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Associations between neighborhood built environment and cognition vary by apolipoprotein E genotype: Multi-Ethnic Study of Atherosclerosis

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Abstract

We examined whether neighborhood built environment (BE) and cognition associations in older adults vary by apolipoprotein E (APOE) genotype, a genetic risk factor for Alzheimer's disease (AD). We conducted a cross-sectional analysis of 4,091 participants. Neighborhood characteristics included social and walking destination density (SDD, WDD), intersection density, and proportion of land dedicated to retail. Individuals were categorized as APOE ε2 (lower AD risk), APOE ε4

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(higher AD risk), or APOE ε3 carriers. Among APOE ε2 carriers, greater proportion of land dedicated to retail was associated with better global cognition, and greater SDD, WDD, intersection density, and proportion of land dedicated to retail was associated with better processing speed. These associations were not observed in APOE ε3 or ε4 carriers. APOE ε2 carriers may be more susceptible to the potentially beneficial effects of denser neighborhood BEs on cognition; however, longitudinal studies are needed.

Keywords

cognition; neighborhood; built environment; older adults; apolipoprotein E; environment

INTRODUCTION

Beyond individual-level risk factors for cognitive decline (e.g., genetics, education), the neighborhood environment may positively or negatively influence one's ability to maintain cognitive function with age. Older adults spend less time outside their neighborhoods than younger adults, and thus the neighborhood environment increases in importance with age. Evidence is accumulating for an association between lower neighborhood socioeconomic status (NSES) and worse cognition in older adults, independent of individual-level SES (Aneshensel et al., 2011, Clarke et al., 2012, Sheffield and Peek, 2009) Studies also suggest physical aspects of the neighborhood, the built environment (BE) (e.g., roads, sidewalks, buildings), may be associated with cognition in older adults. Although the literature on this topic is still nascent and the findings to date are mixed, there is some evidence for a positive association between BE characteristics typically associated with increasing urban density and better cognition in older adults (Besser et al., 2017). For example, community aspects such as neighborhood greenness (Brown et al., 2018) (e.g., park space) and access to a community center (Clarke et al., 2015) have been associated with lower Alzheimer's disease (AD) risk and slower cognitive decline, respectively. Greater land use mix (i.e., mix of residential and retail/commercial land uses) that accompanies denser urban environments has been associated with lower odds of dementia in a UK cohort (Wu et al., 2015). However, other study findings have been contradictory, suggesting that neighborhood characteristics generally considered to be beneficial for other social/health outcomes are associated with worse cognitive functioning. For instance, greater access to social and walking destinations (e.g., post office, restaurants) has been associated with worse cognition in non-demented older adults of Hispanic and African American ethnicity (Besser et al., 2018). These associations were not observed in non-Hispanic whites.

The neighborhood BE has been associated with health outcomes such as physical activity, obesity, and mental health (Mayne et al., 2015, Ferdinand et al., 2012, Mair et al., 2008, Barnett et al., 2018, Barnett et al., 2017, Hirsch et al., 2014b, Moore et al., 2016, Hirsch et al., 2014a). These associations with health may be operating through neighborhood effects on individual behaviors or exposures such as utilitarian walking, diet, mental stimulation, and social engagement or isolation (Cassarino and Setti, 2015, Wells et al., 2010). The neighborhood environment may delay or accelerate the onset of cognitive impairment through these behavioral mechanisms by serving as an upstream influence. The BE may

provide increased or decreased opportunities for physical activity, social engagement, or mental stimulation; may expose individuals to air pollutants; and may elicit different levels of stress through related factors such as traffic and noise. Denser urban environments are associated with taller buildings (that can restrict air flow), more connected streets, greater vehicular and pedestrian traffic, and social interactions with strangers, and therefore, may increase air pollution exposure and stress among residents who choose to walk in their neighborhoods. Both air pollution and stress have been associated with poorer cognitive function in past studies (Peters et al., 2019, Turner et al., 2017). The extant literature on the BE and cognition is too limited to date (Besser et al., 2018, Besser et al., 2017, Wu et al., 2017) and thus cannot yet provide the most plausible mechanisms or direction of the associations relating various neighborhood BE characteristics to cognition. However, it is reasonable to assume that the mechanism and the direction or presence of a BE-cognition association may depend on the BE characteristic under study, and more than one mechanism may be at play. For instance, better access to bus and train stops in the neighborhood may be associated with both increased physical activity (i.e., walking to the transit stop) and cognitive stimulation through navigating the neighborhood environment, which thereby improves cognition.

Prior studies, although still limited in number, suggest that the neighborhood may influence cognition in older adults differentially depending on individual-level characteristics (Aneshensel et al., 2011, Besser et al., 2018, Basta et al., 2008, Boardman et al., 2012, Clarke et al., 2012, Glass et al., 2009, Lang et al., 2008, Lee et al., 2011, Shih et al., 2011, Wight et al., 2006, Magaziner and Cadigan, 1989). For example, studies have shown that the association between NSES and cognition/dementia risk varies by individual-level SES (Aneshensel et al., 2011, Basta et al., 2008), age (Lang et al., 2008, Shih et al., 2011), and sex (Letellier et al., 2018). In a systematic literature review, a number of studies suggested effect modification of the BE-cognition association by individual-level factors such as race/ethnicity and SES (Besser et al., 2017). Consideration of effect modification is critical for improved understanding of the causal mechanisms underlying the relationship between neighborhood environment and cognition. If BE-cognition associations do in fact frequently vary depending on individual-level characteristics such as sex, race, and genetics, it is important to study and acknowledge this variation to inform future interventions and policies that may be unsuccessful without considerations of this potential variation.

