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Neighborhood environment associations with cognitive function and structural brain measures in older African Americans

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Abstract

Background Since older adults spend significant time in their neighborhood environment, environmental factors such as neighborhood socioeconomic disadvantage, high racial segregation, low healthy food availability, low access to recreation, and minimal social engagement may have adverse effects on cognitive function and increase susceptibility to dementia. DNA methylation, which is associated with neighborhood characteristics as well as cognitive function and white matter hyperintensity (WMH), may act as a mediator between neighborhood characteristics and neurocognitive outcomes.

Methods In this study, we examined whether DNA methylation in peripheral blood leukocytes mediates the relationship between neighborhood characteristics and cognitive function ($N=542$) or WMH ($N=466$) in older African American (AA) participants without preliminary evidence of dementia from the Genetic Epidemiology Network of Arteriopathy (GENOA).

Results For a 1-mile buffer around a participant's residence, each additional fast food destination or unfavorable food store with alcohol per square mile was nominally associated with a 0.05 (95%CI: 0.01, 0.09) and a 0.04 (0.00, 0.08) second improvement in visual conceptual tracking score, respectively. Also, each additional alcohol drinking place per square mile was nominally associated with a 0.62 (0.05, 1.19) word increase in delayed recall score, indicating better memory function (all $p<0.05$). Neighborhood characteristics were not associated with WMH. We did not find evidence that DNA methylation mediates the observed associations between neighborhood characteristics and cognitive function.

Conclusions The presence of fast food destinations and unfavorable food stores with alcohol was associated cognitive measures, possibly due to greater social interaction provided in these venues. However, replication of these findings is necessary. Further examination of the potential pathways between the neighborhood environment and cognitive function/WMH may allow the development of potential behavioral, infrastructural, and pharmaceutical interventions to facilitate aging in place and healthy brain aging in older adults, especially in marginal populations that are most at risk.

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Keywords Neighborhood environment, Food environment, Cognitive health, Healthy aging, Cognitive function, White matter hyperintensity, Fast food, Alcohol, Built environment, Social environment

Background

Dementia is preceded by a noticeable decline in cognitive abilities that becomes severe enough to interfere with daily functioning [1]. Among US adults ages 65 and older, approximately 10% have dementia and 22% have mild cognitive impairment (MCI) [2]. Dementia, which includes Alzheimer's disease (AD), vascular dementia (VaD), and other types of dementia, places a substantial burden on family, friends, and healthcare systems [3]. Cerebral small vessel disease (SVD), detected on magnetic resonance imaging (MRI) as white matter hyperintensities (WMH), causes one quarter of all ischemic strokes and is associated with cognitive function [4] and VaD [5–7]. To date, there are no effective treatments available to prevent or cure dementia. However, some research suggests that performing cognitively stimulating exercises and treating cardiovascular risk factors may delay or prevent the onset of dementia and reduce its associated pathology [1, 8]. While individual-level factors, such as educational attainment [9, 10], smoking habits [11], and physical activity [12, 13], are associated with cognitive function, there is growing interest in how neighborhood characteristics may shape health behaviors and health outcomes in older adults [14, 15].

Neighborhoods are defined as living environments that possess both physical and social attributes that may affect the health of their residents [16]. Specifically, characteristics of the neighborhood social environment, such as fewer destinations within walking distance that allow for social interaction and community, and low neighborhood socioeconomic status (SES) are associated with lower levels of cognitive function [17–20] and higher incidence of ischemic stroke [21, 22] in older adults. Since older adults spend a large proportion of their time in their neighborhood environment [23], factors such as neighborhood socioeconomic disadvantage [24], high racial segregation [25–28], low healthy food availability [29], low access to recreation [30, 31], and minimal social engagement [32] may have adverse effects on cognitive function and SVD and may also increase susceptibility to dementia [24–32]. As such, access to specific neighborhood infrastructures that may counteract these factors, such as increased access to healthy food, educational resources, safe and walkable neighborhoods, and recreational community activities, may support cognitive health among older adults aging in place [17]. Understanding how characteristics of neighborhood environments and how the accessibility of resources pertaining to healthy food and social and recreational activities impact the underlying molecular mechanisms of dementia pathology may allow us to develop better interventions to prevent disease onset.

