)
Family income								
<$30,000/year	1200	86.9 (6.2)	1194	9.5 (3.1)	1194	5.2 (2.1)	1119	45.3 (16.7)
≥$30,000/year	2785	90.4 (6.1)	2779	10.0 (2.6)	2779	6.1 (2.4)	2535	55.7 (16.5)
At least one APOE ε4 allele								
Yes	1021	88.9 (6.6)	1017	9.6 (2.7)	1017	5.7 (2.3)	928	51.6 (17.5)
No	2847	89.4 (6.3)	2838	9.9 (2.8)	2838	5.8 (2.3)	2604	52.6 (17.2)

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol

APPENDIX 3.3. COMPARISON OF EXCLUDED PARTICIPANTS FROM EXAM 1 AND ANALYTIC SAMPLE

Characteristic	Exam 1 Exclusions	Analytic Sample	p-value
Sample size, n	2,691	4,123	NA
Male, n (%)	1259 (46.8%)	1954 (47.4%)	0.62
Education, n (%)			<0.0001
< High school degree	781 (29.2%)	444 (10.8%)	
High school degree	530 (19.8%)	706 (17.2%)	
Some college, no bachelor's degree	698 (26.1%)	1239 (30.1%)	
Bachelor's degree or higher	665 (24.9%)	1728 (42.0%)	
Married, n (%)	1470 (55.4%)	2649 (64.9%)	<0.0001
Race/ethnicity, n (%)			<0.0001
White/Caucasian	841 (31.3%)	1781 (43.2%)	
Chinese-American	325 (12.1%)	479 (11.6%)	
Black/African American	813 (30.2%)	1079 (26.2%)	
Hispanic	712 (26.5%)	784 (19.0%)	
Family income ≥$30,000/year at Exam 1, n (%)	1202 (47.6%)	2888 (71.9%)	<0.0001
At least 1 APOE ε4 allele, n (%)	693 (27.6%)	1021 (26.4%)	0.29

Abbreviations: APOE = apolipoprotein E; NA = not applicable

Number missing (Exam 1 excluded sample, analytic sample): APOE (n=434, n =255); income (n=273, n =138); education (n=23, n =6); marital status (n=74, n =39)

APPENDIX 3.4. COMPARISON OF ANALYTIC SAMPLE AND EXCLUDED PARTICIPANTS FROM EXAM 5

	Exam 5 Exclusions (n=593)		Analytic Sample (n=4,123)		
Characteristic	Total n	Statistics	Total n	Statistics	p-value
Cognitive test scores, mean (SD)					
CASI	468	66.1 (20.9)	4,123	89.2 (6.4)	<0.0001
DSF	467	8.1 (2.9)	4,110	9.8 (2.7)	<0.0001
DSB	467	3.8 (2.1)	4,110	5.8 (2.3)	<0.0001
DS	400	30.8 (19.7)	3,764	52.3 (17.3)	<0.0001
BE measures, mean (SD)					
Social destination density (1/2-mile)[a]	502	158.3 (202.2)	4123	142.8 (229.5)	0.15
Walking destination density (1/2-mile)[a]	502	89.7 (115.8)	4123	65.8 (104.3)	<0.0001
Intersection density (1/2-mile)[a]	502	0.81 (0.47)	4123	0.78 (0.52)	0.18
Proportion residential (1/2-mile)[a,b]	469	0.44 (0.16)	3848	0.47 (0.17)	0.0004
Proportion retail (1/2-mile)[a,b]	469	0.058 (0.050)	3848	0.047 (0.051)	<0.0001
Distance to nearest bus stop (m)	470	472 (2458)	3856	1128 (8788)	0.11
Distance to nearest train stop (m)	397	3693 (5999)	3233	5223 (12406)	0.02
Population density (1/2-mile)[a] (1000 persons/km^2)	502	10066 (11971)	4123	6743 (9594)	<0.0001

Abbreviations: APOE = apolipoprotein E; CES-D = Center for Epidemiologic Studies Depression scale; BMI = body mass index; PA = physical activity; COPD = chronic obstructive pulmonary disease; BP = blood pressure

[a] Measured within ½ mile radius of participant's home

[b] e.g., if proportion residential = 0.37, percent of the neighborhood that is residential = 37%

APPENDIX 3.5. NEIGHBORHOOD BUILT ENVIRONMENT CHARACTERISTICS OF OVERALL SAMPLE AND STRATIFIED BY INDIVIDUAL-LEVEL EDUCATION AND RACE/ETHNICITY

BE measure		n	Mean (SD)	25%	50%	75%	Range
Social destination density[a]	Total	4123	142.8 (229.5)	17.8	47.1	134.9	0.0-1671.7
	Low education	1150	116.4 (171.5)	19.1	45.8	120.9	0.0-1454.1
	High education	2967	153.2 (247.9)	17.8	47.1	148.8	0.0-1671.7
	Non-Hispanic White	1781	166.0 (282.7)	12.7	36.9	141.2	0.0-1604.3
	Chinese-American	479	77.3 (84.9)	30.5	54.7	98.0	0.0-896.9
	African-American	1079	124.7 (183.3)	20.4	54.7	127.2	0.0-1671.7
	Hispanic	784	155.1 (201.3)	20.4	50.9	269.7	0.0-1454.1
Walking destination density[a]	Total	4123	65.8 (104.3)	5.1	19.1	64.9	0.0-716.3
	Low education	1150	66.6 (99.5)	6.4	20.4	68.7	0.0-534.3
	High education	2967	65.7 (106.2)	3.8	17.8	62.3	0.0-716.3
	Non-Hispanic White	1781	63.8 (109.6)	2.5	15.3	56.0	0.0-716.3
	Chinese-American	479	43.3 (47.1)	11.4	26.7	61.1	0.0-338.4
	African-American	1079	57.5 (96.6)	3.8	15.3	42.0	0.0-623.4
	Hispanic	784	95.9 (120.3)	10.2	29.3	180.7	0.0-534.3
Intersection density[a]	Total	4123	0.78 (0.52)	0.44	0.67	1.00	0.00-4.87
	Low education	1150	0.75 (0.44)	0.46	0.70	0.94	0.00-3.51
	High education	2967	0.79 (0.55)	0.43	0.67	1.04	0.00-4.87
	Non-Hispanic White	1781	0.80 (0.61)	0.36	0.67	1.15	0.00-4.87
	Chinese-American	479	0.81 (0.43)	0.55	0.66	0.88	0.13-3.08
	African-American	1079	0.70 (0.47)	0.36	0.61	0.89	0.00-3.62
	Hispanic	784	0.82 (0.39)	0.54	0.76	1.03	0.01-3.51
Proportion residential[a]	Total	3848	0.47 (0.17)	0.35	0.47	0.59	0.0-0.94
	Low education	1101	0.46 (0.15)	0.34	0.46	0.57	0.02-0.91
	High education	2742	0.48 (0.17)	0.35	0.47	0.61	0.00-0.94
	Non-Hispanic White	1629	0.47 (0.17)	0.34	0.47	0.59	0.00-0.92
	Chinese-American	452	0.53 (0.17)	0.43	0.55	0.64	0.02-0.94
	African-American	1020	0.50 (0.17)	0.37	0.48	0.62	0.04-0.91
	Hispanic	747	0.42 (0.14)	0.31	0.41	0.52	0.02-0.91
Proportion retail[a]	Total	3848	0.047 (0.051)	0.002	0.026	0.085	0.000-0.303