Gene-environment interactions (Seabrook and Avison, 2010), previously associated with health indicators such as smoking (Boardman et al., 2010), alcohol consumption (Heath et al., 1989), and depression (Kendler et al., 1995), may be important to consider in neighborhood environment and cognition studies. Genetic risk factors for dementia disorders may be associated with residential location (e.g., certain neighborhoods have racial/ethnic compositions from historic migration, mobility, and access patterns; prevalence of Alzheimer's disease related genetic risks differs by race/ethnicity (Farrer et al., 1997)). In addition, the magnitude of the assocation between the BE and cognition may vary depending on one's genetic susceptibility to environmental exposures. Thus, genetic factors may confound BE-cognition associations, but additionally may moderate how environments affect cognition (Boardman et al., 2013).

An individual's apolipoprotein E (APOE) genotype is one such example of a genetic risk factor that may moderate associations between the environment and health, including BE-cognition associations. Individuals who carry one copy of the APOE ε4 allele are at a 3-fold increased risk of developing Alzheimer's disease, and individuals with two copies of the ε4 allele have an 8 to 12-fold increased risk (Alzheimer's Association, 2019). In contrast, those who do not possess the ε4 allele (ε3 and ε2 allele carriers) have either a neutral risk (ε3) or are at a decreased risk of developing Alzheimer's disease (ε2 carriers). Importantly, the APOE alleles do not appear to carry a linear association with AD risk, when comparing ε2, ε3, and ε4 carriers. The presence of ε4 alleles has been estimated to account for 65% of Alzheimer's disease cases, whereas the absence of the protective ε2 allele accounts for only 23% of Alzheimer's cases (Corder et al., 1994). In the context of this particular study, the APOE genotype may moderate the BE-cognition associations directly or possibly APOE genotype moderates the association between health behaviors and cognition (Podewils et al., 2005), and this moderation is thus observed when focused on BE-cognition associations (as BEs can affect health behaviors).

Only three known studies have investigated effect modification of the neighborhood environment-cognition association by APOE genotype (Lee et al., 2011, Cherrie et al., 2018, Boardman et al., 2012). Two studies found that the association between neighborhood psychosocial disorder (e.g., graffiti) and cognition was stronger in APOE ε4 carriers than non-carriers (Boardman et al., 2012, Lee et al., 2011), and the third found the association between greater neighborhood park space in earlier life was associated with slower cognitive decline in late-life in APOE ε4 non-carriers only (Cherrie et al., 2018). In contrast to the previous studies, this study examines new BE characteristics (neighborhood social and walking destination density, intersection density, and proportion of land dedicate to retail) and further stratifies into three major APOE genotypes (ε2, ε3, and ε4 carriers). Studies of APOE genotype in the Alzheimer's disease literature typically focus on comparing ε4 carriers and ε4 non-carriers because the ε4 allele confers increased risk for Alzheimer's disease, compared to ε2 (protective) and ε3 carriers (most prevalent in the population). Additionally, many studies do not have a reasonable sample size to separate out ε2 carriers as they are much rarer, and thus focus on comparing ε4 carriers and non-carriers. Therefore, the large sample size afforded by the Multi-Ethnic Study of Atherosclerosis data set used in this study provides a unique opportunity to study how BE-cognition associations may differ by the three genotypes.

In addition to the previous finding for a positive association between neighborhood park space and slower cognitive decline among only those with no APOE ε4 allele (Cherrie et al., 2018), other studies have found that only APOE ε4 non-carriers demonstrate significant associations between health behaviors (e.g., diet, cognitive stimulation (Krell-Roesch et al., 2017, Martinez-Lapiscina et al., 2014)) and cognitive benefits. The reasons for these associations among ε4 non-carriers alone are unclear, but may have to do with the protective influence of the ε2 allele.

We hypothesized that greater social and walking destination density, greater intersection density, greater proportion of land dedicated to retail (all consistent with increasing urban density) would be more strongly associated with cognition in APOE ε2 and ε4 carriers

compared to ε3 carriers. In this study, we propose an interaction between the protective benefits of the ε2 allele and of the BE on cognition, and thus a stronger association in ε2 than in ε3 carriers (who are not expected to experience protective effects on cognition based on their genetic risk). We posit that neighborhood residents will more often walk and frequent local places in neighborhoods that have a greater density of social and walking destinations, greater amounts of land dedicated to retail destinations, and greater accessibility to those destinations via the street network (i.e., greater intersection density). In turn, the positive health and social behaviors associated with getting out of the house and into the neighborhood will be associated with better cognition. Research is needed on the specific BE characteristics that may be associated with improved and maintained cognition in older adults, in order to provide practical evidence for targeted interventions, plans, and policies to allow aging in place and health brain aging. We focus on BE measures that have been studied little to date in relation to cognition in older adults and that are plausibly related to cognition. This is also one of the first known studies to examine how BE-brain aging associations may vary by APOE genotype.