Epigenetic modifications, such as DNA methylation, are molecular mechanisms that regulate gene expression without changing the underlying DNA sequence. DNA methylation, or the addition of a CH_3 (methyl) group at a cytosine base followed by a guanine base (CpG site), is one of the most commonly studied epigenetic mechanisms. DNA methylation has been proposed as a potential mechanistic link between environmental exposures and downstream diseases because it is responsive to environmental stimuli, is dynamic across the life course, and is potentially reversible [33]. Given the regulatory role of DNA methylation on gene expression, as well as the association between CpG sites and aging [34], there has been a growing interest in understanding the extent to which DNA methylation contributes to age-related diseases such as Alzheimer's and related dementia risk [35–39].

Previous studies have linked several individual- and neighborhood-level social disadvantage indicators, including low adult SES [35, 36] and living in disadvantaged neighborhoods [37–39], to DNA methylation patterns. After adjusting for individual SES, neighborhood socioeconomic disadvantage and social environment were also associated with DNA methylation in stress- and inflammation-related genes [38]. In addition, epigenome-wide association studies (EWAS) have shown associations between methylation and cognitive function [40, 41] and WMH [42, 43]. Since DNA methylation has been associated with both neighborhood-level factors and cognitive function/WMH, it may act as a mediator between neighborhood-level risk factors and cognitive outcomes. To date, a handful of studies have examined whether epigenome-wide markers mediate the effects of social disadvantage on health outcomes and risk factors. For example, in the New England Family Study, epigenetic markers from adipose tissue partially mediated the association between individual-level social disadvantage and body mass index in adulthood [44, 45]. In the Multi-Ethnic Study of Atherosclerosis (MESA), methylation from monocytes partially mediated the associations between adult SES and/or neighborhood socioeconomic disadvantage and several Cardiovascular disease risk factors [46]. To our knowledge, no studies have examined epigenetic mediation in the association between neighborhood characteristics and cognitive function/WMH.

African Americans (AA) have a greater burden of and risk for developing dementia [47–50] and stroke [51], compared to non-Hispanic Whites (NHW). Underlying causes of these disparities remain poorly understood but are likely due to multifactorial and multilevel factors that occur over the life-course. For example, differences in cognitive performance and dementia risk in AA may in part be caused by racial disparities in education (amount and quality) [52, 53], availability of material and social resources [54], access to favorable food and physical activity environments [55], exposure to discrimination [56], and neurotoxicants [57, 58]. A previous study in Atherosclerosis Risk in Communities (ARIC) found that reducing hypertension, obesity, and physical inactivity through targeted interventions could significantly lower dementia rates among Black individuals, particularly by addressing structural barriers to health [59]. While studies have examined individual-level risk factors as explanations for racial/ethnic disparities (e.g., socioeconomic, psychosocial, genetic, epigenetic, and biological), there is increasing interest in the role of the neighborhood on health outcomes in AA populations. Altogether, AA are more likely to live in neighborhoods with factors that may affect their stress levels (e.g., higher discrimination, lower educational attainment, and lower SES) that over time may result in physiological dysregulation [27] that ultimately leads to hypertension, diabetes, coronary heart disease, and depression. Dysregulation of neurocognitive processes may also lead to cognitive decline or dementia.

To better understand the mechanisms underlying relationships between neighborhood environment and dementia risk factors in older AA, we used high-dimensional mediation methods to identify DNA methylation sites (CpGs) in peripheral blood leukocytes that may mediate the relationship between neighborhood-level factors and cognitive function or WMH in the Genetic Epidemiology Network of Arteriopathy (GENOA) study.