	Low education	1101	0.047 (0.049)	0.003	0.026	0.086	0.000-0.268
	High education	2742	0.047 (0.052)	0.002	0.027	0.084	0.000-0.303
	Non-Hispanic White	1629	0.039 (0.051)	0.000	0.014	0.066	0.000-0.278
	Chinese-American	452	0.069 (0.054)	0.026	0.062	0.102	0.000-0.303
	African-American	1020	0.045 (0.049)	0.000	0.029	0.079	0.000-0.240
	Hispanic	747	0.053 (0.047)	0.007	0.046	0.095	0.000-0.196
Distance to nearest bus stop (m)	Total	3856	1128 (8788)	58	158	397	0-300582
	Low education	1103	1477 (9712)	71	159	380	0-147761
	High education	2748	990 (8394)	51	157	400	0-300582
	Non-Hispanic White	1633	1213 (10965)	60	170	452	0-300582
	Chinese-American	452	1283 (5442)	100	234	483	0-70304
	African-American	1021	563 (3181)	39	133	347	0-81647
	Hispanic	750	1621 (10156)	47	128	311	0-143381
Distance to nearest train stop (m)	Total	3233	5223 (12406)	498	2106	7341	7-326011
	Low education	934	6500 (13735)	556	3327	8858	0-172451
	High education	2294	4707 (11798)	486	1794	6237	6-326011
	Non-Hispanic White	1314	5561 (14682)	563	2397	8588	14-326011
	Chinese-American	452	5595 (9615)	1234	3083	5347	103-91460
	African-American	719	2024 (5476)	358	902	2273	42-104098
	Hispanic	748	7481 (13680)	372	4581	10074	7-168573
Population density[a] (persons/km^2)	Total	4123	6743 (9594)	1223	2767	6394	3 - 54483
	Low education	1150	7336 (10058)	1483	3014	6614	0-45288
	High education	2967	6523 (9407)	1109	2669	6349	9-54483
	Non-Hispanic White	1781	5549 (8501)	881	2083	5810	3-54483
	Chinese-American	479	3800 (2424)	2223	3447	4889	344-20590
	African-American	1079	7036 (9969)	1001	2797	6351	17-40819
	Hispanic	784	10851 (12421)	2012	3601	22096	36-46545

Abbreviations: BE = built environment

[a] Measured within ½ mile radius of participant's home

APPENDIX 3.6. CORRELATION BETWEEN BUILT ENVIRONMENT MEASURES

		Pearson correlation coefficient p-value							
BE measure	Variable	1	2	3	4	5	6	7	8
Social destination density[a]	1	-	**0.92** **<0.0001**	**0.62** **<0.0001**	-0.41 <0.0001	**0.63** **<0.0001**	-0.07 <0.0001	-0.22 <0.0001	**0.80** **<0.0001**
Walking destination density[a]	2	-	-	**0.61** **<0.0001**	-0.45 <0.0001	**0.68** **<0.0001**	-0.07 <0.0001	-0.23 <0.0001	**0.91** **<0.0001**
Intersection density[a]	3	-	-	-	-0.42 <0.0001	0.47 <0.0001	-0.08 <0.0001	-0.22 <0.0001	0.50 <0.0001
Proportion residential[a]	4	-	-	-	-	-0.33 <0.0001	-0.02 0.17	0.01 0.51	-0.38 <0.0001
Proportion retail[a]	5	-	-	-	-	-	-0.04 0.02	-0.20 <0.0001	0.62 <0.0001
Distance to nearest bus stop (m)	6	-	-	-	-	-	-	**0.92** **<0.0001**	-0.07 <0.0001
Distance to nearest train stop (m)	7	-	-	-	-	-	-	-	-0.24 <0.0001
Population density[a] (persons/km^2)	8	-	-	-	-	-	-	-	-

Abbreviations: BE = built environment

[a] Measured within ½ mile radius of participant's home

APPENDIX 3.7. UNADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT MEASURES AND COGNITIVE TEST SCORES

	Estimate[b] (95% CI)			
BE measure	CASI	DSF	DSB	DS
Social destination density[a]	**0.0026*** **	0.0002	**0.0009*** **	**0.0081*** **
	(0.0017, 0.0035)	(-0.0008, 0.0012)	**(0.0004, 0.0014)**	**(0.0042, 0.0119)**
Walking destination density[a]	**0.0033*** **	0.0004	**0.0011*** **	**0.0098** **
	(0.0016, 0.0050)	(-0.0011, 0.0018)	**(0.0008, 0.0013)**	**(0.0032, 0.0165)**
Intersection density[a]	0.14	0.01	**0.13* **	-0.02
	(-0.24, 0.52)	(-0.18, 0.19)	**(0.02, 0.25)**	(-1.29, 1.26)
Proportion residential[a]	0.38	0.81	0.33	4.52
	(-2.91, 3.68)	(-0.08, 1.70)	(-0.92, 1.57)	(-6.90, 15.94)
Proportion retail[a]	-1.58	1.59	-0.27	-0.75
	(-4.63, 1.47)	(-1.30, 4.49)	(-1.16, 0.61)	(-22.31, 20.80)
Distance to nearest bus stop (km)	0.0083	-0.0055	**-0.0095*** **	**-0.0264** **
	(-0.0136, 0.0302)	(-0.0139, 0.0029)	**(-0.0105, -0.0084)**	**(-0.0462, -0.0066)**
Distance to nearest train stop (km)	-0.0002	-0.0024	**-0.0077*** **	**-0.0183* **
	(-0.0304, 0.0300)	(-0.0087, 0.0039)	**(-0.0106, -0.0047)**	**(-0.0361, -0.0006)**
Population density[a] (1000 persons/km^2)	0.0084	-0.0140	0.0035	-0.0154
	(-0.0422, 0.0590)	(-0.0336, 0.0056)	(-0.0107, 0.0178)	(-0.1576, 0.1268)