MATERIALS AND METHODS

The sample was derived from the 4,716 participants completing Exam 5 (2010–2012) of the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort study of subclinical cardiovascular disease. MESA employed population-based methods to enroll 45- to 84-year-olds starting in 2000. Participants originated from six US regions (Forsyth County, North Carolina; New York, New York; Baltimore, Maryland; St. Paul, Minnesota [MN]; Chicago, Illinois; Los Angeles, California), and were oversampled to include a greater proportion of African Americans, Chinese-Americans, and Hispanics. The racial/ethnic composition of the MESA sites differed and thus the oversampling strategies and resulting distribution of the sample by site was based on those underlying population demographics. Details about MESA have been published elsewhere (Bild et al., 2002). Participants were excluded if they were: 1) missing all cognitive tests; 2) missing all BE measures; 3) taking medication for Alzheimer's disease symptoms (N-methyl-D asparate receptor blockers, acetylcholinesterase inhibitors); 4) indicated as having possible dementia (reviewed International Classification of Disease [ICD] codes (Fujiyoshi et al., 2016)); or 5) missing APOE genotype data.

Participant characteristics

Baseline characteristics included age, sex, education, race/ethnicity, marital status, and family income. Clinical characteristics included depressive symptoms (Center for Epidemiologic Studies Depression scale [CES-D] score≥16), current smoker, high systolic (>140 mmHg) and diastolic (>90 mmHg) blood pressure, self-reported diabetes and emphysema/chronic obstructive pulmonary disease (COPD), and medication use for hypertension, hypercholesterolemia, and depression.

APOE protein isoforms were assayed using single nucleotide polymorphism (SNP) genotyping (rs7412 and rs429358). For the current study, APOE categories were defined as follows: ε2 carriers include those with the ε2,ε2 or ε2,ε3 genotype; ε4 carriers included those with one or two ε4 alleles; and ε3 carriers included those with the ε3,ε3 genotype.

APOE ε3 allele carriers were chosen as the reference group because they are the most prevalent genotype and they carry neutral risk in comparison to ε2 carriers (protective) and ε4 carriers (increased risk of Alzheimer's disease).

The first three principal components (PC) of ancestry (PC1-PC3) (Price et al., 2006), previously derived under the MESA SNP Health Association Resource (SHARe) project, were included in the adjusted models. The first three PCs were determined to account for 78% of the ancestral variation in the MESA sample. Ancestry, here referring to genetic differences in groups that arise from mixing of previously genetically isolated groups (admixture) and systematic genetic differences in populations by region (population stratification), is important to control for as a confounder in studies with a primary focus on genetic risk factors for disease, such as the APOE genotype. The concept of ancestry, although related to race and ethnicity, is a separate construct that focuses on the genetic variation of populations. In contrast, an individual's self-reported race and ethnicity are best thought of as constructs that capture the social and cultural factors that shape an individual's health and behavior, social influences that are not readily captured by ancestry. Therefore, in this study, both ancestry and race/ethnicity were controlled for in the adjusted analyses.

Cognitive and BE measures

MESA Exam 5 participants completed three cognitive tests. The Cognitive Abilities Screening Instrument (CASI) (Teng et al., 1994) (version 2) is a culturally sensitive measure of global cognition using 25 items to assess nine cognitive domains (short-term memory, long-term memory, attention, concentration, orientation, language, verbal fluency, visual construction, and abstraction/judgment). The range of scores of the CASI is 0 to 100, with higher scores indicating better global cognition. Digit Span, a subtest of Wechsler Adult Intelligence Scale [WAIS-III] (Wechsler, 1997), measures working memory. Participants are asked to repeat an increasing span of randomly ordered digits (e.g., 1-9-4) forward (DSF; range: 0–16) and then backward (DSB, range: 0–14), where higher scores indicated better memory. DSF and DSB were analyzed separately because they assess slightly different aspects of working memory. The Digit Symbol Coding test (DSC; range: 0–133), a subtest of WAIS-III (Wechsler, 1997), measures processing speed. Respondents have 120 seconds to transcribe matching symbols for a series of randomly ordered numbers (using a legend with number and symbol pairs). Higher scores indicate better processing speed. Additional details on MESA's cognitive measures are available elsewhere (Fitzpatrick et al., 2015). To aid in interpretation of the regression findings, raw cognitive test scores were converted into standardized z-scores for each test based on the sample's mean and standard deviation.