Methods

Sample

The Genetic Epidemiology Network of Arteriopathy (GENOA) is a community-based longitudinal study intended to examine the genetic effects of hypertension and related target organ damage [60]. European American (EA) and African American (AA) hypertensive sibships were recruited if at least two siblings were clinically diagnosed with hypertension before age 60. All other siblings were invited to participate, regardless of hypertension status. Exclusion criteria included secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, active malignancy, or serum creatinine levels > 2.5 mg/dL. Race/ethnicity was self-reported as non-Hispanic White or non-Hispanic Black. Next, genetic principal components (PCs) were used to confirm that the non-Hispanic Black participants clustered between European (CEU) and African (YOR) samples from 1000 Genomes Project Phase 1 (2012) [61], while non-Hispanic White participants clustered with European ancestry samples.

In phase I (1996–2001), 1854 AA participants (Jackson, MS) and 1583 EA participants (Rochester, MN) were recruited [60]. In phase II (2000–2004), 1482 participants AA participants and 1239 EA participants were successfully followed up, and their potential target organ damage from hypertension was measured. Demographics, medical history, clinical characteristics, medication use, and blood samples were collected in each phase. Methylation levels were measured only in AA participants using blood samples collected in phases I and II.

In an ancillary study, the Genetics of Microangiopathic Brain Injury (GMBI; 2001–2006), 1010 AA and 967 EA GENOA participants underwent a battery of established cognitive tests to assess measures of cognitive function [62, 63]. White matter hyperintensity (WMH) was also measured using brain magnetic resonance imaging (MRI) for the majority of GMBI participants. The GMBI exam occurred approximately 1 year after the participant completed phase II (mean time between phase II and GMBI = 1.1 years, SD = 1.0 year). Written informed consent was obtained from all participants, and approval was granted by participating institutional review boards (University of Michigan, University of Mississippi Medical Center, and Mayo Clinic).

After excluding participants with missing neurocognitive test data ($n = 93$) and neighborhood density measures ($n = 4$), we had a total of 913 AA participants with available demographic, cognitive, and neighborhood data (Additional File 1: Fig. S1). Since participants with a history of stroke or dementia may have had changes in general cognitive function that differed from non-pathological cognitive aging, we excluded those with a history of stroke ($n = 40$) and/or preliminary evidence of dementia indicated by a Mini-Mental State Examination Score (MMSE) of < 24 ($n = 52$). Participants younger than age 45 were also excluded ($n = 96$). After further excluding participants missing genetic PCs ($n = 183$), a total of 542 and 477 participants were available with neighborhood spatial (density measures) and neighborhood socioeconomic disadvantage analyses, respectively (Additional File 1: Fig. S1). For WMH analyses, a total of 466 and 404 participants were available for neighborhood spatial (density measures) and neighborhood socioeconomic disadvantage analyses, respectively (Additional File 1: Fig. S2).

Measures

Measures of cognitive function

The following four cognitive domains were evaluated: delayed recall (Rey Auditory Verbal Learning Test [RAVLT]), processing speed (Digit Symbol Substitution Test [DSST]), word fluency (Controlled Oral Word Association Test [COWA-FAS]), and visual conceptual tracking (Trail Making Test A [TMTA]) [62–64]. All cognitive domains were coded so that a higher score corresponds to better cognitive function. See Additional File 2: Supplementary Methods for details.

In addition to analyzing individual cognitive domains, we assessed a summary measure of general cognitive function, which is often quantified using cognitive tests in multiple cognitive domains [65]. In this study, general cognitive function was calculated as the first unrotated principal component (FUPC) from a principal component analysis (PCA) of the four cognitive domains in the full sample ($N=542$). The FUPC accounted for 57% of the total variance in the cognitive measures and loading factors of the four measures were 0.61 for delayed recall (RAVLT), 0.88 for processing speed (DSST), 0.70 for word fluency (COWA-FAS), and 0.81 for visual conceptual tracking (TMTA).