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol

* Significant at alpha=0.05, ** significant at alpha=0.01, *** significant at alpha=0.001

[a] Measured within ½ mile radius of participant's home

[b] provide up to 4 decimal values as needed

APPENDIX 3.8. ADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT MEASURES AND COGNITIVE TEST SCORES, ¼-MILE MEASURES

	Adjusted estimate[b,c] (95% CI)			
BE measure (1/4-mile radius)	CASI	DSF	DSB	DS
Social destination density[a]	-0.0006	0.0001	-0.0002	0.0008
	(-0.0014, 0.0002)	(-0.0003, 0.0005)	(-0.0006, 0.0002)	(-0.0024, 0.0041)
Walking destination density[a]	-0.0002	0.0005	-0.0006	0.0013
	(-0.0018, 00014)	(-0.0004, 0.0014)	(-0.0013, 0.0002)	(-0.0040, 0.0066)
Intersection density[a]	**-0.30***	-0.02	-0.05	-1.13
	(-0.59, 0.01)	(-0.16, 0.13)	(-0.15, 0.06)	(-2.56, 0.29)
Proportion residential[a]	0.39	-0.34	0.16	1.23
	(-0.21, 0.99)	(-1.14, 0.45)	(-0.01, 0.32)	(-1.47, 3.93)
Proportion retail[a]	1.14	**1.83***	-0.12	**6.12****
	(-1.43, 3.70)	(0.22, 3.44)	(-0.99, 0.74)	(1.59, 10.65)
Population density[a] (1000 persons/km^2)	**-0.0141***	0.0023	0.0011	0.0235
	(-0.0269, -0.0014)	(-0.0101, 0.0148)	(-0.0063, 0.0084)	(-0.0677, 0.1148)

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol

Boldface indicates statistical significance (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, sex, race/ethnicity, income, married, presence of at least 1 APOE ε4 allele, and neighborhood SES

[c] provide up to 4 decimal values as needed

APPENDIX 3.9. ADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT MEASURES AND COGNITIVE TEST SCORES, 1-MILE MEASURES

	Adjusted estimate[b,c] (95% CI)			
BE measure (1-mile radius)	CASI	DSF	DSB	DS
Social destination density[a]	-0.0010	0.0003	0.0001	0.0024
	(-0.0030, 0.0011)	(-0.0005, 0.0012)	(-0.0009, 0.0010)	(-0.0028, 0.0076)
Walking destination density[a]	-0.0023	0.0008	0.0000	0.0004
	(-0.0060, 0.0014)	(-0.0013, 0.0028)	(-0.0019, 0.0020)	(-0.0058, 0.0065)
Intersection density[a]	-0.42	0.0177	-0.03	-0.08
	(-0.89, 0.05)	(-0.17, 0.21)	(-0.23, 0.17)	(-0.95, 0.78)
Proportion residential[a]	0.14	-0.45	0.10	**2.86***
	(-1.06, 1.34)	(-1.37, 0.47)	(-0.31, 0.51)	(0.12, 5.60)
Proportion retail[a]	1.08	**2.63****	-0.0076	**6.52*****
	(-8.32, 10.48)	(0.86, 4.40)	(-1.8313, 1.8160)	(3.37, 9.67)
Population density[a] (1000 persons/km^2)	-0.0221	0.0086	**0.0124****	0.0003
	(-0.0479, 0.0038)	(-0.0197, 0.0368)	(0.0043, 0.0204)	(-0.0870, 0.0877)

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol

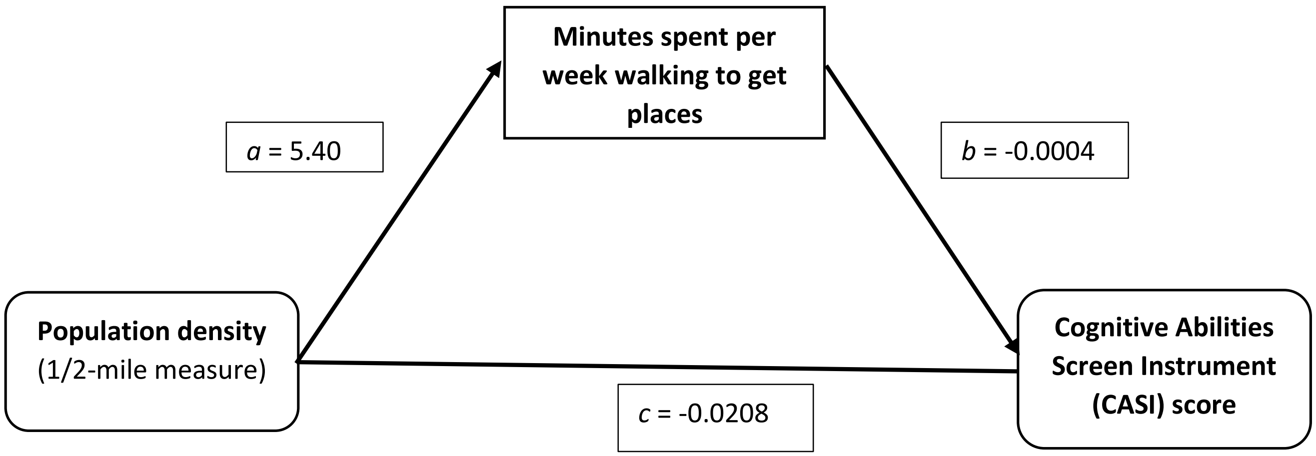
Boldface indicates statistical significance (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, sex, race/ethnicity, income, presence of at least 1 APOE ε4 allele, and neighborhood SES