The neighborhood measures are a subset of those previously developed from the ancillary MESA Neighborhood Study (Diez Roux et al., 2016). The percent of the ½-mile radial area (buffer) surrounding the participant's home dedicated to retail (hereafter termed 'proportion retail') was calculated by dividing the retail area by the total buffer area (m^2). Shopping centers, food stores, convenience stores, restaurants, bars/night clubs, clothing stores, and any other land parcel devoted to retail use (selling goods or services) were classified as retail. Retail destinations are of interest because they may promote older adults to walk in their neighborhood and this particular measure quantifies the coverage of retail destinations

in the neighborhood environment. Intersection density (measure of street connectivity/accessibility to neighborhood destinations) was calculated by dividing road intersection counts for the ½-mile buffer surrounding the home by the total buffer area. The simple densities of social engagement destinations and walking destinations per square mile were calculated for the ½-mile buffers. Social destinations included beauty shops/barbers; performance-based entertainment (e.g., opera, movie theaters); participatory entertainment (e.g., bowling); sports/professional stadium entertainment; coin operated amusements and gambling; amusement parks, carnivals, and rodeos; membership sports and recreational clubs; libraries; museums and art galleries; zoos, aquariums, and arboretums; civil and political clubs; religious organizations; eating and dining places; and night clubs/bars. Walking destinations included the postal service, drug stores and pharmacies, banks, non-beverage food stores (e.g., grocery), non-beverage dining places (e.g., fast food), and non-alcoholic drinking places. The social and walking destination variables overlap little (only regarding eating and dining places). Although, the destinations in the proportion retail measure overlap with the destinations included in the social and walking destination variables, proportion retail is a different way of measuring non-residential neighborhood destinations (measures coverage versus density). Including all of these measures in this study can help inform BE-cognition research on the measures that may be most strongly associated with cognition.

Neighborhood SES was available at the US Census Bureau tract level and was based on 2010–2011 American Community Survey data. The measure was previously derived in a principal components analysis based on seven neighborhood characteristics (created from MESA Neighborhood Study (Diez Roux et al., 2016)): 1) percent of neighborhood residents with a managerial occupation; 2) percent of residents with a bachelor's degree; 3) percent of residents with a high school degree; 4) percent of residents with an annual household income >$50,000; 5) median household income; 6) percent rental income; 7) and median home value. All of the main analyses included the BE measures in continuous format. For ease of interpretation of the regression results, the BE variable values were transformed into z-scores based on the sample's mean and standard deviation for each BE characteristic.

Statistical methods

Demographics, clinical characteristics and APOE genotypes were described using means and standard deviations or frequencies and percentages. Statistically significant differences in mean neighborhood BE values and cognitive test scores by APOE genotype were evaluated using unadjusted linear regression with APOE genotype comparison groups entered as two dummy variables (ε2 carriers versus ε3 carriers; ε4 carriers versus ε3 carriers).

To examine effect modification, we employed unadjusted and adjusted linear regression models using generalized estimating equations that accounted for non-independence of observations within neighborhoods, clustering on US Census Bureau tract as a proxy for neighborhood. Sixteen models were run to examine each BE measure (independent variable) and cognitive test (dependent variable) combination. BE variables were included separately in the models because they are moderately to highly correlated with each other (Pearson

correlation coefficients were calculated). Combining them into a single BE index measure would limit the ability to translate research findings into practical and easy to interpret policy and planning recommendations. The tables present the adjusted associations stratified by APOE genotype (for ε2, ε3, and ε4 carriers). Effect modification was tested using BE measure×APOE genotype interaction terms in the adjusted models (reference group: ε3 carriers). Multivariable models adjusted for study site, age, sex, race/ethnicity, education, income, marital status, neighborhood SES, the first three principal components of ancestry, comorbidities (arthritis, diabetes, emphysema/COPD, cardiovascular and cerebrovascular disease), and two perceived neighborhood psychosocial disorder variables (Likert scale, 1 to 5: neighbors do not get along, neighborhood violence). Only statistically significant interactions ($p<0.05$) with at least one corresponding, statistically significant within-strata association (e.g., in APOE ε2 carriers) are summarized in the results. Tables include significance at alphas of 0.05, 0.01, and 0.001, providing reference p-values for consideration of multiple comparisons (e.g., Bonferroni-adjusted significance level (Perneger, 1998) would be: 0.05/16= 0.003; where 16 is the number of regression models run).

Five sensitivity analyses were conducted. The first involved separately excluding race/ethnicity or the first three principal components of ancestry from the adjusted models, as they are related constructs, to confirm that inclusion of both sets of variables does not produce unstable results due to collinearity. The second examined if the results were similar when using network ratio, a different measure of street connectivity (i.e., accessibility to neighborhood amenities), instead of intersection density. Network ratio was calculated by dividing the buffer area measured by taking ½-mile distances from home using the street network (versus radial buffers surrounding the home) by the total area of the radial buffer. The maximum value is 1 (very connected street network) and the minimum is zero (totally unconnected). Intersection density was chosen as the primary measure of street connectivity for this paper due to its greater transparency in explanation and interpretation. The third sensitivity analysis used 1-mile buffers instead of ½-mile buffers to define the neighborhood measures. Half-mile buffers were chosen to define neighborhoods in this study as it was hypothesized that the area closer to the home (i.e., within a ½-mile versus 1-mile) is more important for older adults who experience increased frailty and disability and shrinking life space with age. Additionally, 1,000 meters (approximately half a mile) has been previously shown to be the distance adults walk to destinations in their neighborhoods (de Keijzer et al., 2018). The fourth sensitivity analysis used neighborhood BE variables measured in quartiles instead of continuous measures to assess if the associations with CASI and DSC by APOE genotype appeared to be linear in nature. Lastly, depression (CESD≥16) was controlled for in the adjusted models to determine if the findings changed considerably, as depression is a known predictor of cognition (but also a potential mediator of the BE-cognition association).