White matter hyperintensity

Presence of WMH in brain samples indicates areas of ischemic damage to small vessels and surrounding areas. Brain magnetic resonance images were measured from magnetic resonance imaging (MRI), using Signa 1.5 T MRI scanners (GE Medical Systems, Waukesha, WI, USA) at Mayo Clinic [66]. For additional details, see Smith et al. [67] WMH and total brain volume in the corona radiata and periventricular zone were quantified from axial fluid-attenuated inversion recovery (FLAIR) images [68]. Brain scans with cortical infarctions were excluded from the analyses because of the distortion of WMH volume estimates that would be introduced in the automated segmentation algorithm. Models assessing WMH were adjusted for total intracranial volume (TIV). Distributional plots indicated that the measures of WMH are right-skewed, so the WMH variable was transformed as $\ln(\text{WMH}+1)$.

DNA methylation

Genomic data was extracted from stored peripheral blood leukocytes from 1106 AA GENOA participants from phase I and 304 AA participants from phase II using the AutoGen FlexStar (AutoGen, Holliston, MA). Bisulfite conversion was performed with the EZ DNA Methylation Kit (Zymo Research, Irvine, CA), and methylation was measured using the Illumina HumanMethylationEPIC BeadChip. The raw intensity data was visualized using the shinyMethyl R package [69] to identify sex mismatches and outliers, which were removed. Samples with incomplete bisulfite conversion were identified using Qcinfo in the *Enmix* R package [70] and removed. Background correction and dye-bias normalization were performed using Noob in the *Minfi* R package [71, 72]. Sample identity was verified using 59 SNP probes on the EPIC array, and mismatched samples were removed. Probe-type bias was adjusted using the Regression on Correlated Probes (RCP) method [73]. Probes with detection p-value $< 10^{-16}$ were considered successfully detected, and probes and samples with detection rate < 10% were removed [74]. We also excluded cross-reactive probes [75] and probes with a SNP at the target CpG site or within a single-base extension. After quality control, a total of 1396 samples ($N=1100$ from phase I and $N=294$ from phase II) and 857,121 CpG sites were available for analysis. For this analysis, all methylation data were from phase I samples. White blood cell proportions for CD8+T lymphocytes, CD4+T lymphocytes, natural killer cells, B cells, monocytes, and granulocytes were estimated using the Houseman method [76]. For each CpG site prior to analysis, the methylation beta-values [77, 78] were pre-adjusted for batch effects (sample plate, row, and column) and white blood cell proportions using linear mixed modeling, and the resulting residuals were added to the mean values.

Genotype data

Genetic PCs were estimated from genotype data obtained from the Illumina HumanOmni2.5 arrays, as previously described [79].

Individual-level measures

Age was assessed at cognitive testing. The respondent's highest level of educational attainment was categorized as (1) less than high school degree/GED (reference group), (2) high school degree or GED, and (3) at least 4 years of college or trade/technical school. Smoking has a substantial impact on the epigenome [80], so we used smoking data from the same timepoint as the DNA methylation measures (phase I). Participants were categorized as current, former, or never smokers (reference group).

Neighborhood characteristics

GIS-based measures

Densities of neighborhood destinations were derived from the National Establishment Time Series (NETS) [81] data (1996–2015). Simple densities per square mile were created for ½-mile, 1-mile, and 3-mile buffer sizes around home addresses of GENOA participants at phase I using ArcGIS V.9.3 (ESRI, Inc., Redlands, California)

[82–84]. We used 1-mile buffer in our primary analysis, as previous studies have done [85, 86], and examined ½- and 3-mile buffers in sensitivity analysis. Kernel densities per square mile, with greater weighting towards destinations located closer to the home of a participant, were also created for GENOA participants using the kernel density command in ArcGIS V.9.3 [82–84] for the same buffer sizes; these were also explored in sensitivity analysis.