[c] provide up to 4 decimal values as needed

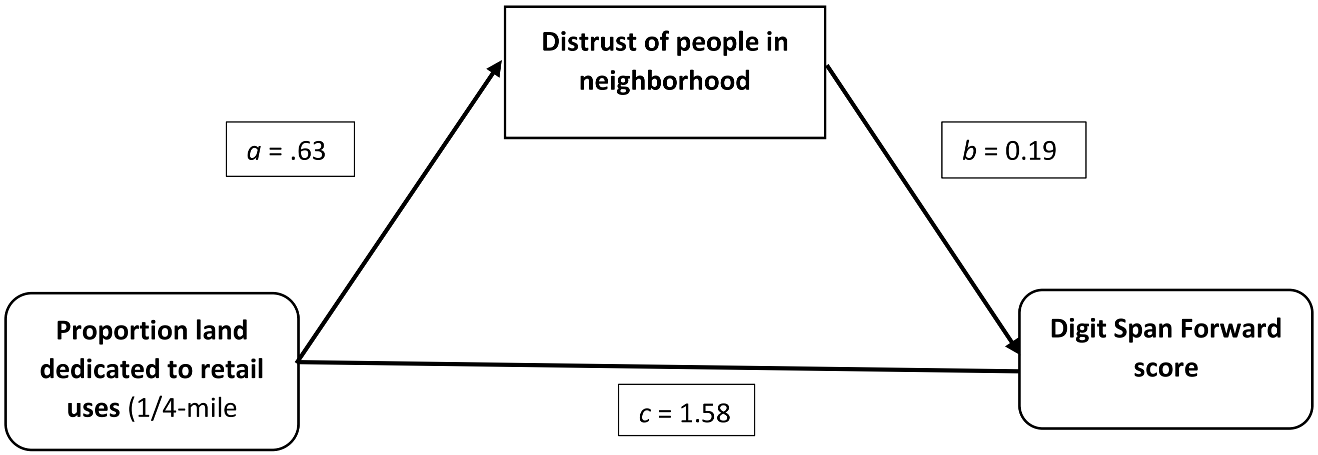
APPENDIX 3.10. MEDIATION OF ASSOCIATION BETWEEN POPULATION DENSITY AND COGNITIVE ABILITIES SCREENING INSTRUMENT SCORE



Indirect effect estimate: -0.0022 (95% CI: -0.0038, -0.0005)

Total effect estimate: -0.0208 + -0.0022 = -0.0230

APPENDIX 3.11. MEDIATION OF ASSOCIATION BETWEEN PROPORTION LAND DEDICATED TO RETAIL USE AND DIGIT SPAN FORWARD SCORE



Indirect effect estimate: 0.12 (95% CI: 0.02, 0.22)

Total effect estimate: 1.58 + 0.12 = 1.70

APPENDIX 3.12. PRIMARY LANGUAGE AND BIRTH COUNTRY BY RACE/ETHNICITY

	Participant's race			
Variable	White/Caucasian	Chinese-American	Black/African American	Hispanic
Birth country				
US	1658 (93.2%)	23 (4.8%)	983 (91.4%)	299 (38.1%)
Puerto Rico	0 (0.0%)	0 (0.0%)	0 (0.0%)	73 (9.3%)
Other country	121 (6.8%)	456 (95.2%)	92 (8.6%)	412 (52.6%)
Primary language				
English	1781 (100.0%)	101 (21.1%)	1079 (100.0%)	442 (56.4%)
Spanish	0 (0.0%)	0 (0.0%)	0 (0.0%)	342 (43.6%)
Chinese	0 (0.0%)	378 (78.9%)	0 (0.0%)	0 (0.0%)

Number missing birth country: white/Caucasian, n=2; Black/African American, n=4

APPENDIX 4.1. PAPER 3 ABSTRACT

The neighborhood built environment (BE) has been associated with cognition in older adults in the few studies conducted to date, but the direction of the associations is not always consistent with a priori hypotheses. Nevertheless, the existing evidence suggests that certain aspects of the BE, such as living in a neighborhood with a community center or transit stop and with higher street connectivity may be associated with better cognition. Additionally, previous studies focused on neighborhood social characteristics and cognition suggest that the associations may vary by an individual's demographic characteristics. This study aimed to investigate whether cross-sectional associations between neighborhood BE characteristics and cognition in older adults varied by individual-level characteristics: 1) sex; 2) apolipoprotein (APOE) ε4 genotype, a risk factor for Alzheimer's disease dementia; and 3) sedentary behavior. The analytic sample consisted of 4,123 participants who completed Exam 5 (2010-2011) of the Multi-Ethnic Study of Atherosclerosis. Multivariable linear regression models with generalized estimating equations were used to examine effect modification, controlling for age, sex, race/ethnicity, income, marital status, neighborhood socioeconomic status, presence of an APOE ε4 allele, and the first three principal components of genetic ancestry. We found that the association between multiple BE characteristics and cognition varied by sex, APOE ε4 genotype, and sedentary behavior, but not always in the hypothesized directions. A few positive associations were of note: 1) the association between increased proportion land dedicated to retail uses in the ¼-mile surrounding the home and better cognition was stronger in men than women; and 2) increased social destination density measured in the ¼-mile surrounding the home was associated with better cognition in those with low but not high sedentary behavior. Regardless of whether the ¼-mile, ½-mile, or 1-mile BE measures were used, consistent associations were observed between: 1)

increased social and walking destination density and increased population density and worse cognition among APOE ε4 carriers; and 2) increased population density and worse cognition among those with low sedentary behavior. Our study provides evidence that the BE is associated with cognition in older adults and that the associations are modified by individual-level characteristics. Future work is needed to elucidate the underlying mechanisms that may explain the differential susceptibility of individuals to the effects of the BE, which may include mechanisms related to stress, physical activity, and social engagement and support.

APPENDIX 4.2. UNADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT MEASURES AND COGNITION, STRATIFIED BY SEX

		Estimate (95% CI)			
BE characteristic	Sex	CASI	DSF	DSB	DS
Social destination density[a]	M	**0.0021**[†††]	**0.0002***	**0.0008**[†††]	**0.0096**[††, *]
		(0.0017, 0.0026)	**(-0.0009, 0.0012)**	**(0.0003, 0.0012)**	**(0.0030, 0.0162)**
	F	**0.0028**[†††]	**0.0003***	**0.0010**[†††]	**0.0063**[†††, *]
		(0.0013, 0.0043)	**(-0.0005, 0.0012)**	**(0.0006, 0.0015)**	**(0.0044, 0.0081)**
Walking destination density[a]	M	0.0024	**0.0002***	0.0007	**0.0151**[†††, **]
		(-0.0014, 0.0063)	**(-0.0016, 0.0019)**	(-0.0000, 0.0013)	**(0.0069, 0.0233)**
	F	**0.0034**[†††]	**0.0006***	**0.0013**[†††]	**0.0029****
		(0.0018, 0.0050)	**(-0.0006, 0.0017)**	**(0.0007, 0.0019)**	**(-0.0094, 0.0152)**
Intersection density[a]	M	**0.21**[†]	-0.08	**0.17**[†]	0.42
		(0.00, 0.41)	(-0.34, 0.17)	**(0.00, 0.35)**	(-0.64, 1.48)
	F	0.04	0.13	0.11	-0.67
		(-0.65, 0.73)	(-0.02, 0.28)	(-0.09, 0.32)	(-3.10, 1.75)
Proportion residential[a]	M	0.25	0.98	0.12	4.86
		(-3.41, 3.91)	(-0.18, 2.13)	(-1.30, 1.54)	(-6.99, 16.72)
	F	0.67	0.68	0.58	4.94
		(-2.65, 4.00)	(-0.16, 1.51)	(-0.54, 1.71)	(-6.38, 16.26)
Proportion retail[a]	M	1.41	0.99	0.24	**1.15***
		(-8.64, 11.46)	(-1.31, 3.29)	(-1.90, 2.39)	**(-27.91, 30.20)**
	F	**-5.25**[†]	2.31	-0.69	**-3.94***
		(-10.05, -0.45)	(-2.04, 6.66)	(-2.61, 1.23)	**(-22.60, 14.72)**
Distance to nearest bus stop (km)	M	0.0083	**-0.0061**[†]	**-0.0063**[†††, ***]	**-0.0255**[††]
		(-0.0203, 0.0369)	**(-0.0117, -0.0004)**	**(-0.0074, -0.0052)**	**(-0.0419, -0.0092)**
	F	0.0052	-0.0052	**-0.0172**[†††, ***]	-0.0256
		(-0.0079, 0.0184)	(-0.0209, 0.0106)	**(-0.0229, -0.0116)**	(-0.0638, 0.0126)
Distance to nearest train stop (km)	M	0.0022	-0.0042	**-0.0058**[††]	-0.0124
		(-0.0364, 0.0408)	(-0.0088, 0.0004)	**(-0.0095, -0.0022)**	(-0.0350, 0.0103)
	F	-0.0061	-0.0003	**-0.0122**[†††]	**-0.0257**[†††]
		(-0.0207, 0.0085)	(-0.0100, 0.0095)	**(-0.176, -0.0069)**	**(-0.0382, -0.0132)**
Population density[a] (1000 persons/km^2)	M	-0.0169	**-0.0232**[**]	-0.0096	0.0079