RESULTS

The final sample consisted of the 4,091 participants meeting the eligibility criteria (Appendix Figure 1). Participants were a mean age of 69.5 years (standard deviation [SD]=9.3), 53% were women, 69% were college educated, and 65% were married (65%) (Table 1). Twenty-seven percent were APOE ε4 carriers, 13% ε2 carriers, and 61% ε3

carriers. Forty-two percent of the sample were white, 12% Chinese, 25% African American, and 21% Hispanic (Table 1) (Whites originated from all sites, Chinese from Chicago and LA sites; African Americans from all sites but MN, and Hispanics from NY, MN, and LA). Fourteen percent had depressive symptoms, 34% were obese, 32% had arthritis, and 55% had hypertension (Table 2).

Compared to the participants included in the analytic sample, those excluded based on the eligibility criteria above were older, less educated, and had lower income, with no differences observed between their BE characteristics or APOE genotype (Appendix Table 1). No known population-based studies are available for APOE genotype prevalence among non-demented older adults to compare with the APOE genotype distributions in this sample, and in addition, APOE allele frequency has been previously demonstrated to vary based on geographic region/ethnicity (ALZGENE).

The mean BE measure values (½-mile buffers) did not differ by APOE genotype (Table 3). CASI and DSB scores did not differ by APOE genotype, whereas the mean DSF score was slightly lower in APOE ε4 carriers (9.5) versus ε3 carriers (9.7) and the mean DSC score was slightly lower in ε2 carriers (48.9) than ε3 carriers (51.4).

Additional analyses are in the supplement. The three principal components of ancestry were not associated with the BE measures (Appendix Table 2) but were associated with the cognitive measures (data not shown). A matrix of the participants in each quartile of the four BE measures demonstrates that the measures are highly correlated (range: r= 0.5–0.9) (Appendix Table 3). For instance, of the 1,022 participants living in the highest quartile of social destination density, 928 lived in the highest quartile of walking destination density and 773 lived in the highest quartile of intersection density. Unadjusted regression analyses are reported in Appendix Table 4.

APOE genotype was an independent predictor of cognition in the adjusted models (data not shown). APOE genotype modified associations between proportion retail and CASI scores and between the four BE measures and DSC scores in adjusted analyses (Table 4). Greater proportion retail was associated with higher CASI and DSC scores among APOE ε2 carriers, associations not observed for ε4 or ε3 carriers. Additionally, greater social destination, walking destination, and intersection density were associated with higher DSC scores among APOE ε2 carriers, but not among ε4 or ε3 carriers. Referring to the Bonferroni-adjusted significant level (p=0.003), only effect modification of the proportion retail-CASI association remained significant. Nonetheless, it must be noted that the use of a stringent significance level to account multiple comparisons is often considered too conservative.

Sensitivity analyses.

Separately removing either race/ethnicity or the principal components of ancestry from the adjusted models did not substantially change the results (Appendix Table 5). Although adjusted estimates generally remained similar when using either the intersection density or network ratio measures, effect modification by APOE genotype was not present for the network ratio-DSC association as it was for the intersection density-DSC association

(Appendix Table 6). Mean values for the BE variables measured using 1-mile buffers are presented in Appendix Table 7. APOE genotype continued to modify the association between proportion retail and social destination density measures and DSC when using 1-mile buffers (Appendix Table 8). However, effect modification of the walking destination density-DSC and intersection density-DSC associations was no longer present using 1-mile buffers. APOE ε2 carriers demonstrated increasingly stronger associations between each of the four BE measures and DSC when transitioning from the lowest to the highest quartile of each BE characteristic, suggesting a linear trend in associations with DSC (Appendix Table 9). Lastly, additionally controlling for depression resulted in little change to the regression estimates in Table 4 (data not shown).

CONCLUSIONS

This cross-sectional study suggest that associations between neighborhood BE characteristics and cognition in non-demented older adults may vary by APOE genotype. Unlike APOE ε3 carriers, ε2 carriers living with a greater proportion retail in their neighborhoods had better global cognition, and ε2 carriers living with greater social and walking destination densities, intersection densities, and proportion retail had better processing speed. These associations were not observed among APOE ε4 or ε3 carriers. For instance, a 6 SD increase in the proportion retail in the ½-mile surrounding the home (sample's range) was associated with a 0.84 SD better CASI score among APOE ε2 carriers. A 7.4 SD increase in the number of social destinations in the ½-mile surrounding the home (range observed in sample) was associated with a 0.97 SD better DSC score. These are clinically significant differences in cognitive test scores between those living in neighborhoods with the highest and lowest values for a given BE characteristic. Cognitive test scores that are at least 1 SD worse than scores for a normative/reference population are frequently used by clinicians as evidence of mild cognitive impairment (Langa and Levine, 2014). No differences were observed in the neighborhood BE-cognition associations when comparing APOE ε4 and ε3 carriers.