For each participant, simple densities were estimated for the following 10 types of destinations: fast food restaurants (including both chain and non-chain), total physical activity facilities, total social engagement destinations, alcohol outlets, unfavorable food stores with and without alcohol, healthy (favorable) food stores, popular walking destinations, and total food stores. The modified retail food environment index (MRFEI) was also calculated from the number of healthy and less healthy food retailers within census tracts across states, based on typical food offerings in specific retail stores [87–89]. See Additional File 2: Supplementary Methods for details.

Census measures

Briefly, neighborhood socioeconomic disadvantage was assessed using data collected in the 2000 US Census [90, 91] and American Community Survey (ACS) 2005–2009 [92, 93]. Data was linked to GENOA participant data (phase I; 1995–2000) by census tract using Census and ACS estimates for the closest time period. To derive neighborhood socioeconomic disadvantage, we used six variables that reflected aspects of wealth and income, education, and occupation for each census tract [94]. *Z*-scores for each census tract were estimated for each variable, and neighborhood socioeconomic disadvantage was defined as the sum of *Z*-scores from the six variables, with higher scores indicating more disadvantage. See Additional File 2: Supplementary Methods for details.

Statistical analysis

We first calculated Pearson correlations among the six outcomes (general cognitive function, the four cognitive domains and WMH) and among the 13 neighborhood characteristics (12 density measures and neighborhood socioeconomic disadvantage). Since areas of increased population density (e.g., urban neighborhoods) generally have a higher absolute number of destinations, we next examined the neighborhood characteristics after pre-adjusting for census tract population density using linear modeling. Correlations were calculated among the neighborhood characteristics for simple and kernel densities per square mile for 1-mile buffer sizes.

Associations between neighborhood measures and cognitive function/WMH

To identify which exposures and outcomes have a significant total effect, we tested for association between each neighborhood characteristic (exposure) and general cognitive function, each cognitive domain, or WMH (outcome). We first tested for association between a neighborhood characteristic (socioeconomic disadvantage or simple density measures) and general cognitive function, adjusting for age at cognitive function measurement, sex, current smoking status, the first 5 genetic PCs of ancestry, and family relatedness as a random effect (model 1a). While PCs are likely not a confounder of the relationship between neighborhood and cognitive function/WMH, we included them so that we would have the same adjustment variables in the total effects model as in the mediation models (described below) when we next examine methylation as a mediator of the relationship between neighborhood and cognitive function/WMH. In model 1b, we tested for association between each neighborhood characteristic and WMH, adjusting for the same covariates as model 1a and TIV. In models 2a/2b, we additionally adjusted for census tract population density in 2000 and included census tract as a random effect. We also tested for associations between each neighborhood characteristic and each of the four cognitive domains using model 2a. Associations between neighborhood characteristics and cognitive function/WMH that were significant at $p < 0.05$ in models 1a/1b or 2a/2b were selected for mediation analysis. In sensitivity analysis, we tested the same associations using simple densities at ½- and 3-mile buffers as well as kernel densities at all 3 buffers. Because we were interested in identifying total effects to investigate further under the hypothesis that methylation is a mediator of these relationships, we were interested in any associations meeting a nominal significance level ($p < 0.05$). However, since we conducted a large number of tests, we also assessed whether any were significant after multiple testing using false discovery rate (FDR $q < 0.01$) [95]. The total effects model is outlined below:

$$Y_{2jk} = \beta_0 + \omega X_{1jk} + \boldsymbol{\alpha} C_{1jk} + W_k + \varepsilon_{jk}$$

β_0: intercept value; cognitive function/WMH value when all covariates (neighborhood characteristic (exposure) and confounders) equal zero.

ω: effect estimate of neighborhood characteristic (exposure) on cognitive function/WMH.

X_{1jk}: neighborhood characteristic (exposure) for participant j in sibship k at phase I.

C_{1jk}: set of covariates (age at cognitive function/WMH measurement, sex, and genetic principal components at phase I and TIV for WMH outcome).