		(-0.0726, 0.0389)	**(-0.0474, 0.0010)**	(-0.0237, 0.0046)	(-0.1897, 0.2054)
	F	0.0167	**-0.0048****	0.0125	-0.0860
		(-0.0267, 0.0601)	**(-0.0167, 0.0071)**	(-0.0037, 0.0286)	(-0.1999, 0.0278)

Abbreviations: CI = confidence interval; BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; km = kilometer

* Significant difference between sexes at alpha=0.05, ** significant at alpha=0.01, *** significant at alpha=0.001

[†] Significant within strata (e.g., males) at alpha=0.05, [††] significant at alpha=0.01, [†††] significant at alpha=0.001

[a] Measured by ½ mile radius of participant's home

APPENDIX 4.3. UNADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT MEASURES AND COGNITION, STRATIFIED BY APOE GENOTYPE

		Estimate (95% CI)			
BE characteristic	APOE genotype	CASI	DSF	DSB	DS
Social destination density[a]	ε4+	**0.0017**[††] **(0.0005, 0.0028)**	-0.0000 (-0.0005, 0.0004)	**0.0008**[†††] **(0.0005, 0.0011)**	**0.0093**[†††] **(0.0067, 0.0120)**
	ε4-	**0.0027**[†††] **(0.0021, 0.0033)**	0.0004 (-0.0007, 0.0016)	**0.0010**[†††] **(0.0004, 0.0016)**	**0.0072**[††] **(0.0021, 0.0122)**
Walking destination density[a]	ε4+	-0.0004* (-0.0031, 0.0024)	-0.0003 (-0.0011, 0.0005)	**0.0011**[††, *] **(0.0004, 0.0018)**	**0.0138**[†] **(0.0025, 0.0252)**
	ε4-	**0.0038**[†††, *] **(0.0017, 0.0059)**	0.0010 (-0.0009, 0.0028)	**0.0011**[†††, *] **(0.0008, 0.0013)**	0.0055 (-0.0025, 0.0135)
Intersection density[a]	ε4+	-0.35 (-0.88, 0.18)	**-0.17**[††] **(-0.29, -0.04)**	0.24 (-0.05, 0.54)	-0.12 (-2.78, 2.55)
	ε4-	0.30 (-0.11, 0.70)	0.16 (-0.10, 0.42)	**0.15**[†] **(0.00, 0.30)**	-0.17 (-1.51, 1.17)
Proportion residential[a]	ε4+	1.52 (-2.73, 5.77)	0.80 (-0.18, 1.78)	0.28 (-0.87, 1.44)	3.24 (-9.44, 15.93)
	ε4-	-0.06 (-3.68, 3.56)	0.72 (-0.19, 1.62)	0.31 (-1.10, 1.72)	6.25 (-5.13, 17.62)
Proportion retail[a]	ε4+	-2.34 (-10.33, 5.66)	2.16 (-1.68, 5.99)	0.50 (-0.68, 1.69)	9.52 (-29.40, 48.44)
	ε4-	**-3.00**[†] **(-5.93, -0.07)**	2.26 (-2.81, 7.33)	-0.28 (-1.77, 1.21)	-8.20 (-25.93, 9.53)
Distance to nearest bus stop (km)	ε4+	**-0.03*** **(-0.06, 0.00)**	-0.0001 (-0.0109, 0.0108)	**-0.0142**[†††] **(-0.0198, -0.0085)**	-0.0198 (-0.1029, 0.0633)
	ε4-	**0.01*** **(-0.01, 0.03)**	-0.0073 (-0.0154, 0.0009)	**-0.0101**[†††] **(-0.0111, -0.0091)**	**-0.0299**[†††] **(-0.0440, -0.0159)**
Distance to nearest train stop (km)	ε4+	**-0.0288**[†] **(-0.0566, -0.0010)**	0.0023 (-0.0092, 0.0139)	-0.0029 (-0.0097, 0.0039)	-0.0061 (-0.0842, 0.0719)
	ε4-	0.0027 (-0.0264, 0.0318)	-0.0045 (-0.0114, 0.0024)	**-0.0095**[†††] **(-0.0129, -0.0061)**	**-0.0198**[††] **(-0.0329, -0.0067)**

Population density[a] (1000 persons/km^2)	ε4+	**-0.0674†††, **** **(-0.1025, -0.0323)**	**-0.0175*** **(-0.0447, 0.0097)**	0.0020 (-0.0090, 0.0130)	-0.0621 (-0.1952, 0.0710)
	ε4-	**0.0259**** **(-0.0383, 0.0901)**	**-0.0083*** **(-0.0216, 0.0050)**	0.0064 (-0.0094, 0.0223)	-0.0400 (-0.1726, 0.0926)

Abbreviations: CI = confidence interval; BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; km = kilometer; APOE = apolipoprotein

* Significant difference between APOE ε4 genotype at alpha=0.05, ** significant at alpha=0.01, *** significant at alpha=0.001

† Significant within strata (e.g., APOE ε4+) at alpha=0.05, †† significant at alpha=0.01, ††† significant at alpha=0.001