Four known studies are pertinent to our findings because they examine how APOE genotype may modify the association between neighborhood environment characteristics and brain aging outcomes. The first investigated the influence of neighborhood psychosocial disorder (e.g., graffiti) and APOE genotype on cognitive decline of older adults in Chicago, Illinois (Boardman et al., 2012). The authors found greater cognitive decline amongst APOE ε4 carriers in neighborhoods with the lowest social disorder. The second study examined whether APOE genotype was an effect modifier of cross-sectional associations between neighborhood psychosocial disorder and cognition among older adults in Baltimore, Maryland (Lee et al., 2011). Unlike the other study's findings, compared to APOE ε4 non-carriers living in the least hazardous neighborhoods (reference group), APOE ε4 carriers living in most hazardous neighborhoods had the poorest cognitive performance. Additionally, neither APOE ε4 carriers living in the least hazardous neighborhoods nor APOE ε4 non-carriers living in the most hazardous neighborhoods were found to be different than the reference group.

The results from the cross-sectional study above may be explained by the biological stress resulting from psychosocially hazardous environments. Prior studies have found effect modification of the association between APOE genotype and cognition by lead exposure, diabetes, and peripheral vascular disease, factors that may increase neurological vulnerability in ways similar to biological stress (Blair et al., 2005, Haan et al., 1999, Stewart et al., 2002). Additionally, a synergistic interaction has been reported between APOE genotype and cortisol levels in relation to cognitive performance (high cortisol and one ε4 allele: language score decrease equivalent to an 8-year age increase; high cortisol and two ε4 alleles: score decrease equivalent to a 33-year age increase) (Lee et al., 2008). Elements of neighborhood psychosocial disorder (i.e., neighbors get along, violence) were controlled for in this study without notably different findings. In the current study, APOE ε4 carriers did not demonstrate BE-cognition associations. The two previous studies compared APOE ε4 carriers and non-carriers without examining ε2 carriers specifically as in this study. Additionally, the previous studies measured the social environment and not the BE. This study presents novel findings of an interaction between APOE genotype and neighborhood BE factors consistent with increasing urban density.

The third related study investigated whether APOE genotype modifies the association between neighborhood walkability and brain imaging outcomes among Australian older adults (Cerin et al., 2017). APOE ε4 carriers living in neighborhoods with higher walkability (e.g., higher densities of social and walking destinations) showed less brain atrophy over time compared to APOE ε4 non-carriers. As in the two previous studies focused on neighborhood psychosocial disorder, the imaging study did not examine APOE ε2 carriers (without the ε4 allele) specifically. The results from the current study could be extended to investigate neighborhood BE and imaging outcomes among APOE ε2 carriers to determine whether they display less brain atrophy than the other APOE genotypes, lending biological plausibility to the observed associations.

The fourth relevant paper found that APOE ε4 non-carriers performed better over time in late life if they were exposed to greater park space in childhood and earlier adulthood (Cherrie et al., 2018). Therefore, the benefits of neighborhood park space on cognitive aging appeared to be restricted to those who were not at higher risk for dementia. Those paper findings are consistent with this study in which only APOE ε2 carriers (i.e., ε4 non-carriers) were found to have positive associations with the neighborhood BE.

Processing speed as measured via the DSC was the cognitive domain primarily associated with neighborhood BE characteristics among the APOE ε2 carriers. Increases in physical activity have been associated with improved processing speed among older individuals, and denser neighborhood environments have been shown to increase total physical activity in past studies (Frederiksen et al., 2015, Saelens et al., 2014, Sallis et al., 2009). It is also possible that complex, dense neighborhood environments require more cognitive processing than suburban/rural neighborhoods, or they offer more opportunities for social interaction and stress reduction. Stress has been associated with worse processing speed (Ouanes and Popp, 2019) and thus another potential mechanism is that neighborhood BEs offer opportunities for stress reduction (e.g., walking in the neighborhood or social engagement) that can help maintain or improve processing speed. It is possible that neighborhood

environments are particularly beneficial to processing speed, compared to the other cognitive domains examined in this study. Few studies have investigated BE-cognition associations to date, and thus future studies should consider additional cognitive domains (e.g., language, executive function).

Our findings suggest that the potential cognitive benefits of living in denser neighborhood BEs may be limited to those with a reduced genetic risk for cognitive decline, APOE ε2 carriers, and may not exist for APOE ε4 carriers as we had hypothesized. Some studies, such as those previously mentioned above (Krell-Roesch et al., 2017, Martinez-Lapiscina et al., 2014), have found that behaviors beneficial to cognitive health (e.g., diet) only have an effect on non-ε4 carriers. The positive influence of neighborhood environments on cognition may be strongest among individuals with APOE genotypes at the lowest risk for Alzheimer's disease, as the risk of cognitive decline among APOE ε4 carriers may be difficult to overcome. However, future studies will need to replicate our findings using diverse, longitudinal cohorts.