W_k: random effect (familial relatedness; independent and normal distribution) in sibship k.

ε_{jk}: residual error (independent and normal distribution) for participant j in sibship k.

Y_{2jk}: cognitive function/WMH for participant j in sibship k at phase II.

Mediation analysis

If a significant association (total effect) was identified between a neighborhood characteristic and a cognitive/WMH outcome, we conducted an epigenome-wide high-dimensional mediation analysis to identify CpG sites that may partially mediate the relationship. We used a cross-product-based mediation approach in which the mediation effect is obtained by multiplying the exposure-mediator effect (β_1) and the mediator-outcome effect (β_3; see Eqs. 1 and 2). We obtained these parameters for each exposure and outcome tested using linear mixed models to separately estimate the association between neighborhood characteristics with DNA methylation (mediator), while adjusting for covariates (Eq. 1), and the association between DNA methylation and cognitive function/WMH, while adjusting for the corresponding exposure tested and the same set of covariates (Eq. 2). The covariate sets in Eqs. 1 and 2 are the same as in models 1a/b and 2a/b. The specified models (Eqs. 1 and 2) for a given exposure-outcome association are outlined below:

$$M_{jk} = \beta_0 + \beta_1 X_{1jk} + \boldsymbol{\alpha} V_{1jk} + W_k + \varepsilon_{jk} \quad (1)$$

$$Y_{2jk} = \beta_0 + \beta_2 X_{1jk} + \beta_3 M_{jk} + \boldsymbol{\alpha} V_{1jk} + W_k + \varepsilon_{jk} \quad (2)$$

β_0: intercept value; cognitive function/WMH value when all covariates (neighborhood characteristic (exposure) and confounders) equal zero.

M_{jk}: DNA methylation (mediator; beta-value) for participant *j* in sibship *k*.

X_{1jk}: neighborhood characteristic (exposure) for participant *j* in sibship *k* at phase I.

V_{1jk}: adjustment covariates for participant *j* in sibship *k* at phase I.

W_k: random effect (familial relatedness; independent and normal distribution) in sibship *k*.

ε_{jk}: residual error (independent and normal distribution) for participant *j* in sibship *k*.

Y_{2jk}: cognitive function/WMH (outcome) for participant *j* in sibship *k* at phase II.

β_1: effect estimate of neighborhood characteristic (exposure) on DNA methylation (mediator).

β_2: direct effect estimate of the neighborhood characteristic (exposure) on cognitive function/WMH (outcome).

β_3: effect estimate of DNA methylation (mediator) on cognitive function/WMH (outcome), adjusting for the direct effect (β_2).

Using Eqs. 1 and 2, the epigenetic mediation effect was tested using the following:

H_0: $\beta_1\beta_3 = 0$.

H_A: $\beta_1\beta_3 \neq 0$.

The null hypothesis was comprised of three sub-hypotheses: (1) H_{01}: $\beta_1 = 0$, $\beta_3 \neq 0$; (2) H_{10}: $\beta_1 \neq 0$, $\beta_3 = 0$; and (3) H_{00}: $\beta_1 = \beta_3 = 0$. We performed parallel one-at-a-time mediation hypothesis testing. With a total of M mediators, we denote π_{01}, π_{10}, and π_{00} as the true proportions of ($\beta_1 = 0$, $\beta_3 \neq 0$), ($\beta_1 \neq 0$, $\beta_3 = 0$), and ($\beta_1 = \beta_3 = 0$) among all M tests. Figure 1 shows a directed acyclic graph (DAG) of the hypothesized associations. To test for the mediation effect, we used the Sobel-comp [96] method in the *medScan* package in R, which uses a corrected mixture reference distribution for Sobel's test statistic according to the composite structure of the null hypothesis. We considered $p < 0.05$ to be significant.