[a] Measured by ½ mile radius of participant's home

APPENDIX 4.4. UNADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT MEASURES AND COGNITION, STRATIFIED BY SEDENTARY BEHAVIOR

		Estimate (95% CI)			
BE characteristic	Sedentary behavior	CASI	DSF	DSB	DS
Social destination density[a]	Low	**0.0032**†††, * **(0.0020, 0.0044)**	**0.0006*** **(-0.0004, 0.0017)**	**0.0012**†††, *** **(0.0006, 0.0018)**	**0.0104**††, *** **(0.0040, 0.0167)**
	High	**0.0014**†††, * **(0.0008, 0.0020)**	**-0.0004*** **(-0.0013, 0.0005)**	**0.0003**†, *** **(0.0000, 0.0006)**	**0.0024**†, *** **(0.0001, 0.0048)**
Walking destination density[a]	Low	**0.0053**†††, * **(0.0029, 0.0076)**	0.0011 (-0.0000, 0.0022)	**0.0018**†††, *** **(0.0014, 0.0022)**	**0.0156**††, *** **(0.0053, 0.0259)**
	High	-0.0002* (-0.0026, 0.0022)	-0.0007 (-0.0026, 0.0013)	**-0.0002***** **(-0.0010, 0.0007)**	**-0.0022***** **(-0.0109, 0.0065)**
Intersection density[a]	Low	0.41* (-0.05, 0.88)	0.01 (-0.21, 0.23)	**0.17**† **(0.02, 0.32)**	**0.76***** **(-0.71, 2.24)**
	High	**-0.44**†, * **(-0.87, -0.01)**	0.00 (-0.40, 0.40)	0.06 (-0.20, 0.31)	**-1.72**†, *** **(-3.12, -0.32)**
Proportion residential[a]	Low	**-0.75**** **(-3.65, 2.15)**	0.84 (-0.13, 1.80)	-0.09*** (-1.32, 1.15)	2.97 (-10.85, 16.79)
	High	**2.17**** **(-1.06, 5.39)**	**0.87**† **(0.02, 1.72)**	**1.04**†, *** **(0.05, 2.03)**	**7.70**† **(0.62, 14.78)**
Proportion retail[a]	Low	-2.04 (-5.63, 1.55)	0.21 (-1.60, 2.02)	-0.32 (-2.27, 1.62)	-2.40 (-34.01, 29.22)
	High	-1.57 -11.70, 8.55	3.70 (-1.95, 9.35)	0.03 (-3.19, 3.25)	2.82 (-20.56, 26.19)
Distance to nearest bus stop (km)	Low	0.0131 (-0.0024, 0.0286)	**-0.0002*** **(-0.0043, 0.0040)**	**-0.0088**††† **(-0.0126, -0.0049)**	**-0.0469**†††, *** **(-0.0571, -0.0367)**
	High	0.0027 (-0.0215, 0.0270)	**-0.0096*** **(-0.0244, 0.0051)**	**-0.0098**††† **(-0.0145, -0.0051)**	**0.0037***** **(-0.0297, 0.0371)**
Distance to nearest train stop (km)	Low	0.0029 (-0.0308, 0.0366)	0.0015 (-0.0024, 0.0054)	**-0.0079**† **(-0.0142, -0.0017)**	**-0.0384**†††, *** **(-0.0505, -0.0263)**
	High	-0.0024 (-0.0256, 0.0208)	-0.0056 (-0.0165, 0.0053)	**-0.0075**††† **(-0.0105, -0.0044)**	0.0119*** (-0.0143, 0.0380)

Population density[a] (1000 persons/km^2)	Low	0.0296 (-0.0196, 0.0789)	-0.0074 (-0.0409, 0.0260)	**0.0116***** **(-0.0066, 0.0298)**	**0.0740***** **(-0.1084, 0.2564)**
	High	-0.0259 (-0.0736, 0.0217)	**-0.0200**††† **(-0.0303, -0.0097)**	**-0.0066***** **(-0.0195, 0.0062)**	**-0.1449**††,*** **(-0.2378, -0.0520)**

Abbreviations: CI = confidence interval; BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; km = kilometer

* Significant difference between APOE ε4 genotype at alpha=0.05, ** significant at alpha=0.01, *** significant at alpha=0.001

[†] Significant within strata (e.g., low sedentary behavior) at alpha=0.05, [††] significant at alpha=0.01, [†††] significant at alpha=0.001

[a] Measured by ½ mile radius of participant's home

APPENDIX 4.5. UNADJUSTED ASSOCIATION BETWEEN TOP THREE PRINCIPLE COMPONENTS OF ANCESTRY AND COGNITIVE MEASURES

	Unadjusted estimate (95% CI)			
Ancestry principle component[a]	CASI	DSF	DSB	DS
PC1	**-2.70***** (-3.28, -2.11)	-0.31 (-0.71, 0.10)	**-1.06***** (-1.22, -0.90)	**-8.56***** (-10.78, -6.34)
PC2	**-5.72***** (-6.44, -5.00)	1.33 (-0.21, 2.86)	**-0.75*** (-1.44, -0.07)	**-4.31***** (-6.81, -1.81)
PC3	**-6.20***** (-7.37, -5.03)	**-7.18***** (-9.71, -4.64)	**-4.09***** (-4.85, -3.33)	**-24.75***** (-35.08, -14.43)

Abbreviations: CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; PC = principle component

* Significant at alpha=0.05, ** significant at alpha=0.01, *** significant at alpha=0.001

[a] 272 participants are missing data on principle components of ancestry

APPENDIX 4.6. UNADJUSTED ASSOCIATION BETWEEN TOP THREE PRINCIPLE COMPONENTS OF ANCESTRY AND BUILT ENVIRONMENT MEASURES

	Unadjusted estimate[b] (95% CI)		
BE measure	PC1	PC2	PC3
Social destination density[a]	-59.1 (-155.2, 37.0)	-143.1 (-327.5, 41.4)	1.11 (-171.8, 174.0)
Walking destination density[a]	-24.8 (-53.7, 4.1)	-31.5 (-90.1, 27.1)	6.1 (-40.9, 53.2)
Intersection density[a]	-0.07 (-0.22, 0.08)	-0.16 (-0.43, 0.12)	-0.04 (-0.18, 0.09)
Proportion residential[a]	0.02 (-0.05, 0.09)	0.08 (-0.01, 0.18)	**-0.06****** (-0.08, -0.04)
Proportion retail[a]	-0.0021 (-0.0085, 0.0043)	0.0037 (-0.0127, 0.0200)	-0.0013 (-0.0106, 0.0081)
Distance to nearest bus stop (km)	-0.83 (-2.13, 0.47)	-1.73 (-5.22, 1.75)	**2.27*** (0.37, 4.17)
Distance to nearest train stop (km)	-2.22 (-4.45, 0.01)	-1.03 (-5.84, 3.77)	**3.89***** (2.02, 5.76)
Population density[a] (persons/km^2)	-427.6 (-1743.4, 888.1)	-2263.2 (-5736.7, 1210.3)	2028.0 (-453.1, 4509.1)