Strengths and Limitations

The principal limitation of this study is its cross-sectional nature. Effect modification that was significant at alpha=0.05 was discussed in the results section but it must be noted that this study made multiple comparisons and only one of the effect modification associations remained significant after referencing a Bonferroni-adjusted p-value. MESA Exam 5 participants who were excluded had less education and lower income than the analytic sample, and the same holds true for Exam 1 participants who were not followed up in Exam 5, and thus generalizability and selection bias are concerns. Although our results are suggestive, longitudinal studies are needed to provide supportive evidence for causal relationships. The four BE measures were chosen because similar measures were previously associated with PA (Cerin et al., 2013, Troped et al., 2017), and increases in PA have been shown to improve cognition (Wang et al., 2014, Angevaren et al., 2008). However, these BE measures have not been validated, and in understanding how the neighborhood BE may differentially influence cognition depending on APOE genotype, additional BE factors may be important such as those related to air pollution or stress. Cognitive testing is a non-obtrusive method to estimate biological changes resulting from environment exposures, but may be confounded by individual-level demographics and cultural factors. Therefore, additional studies of the association between BE exposures and imaging or other biological brain aging measures are needed. While site was controlled for the in the adjusted analyses, residual confounding is possible due to the lack of overlap in the proportion retail values by site (e.g., most participants in Winston Salem have lower values, those in New York City have higher values). Similarly, residual confounding could have resulted due to geographic differences in racial composition, as some race/ethnicities were not represented at a given MESA site. Finally, although we controlled for neighborhood psychosocial disorder (perceived violence, neighbors do not get along), these were self-reported measures. No objective measures were available but would be important to control for in future studies.

Study strengths include the large sample size of multi-racial/ethnic individuals with APOE genotype and neighborhood BE data. The MESA sample, derived from six field sites,

provides a diverse cohort from multiple geographic regions. Our neighborhood definition (½-mile radius surrounding participant's home) is regarded as an improvement to the use of administrative boundaries. For example, defining neighborhoods based on US Census tracts may not adequately represent an older adult's neighborhood, particularly those living at the boundary's edge. In addition, we provided a sensitivity analysis using 1-mile buffers instead of ½-mile buffers, as the most fitting definition of neighborhoods for older adults is unclear and may differ depending on the neighborhood characteristic under study.

This study suggests that APOE genotype modifies the cross-sectional association between the neighborhood BE and cognition in older adults. Given the few related studies conducted to date, new studies using longitudinal data are needed to determine whether APOE ε2 carriers experience slower declines in cognition than ε3 and ε4 carriers with increasing urban density (and the BE factors associated with urban density). In addition, further work is needed to assess if these associations vary depending on residential histories/moves and length of residence in a given neighborhood. Future work should attempt to elucidate the cognitive domains and brain regions most affected by neighborhood BEs, and important mediators in the pathway between the BE and cognition (e.g., stress, air pollution), to help establish biological plausibility. Although neighborhood BEs are difficult to change through low-cost interventions, BE improvements have the potential to affect many individuals. Furthermore, many US regions continue to experience substantial population growth and are thus compelled to alter their development patterns to adapt. Research on the potential influences of the neighborhood BE on cognition and brain aging can help inform recommendations for neighborhood BE improvements to simultaneously address population growth and healthy brain aging. Knowledge of how the BE may affect cognition differentially depending on individual-level characteristics such as APOE genotype will be important to inform such recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Apolipoprotein E (APOE) genotype modified buiit environment-cognition associations
- Specifically, associations generally seen in APOE ε2 but not ε3 or ε4 carriers
- In ε2 carriers, denser built environments associated with better cognition

Table 1.

Demographics of the sample (n=4,091)

Characteristic[a]	
Age at exam 5, mean (SD)	69.5 (9.3)
Women, n (%)	2161 (52.8%)
Education, n (%)	
< High school degree	551 (13.5%)
High school degree	705 (17.3%)
Some college, no bachelor's degree	1204 (29.5%)
Bachelor's degree or higher	1624 (39.8%)
Married, n (%)	2614 (64.6%)
Race/ethnicity, n (%)	
White/Caucasian	1696 (41.5%)
Chinese-American	484 (11.8%)
Black/African American	1038 (25.4%)
Hispanic	873 (21.3%)
Family income ≥$30,000/year, n (%)	2662 (67.4%)

Abbreviations: SD = standard deviation

[a]Missing data: income, n=144; education, n=7

Table 2.

Apolipoprotein E genotype and health characteristics of the sample (n=4,091)

Characteristic[a]	
APOE genotype, n (%)	
APOE ε2	526 (12.9%)
APOE ε3	2482 (60.7%)
APOE ε4	1083 (26.5%)
Depression (CES-D score ≥16), n (%)	574 (14.3%)
Current smoker, n (%)	296 (7.4%)
Body mass index (BMI, kg/m^2), n (%)	
<18.5 (underweight)	33 (0.8%)
18.5–24.9 (normal)	1145 (28.0%)
25–29.9 (overweight)	1531 (37.5%)
≥30 (obese)	1374 (33.7%)
Seated systolic blood pressure >140 mmHg, n (%)	822 (20.1%)
Seated diastolic blood pressure >90mmHg, n (%)	82 (2.0%)
Diabetes (self-reported), n (%)	428 (10.5%)
Hypertension (taking medication), n (%)	2254 (55.1%)
Hypercholesterolemia (taking medication), n (%)	1583 (38.7%)
Emphysema or COPD (self-reported), n (%)	80 (2.0%)
Taking depression medication, n (%)	560 (13.7%)
Arthritis (self-reported), n (%)	1285 (31.8%)
Cardiovascular disease, n (%)	310 (7.6%)
Cerebrovascular disease (stroke/TIA), n (%)	132 (3.2%)

Abbreviations: APOE = apolipoprotein E; CES-D = Center for Epidemiologic Studies Depression scale; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; SD = standard deviation; BMI = body mass index

[a]Missing data: CES-D, n=80; current smoker, n=66; BMI, n=8; systolic and diastolic blood pressure, n=2; emphysema/COPD, n = 6; diabetes, n=19; marital status, n =42; arthritis, n=46; cardiovascular disease, n =2; cerebrovascular disease, n=2

Table 3.