Abbreviations: PC = principle component of ancestry; CI = confidence interval; BE = built environment
* Significant at alpha=0.05, ** significant at alpha=0.01, *** significant at alpha=0.001
[a] Measured by ½ mile radius of participant's home
[b] Each model included BE measure as outcome variable and PC1, PC2, and PC3 variables as the three predictors

APPENDIX 4.7. EFFECT MODIFICATION OF ADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT AND COGNITION BY SEX USING ¼-MILE AND 1-MILE MEASURES

		¼-mile BE measure		1-mile BE measure	
BE measure	Cognitive test	Adjusted estimate (95% CI)[b,c]	M vs F: Interaction p-value	Adjusted estimate (95% CI)[b,c]	M vs F: Interaction p-value
Social destination density[a]	CASI	NA	NA	M: 0.0003 (-0.0013, 0.0020) **F: -0.0023 (-0.0042, -0.0005)***	<0.05
	DSF	M: -0.0001 (-0.0004, 0.0002) F: 0.0003 (-0.0002, 0.0009)	0.04	M: -0.0000 (-0.0008, 0.0007) F: 0.0010 (-0.0000, 0.0020)	<0.05
	DS	M: 0.0024 (-0.0018, 0.0065) F: 0.0000 (-0.0023, 0.0024)	<0.001	M: 0.0042 (-0.0022, 0.0106) F: 0.0015 (-0.0027, 0.0056)	<0.001
Walking destination density[a]	CASI	NA	NA	M: 0.0008 (-0.0025, 0.0041) **F: -0.0044 (-0.0080, -0.0009)***	<0.01
	DSF	M: 0.0001 (-0.0006, 0.0009) F: 0.0007 (-0.0006, 0.0021)	<0.05	M: -0.0006 (-0.0026, 0.0014) F: 0.0023 (-0.0001, 0.0046)	<0.01
	DS	M: 0.0058 (-0.0030, 0.0145) F: -0.0009 (-0.0032, 0.0014)	<0.001	M: 0.0068 (-0.0038, 0.0174) F: -0.0028 (-0.0089, 0.0033)	<0.001
Intersection density[a]	CASI	M: -0.06 (-0.42, 0.30) **F: -0.57 (-0.95, -0.20)****	<0.05	M: -0.15 (-0.73, 0.44) **F: -0.72 (-1.17, -0.27)****	<0.05
	DSF	**M: -0.24 (-0.39, -0.08)**** F: 0.16 (-0.03, 0.34)	<0.05	NA	NA
	DS	M: -0.64 (-2.19, 0.91) F: -1.44 (-3.30, 0.43)	<0.01	M: 0.21 (-1.30, 1.72) F: -0.10 (-1.20, 0.99)	<0.001
Proportion residential[a]	DSB	NA	NA	**M: -0.37 (-0.68, -0.06)*** **F: 0.60 (0.06, 1.13)***	<0.001
Proportion retail[a]	CASI	M: 3.75 (-0.67, 8.18) F: -1.77 (-4.26, 0.72)	<0.05	M: 7.07 (-0.53, 14.66) F: -3.46 (-12.12, 5.20)	<0.01
	DSB	M: 0.86 (-0.32, 2.04) F: -0.74 (-2.15, 0.66)	<0.01	NA	NA
	DS	**M: 9.42 (2.28, 16.56)**** **F: 4.55 (0.73, 8.38)***	<0.001	M: 2.54 (-14.20, 19.28) F: 11.86 (-3.33, 27.06)	<0.01

Population density[a]	CASI	NA	NA	M: -0.0073 (-0.0312, 0.0166) **F: -0.375 (-0.0679, -0.0072)***	<0.01
	DSF	M: -0.0061 (-0.0164, 0.0041) F: 0.0095 (-0.0106, 0.0297)	<0.01	M: -0.0183 (-0.0371, 0.0005) F: 0.0318 (-0.0123, 0.0760)	<0.01
	DS	M: 0.0719 (-0.0619, 0.2057) F: -0.0162 (-0.0809, 0.0484)	<0.001	M: 0.0511 (-0.1110, 0.2131) F: -0.0584 (-0.1411, 0.0242)	<0.001

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; NC = not calculated; interaction was not statistically significant at p<0.05

Boldface indicates statistical significance for that particular sex (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, race/ethnicity, income, married, presence of ≥1 APOE ε4 allele, neighborhood SES, and top three principle components of ancestry

[c] provide up to 4 decimal values as needed

APPENDIX 4.8. EFFECT MODIFICATION OF ADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT AND COGNITION BY APOE GENOTYPE USING ¼-MILE AND 1-MILE MEASURES

		¼-mile measure		1-mile measure	
BE measure	Test	Adjusted estimate (95% CI)[b,c]	ε4+ vs ε4-: p-value	Adjusted estimate (95% CI)[b,c]	ε4+ vs ε4-: p-value
Social destination density[a]	CASI	ε4+: **-0.0010 (-0.0019, -0.0000)*** ε4-: -0.0005 (-0.0012, 0.0002)	<0.05	ε4+: **-0.0020 (-0.0037, -0.0003)*** ε4-: -0.0008 (-0.0025, 0.0010)	<0.01
	DSF	NA	NA	ε4+: -0.0003 (-0.0013, 0.0006) ε4-: 0.0008 (-0.0001, 0.0017)	<0.05
Walking destination density[a]	CASI	ε4+: **-0.0015 (-0.0029, -0.0001)*** ε4-: -0.0000 (-0.0014, 0.0014)	<0.01	ε4+: **-0.0057 (-0.0073, -0.0040)***** ε4-: -0.0008 (-0.0045, 0.0030)	<0.001
	DSF	NA	NA	ε4+: -0.0017 (-0.0045, 0.0011) ε4-: **0.0020 (0.0000, 0.0041)***	<0.001
Intersection density	CASI	ε4+: **-0.72 (-1.28, -0.17)*** ε4-: -0.15 (-0.51, 0.21)	<0.01	NA	NA
	DSF	ε4+: **-0.26 (-0.41, -0.12)***** ε4-: 0.06 (-0.14, 0.26)	<0.001	ε4+: **-0.26 (-0.52, -0.01)*** ε4-: 0.14 (-0.10, 0.38)	<0.01
Proportion residential[a]	CASI	NA	NA	ε4+: 0.16 (-1.51, 1.82) ε4-: **0.40 (0.08, 0.72)***	<0.05
	DSF	ε4+: 0.30 (-0.32, 0.92) ε4-: -0.54 (-1.45, 0.37)	<0.01	NA	NA
Proportion retail	DS	ε4+: 0.35 (-2.36, 3.07) ε4-: -0.20 (-1.12, 0.72)	<0.05	NA	NA
	DSF	NA	NA	ε4+: -0.08 (-3.48, 3.32) ε4-: **3.83 (1.04, 6.62)****	<0.05
Population density[a]	CASI	ε4+: **-0.0449 (-0.0669, -0.0230)***** ε4-: -0.0024 (-0.0119, 0.0070)	<0.05	ε4+: **-0.0615 (-0.0917, -0.0313)***** ε4-: -0.0056 (-0.0300, 0.0189)	<0.001
	DS	ε4+: -0.0272 (-0.1671, 0.1127) ε4-: 0.0241 (-0.0519, 0.1001)	<0.001	ε4+: **-0.1277 (-0.2542, -0.0013)*** ε4-: 0.0178 (-0.0702, 0.1059)	<0.001