Neighborhood characteristics and cognitive test scores by apolipoprotein E genotype

	Mean (SD)			
Measure[a] (sample's range)	**Total n=4,091**	**APOE ε2 n=526**	**APOE ε3 n=2482**	**APOE ε4 n=1083**
Social destination density[b] (range: 0–1671.7)	142.6 (226.7)	148.7 (237.8)	140.7 (228.3)	144.2 (217.7)
Walking destination density[b] (range: 0–716.3)	67.1 (105.3)	70.6 (108.8)	65.9 (104.9)	67.9 (104.4)
Intersection density[b] (range: 0.0049–4.8668)	0.78 (0.52)	0.79 (0.52)	0.78 (0.51)	0.79 (0.55)
Proportion retail[b] (range: 0.0–0.30)	0.047 (0.051)	0.048 (0.050)	0.046 (0.050)	0.049 (0.052)
Cognitive Abilities Screening Instrument[c] (range: 23.2–100.0)	87.8 (8.8)	87.8 (8.4)	87.9 (8.8)	87.4 (8.9)
Digit Span Forward[c] (range: 0–16)	9.7 (2.8)	9.7 (2.8)	9.7 (2.8)	9.5 (2.7)**
Digit Span Backward[c] (range: 0–14)	5.6 (2.4)	5.7 (2.5)	5.7 (2.4)	5.5 (2.3)
Digit Symbol Coding[c] (range: 0–120)	50.8 (18.5)	48.9 (18.6)**	51.4 (18.4)	50.2 (18.5)

APOE = apolipoprotein E;

[a] Missing data: proportion of land retail, n= 268; Cognitive Abilities Screening Instrument, n=6; Digit Span Forward, n=16; Digit Span Backward, n=16; Digit Symbol Coding, n=379;

[b] Measured in ½ mile radius of participant's home;

[c] Raw scores;

Statistically significantly different from APOE ε3 carriers: *alpha=0.05, **alpha=0.05, ***alpha=0.001

Table 4.

Effect modification of adjusted associations between neighborhood built environment and cognition by APOE genotype

		Adjusted estimate[b] (95% CI)			
Neighborhood characteristics	**APOE genotype**	**CASI[c]**	**DSF[c]**	**DSB[c]**	**DSC[c]**
Social destin. density[a]	ε2	−0.01 (−0.08, 0.05)	0.00 (−0.09, 0.10)	−0.02 (−0.14, 0.11)	0.13 (0.05, 0.21) †† ,**
	ε3	−0.02 (−0.07, 0.02)	0.07 (0.01, 0.13) †	−0.01 (−0.07, 0.04)	−0.03 (−0.08, 0.03)
	ε4	−0.01 (−0.09, 0.07)	0.01 (−0.09, 0.10)	−0.02 (−0.12, 0.08)	0.03 (−0.04, 0.11)
Walking destin. density[a]	ε2	0.04 (−0.06, 0.13)	−0.04 (−0.16, 0.07)	−0.05 (−0.19, 0.08)	0.13 (0.04, 0.21) †† ,*
	ε3	−0.02 (−0.07, 0.03)	0.08 (0.01, 0.14) †	−0.03 (−0.09, 0.04)	−0.02 (−0.09, 0.04)
	ε4	−0.04 (−0.14, 0.07)	0.00 (−0.10, 0.10)	−0.02 (−0.13, 0.09)	0.02 (−0.06, 0.10)
Intersection density[a]	ε2	0.02 (−0.05, 0.09)	−0.04 (−0.13, 0.06)	0.00 (−0.11, 0.12)	0.10 (0.04, 0.16) ††† ,*
	ε3	−0.01 (−0.05, 0.03)	0.05 (0.00, 0.11) †	−0.01 (−0.06, 0.04)	−0.03 (−0.08, 0.01)
	ε4	−0.03 (−0.10, 0.03)	−0.04 (−0.11, 0.03)	−0.01 (−0.08, 0.05)	−0.01 (−0.07, 0.04)
Proportion retail[a]	ε2	0.14 (0.05, 0.23) †† ,**	0.02 (−0.09, 0.13)	0.04 (−0.09, 0.17)	0.12 (0.02, 0.22) † ,**
	ε3	−0.02 (−0.06, 0.03)	0.03 (−0.02, 0.08)	−0.05 (−0.10, 0.00)	−0.01 (−0.06, 0.04)
	ε4	−0.01 (−0.08, 0.06)	0.03 (−0.05, 0.12)	−0.01 (−0.09, 0.07)	0.02 (−0.04, 0.09)

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

*Significant difference compared to APOE ε3 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]z-scores measures for ½ mile radius of participant's home

[b] controlling for age, education, race/ethnicity, income, married, neighborhood socioeconomic status, top three principal components of ancestry, site, comorbidities (arthritis, emphysema/COPD, cardiovascular disease, cerebrovascular disease, diabetes), and neighborhood social environment (neighbors do not get along, violence in the neighborhood)

[c] z-score