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; NC = not calculated; interaction was not statistically significant at $p<0.05$

Boldface indicates statistical significance for that particular APOE genotype (*$p<0.05$, **$p<0.01$, ***$p<0.001$)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, race/ethnicity, income, married, presence of ≥1 APOE ε4 allele, neighborhood SES, and top three principle components of ancestry

[c] provide up to 4 decimal values as needed

APPENDIX 4.9. EFFECT MODIFICATION OF ADJUSTED ASSOCIATION BETWEEN BUILT ENVIRONMENT AND COGNITION BY SEDENTARY BEHAVIOR

BE measure	Cognitive test	¼-mile measure: Adjusted estimate (95% CI)[b,c]	¼-mile measure: L vs H: Interaction p-value	1-mile measure: Adjusted estimate (95% CI)[b,c]	1-mile measure: L vs H: Interaction p-value
Social destination density[a]	DSF	**L: 0.0006 (0.0002, 0.0010)**** H: -0.0005 (-0.0011, 0.0002)	<0.01	NA	NA
	DSB	L: 0.0001 (-0.0005, 0.0006) H: -0.0004 (-0.0009, 0.0001)	<0.001	L: 0.0007 (-0.0003, 0.0016) H: -0.0006 (-0.0020, 0.0007)	<0.01
	DS	L: 0.0021 (-0.0024, 0.0065) H: -0.0007 (-0.0022, 0.0009)	<0.001	L: 0.0055 (-0.0022, 0.0132) H: -0.0031 (-0.0070, 0.0008)	<0.001
Walking destination density[a]	DSB	L: -0.0000 (-0.0008, 0.0008) H: -0.0008 (-0.0017, 0.0001)	<0.05	NA	NA
	DS	L: 0.0027 (-0.0025, 0.0080) H: 0.0006 (-0.0047, 0.0059)	<0.05	L: 0.0060 (-0.0044, 0.0164) H: -0.0071 (-0.0156, 0.0015)	<0.05
Proportion retail	DSB	L: 0.11 (-1.18, 1.40) H: 0.06 (-1.44, 1.56)	<0.001	NA	NA
Population density[a]	CASI	**L: -0.0251 (-0.0402, -0.0099)**** H: -0.0000 (-0.0172, 0.0172)	<0.001	**L: -0.0406 (-0.0595, -0.0218)***** H: -0.0008 (-0.0357, 0.0340)	<0.05
	DS	L: 0.0163 (-0.1120, 0.1445) H: 0.0071 (-0.0534, 0.0676)	<0.05	NA	NA

Abbreviations: BE = built environment; CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; NC = not calculated; interaction was not statistically significant at p<0.05

Boldface indicates statistical significance for that particular level of sedentary behavior (*p<0.05, **p<0.01, ***p<0.001)

[a] Measured by ½ mile radius of participant's home

[b] controlling for age, education, race/ethnicity, income, married, presence of ≥1 APOE ε4 allele, neighborhood SES, and top three principle components of ancestry

[c] provide up to 4 decimal values as needed

APPENDIX 4.10. PERCENT MISSING BUILT ENVIRONMENT MEASURES BY SEX, APOE GENOTYPE, AND SEDENTARY BEHAVIOR

BE measure	Male n=1954	Female n=2169	APOE ε4+ n=1021	APOE ε4- n=2847	APOE genotype unknown n=255	Low sedentary behavior n=2144	High sedentary behavior n=1950	Sedentary behavior missing n=29
Social destination density[a]	0%	0%	0%	0%	0%	0%	0%	0%
Walking destination density[a]	0%	0%	0%	0%	0%	0%	0%	0%
Intersection density[a]	0%	0%	0%	0%	0%	0%	0%	0%
Proportion residential[a]	7.1%	6.3%	6.1%	7.0%	5.5%	7.1%	6.1%	13.8%
Proportion retail[a]	7.1%	6.3%	6.1%	7.0%	5.5%	7.1%	6.1%	13.8%
Distance to nearest bus stop	6.9%	6.1%	6.0%	6.8%	5.1%	7.0%	5.7%	13.8%
Distance to nearest train stop	21.5%	21.7%	22.1%	21.4%	22.0%	20.5%	22.8%	24.1%
Population density[a]	0%	0%	0%	0%	0%	0%	0%	0%

Abbreviations: BE = built environment, APOE = apolipoprotein E

[a] Measured by ½ mile radius of participant's home

APPENDIX 4.11. PERCENT MISSING COGNITIVE TESTS BY SEX, APOE GENOTYPE, AND SEDENTARY BEHAVIOR

Cognitive measure	Male n=1954	Female n=2169	APOE ε4+ n=1021	APOE ε4- n=2847	APOE genotype unknown n=255	Low sedentary behavior n=2144	High sedentary behavior n=1950	Sedentary behavior missing n=29
CASI	0%	0%	0.0%	0%	0%	0%	0%	0%
DSF	0.3%	0.4%	0.4%	0.3%	0%	0.3%	0.4%	0%
DSB	0.3%	0.4%	0.4%	0.3%	0%	0.3%	0.4%	0%
DS	9.0%	8.4%	9.1%	8.5%	9.0%	8.3%	9.0%	13.8%

Abbreviations: CASI = Cognitive Abilities Screening Instrument; DSF = Digit Span Forward; DSB = Digit Span Backward; DS = Digit Symbol; APOE = apolipoprotein E

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