Results

Sample characteristics

The sample included 542 AA without dementia (Table 1). Participant age ranged from 45 to 83 years (mean = 62.5 years). More than half of participants (73%) were female. A total of 25.0% had less than a high school degree/GED, 46.5% attained a high school degree/GED, and 28.6% completed at least 4 years of college or trade school. General cognitive function was normally distributed (Fig. 2). Mean delayed recall (RAVLT) score was 7.0 (SD = 3.3) words recalled, mean processing speed (DSST) was 33.8 (SD = 13.0) symbols, mean word fluency (COWA-FAS) score was 29.4 (SD = 11.6) words, and mean visual conceptual tracking (TMTA) score was 63.8 (SD = 35.2) seconds to completion. Participants had a mean WMH of 9.42 cm^3 (SD = 9.19). WMH distribution was severely right skewed but had a normal distribution after log transformation (Fig. 2).

Correlation among cognitive and WMH outcomes

The four cognitive domains were moderately correlated (Pearson r ranged from 0.21 to 0.68), with the highest correlation among processing speed (DSST) and visual conceptual tracking (TMTA) ($r = 0.68$, $p < 0.001$, Additional File 3: Table S1). WMH was negatively and weakly correlated with all the cognitive measures except COWA-FAS (Pearson r ranged from −0.27 to −0.34 for significant correlations).

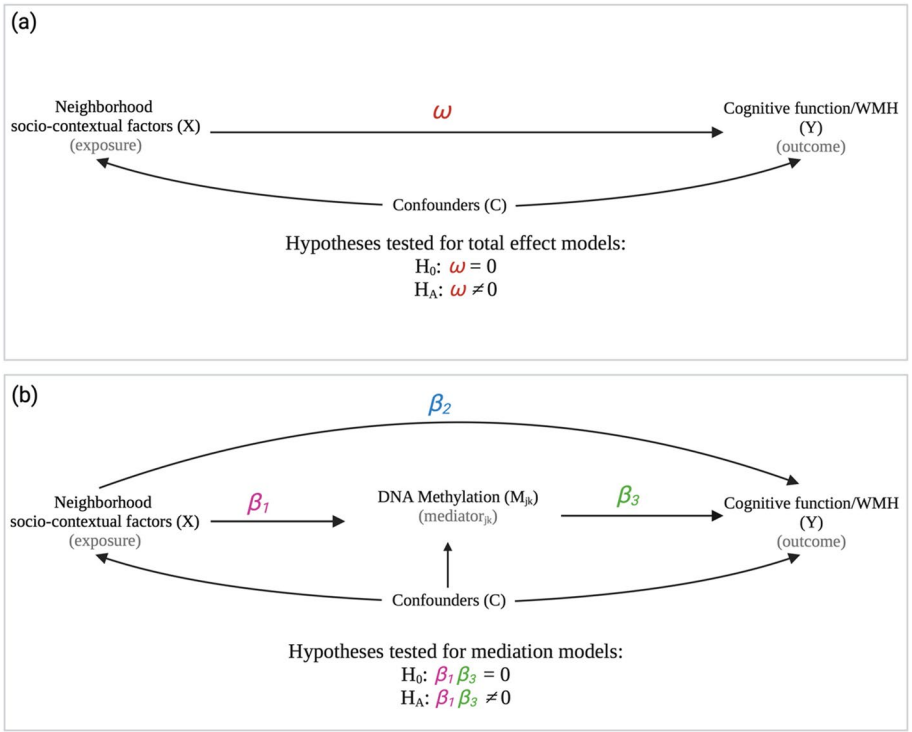

Fig. 1 Directed acyclic graph (DAG) of the hypothesized associations for the epigenetic mediation between neighborhood characteristics (exposures) and cognitive/WMH outcomes. **a** The total effect associations between neighborhood characteristic (X) and cognitive function/WMH (Y). ω is the effect estimate of the neighborhood characteristic on cognitive function/WMH. **b** The mediation effect obtained through the cross-product-based mediation approach obtained by multiplying the exposure-mediator effect (β_1) and the mediator-outcome effect (β_3). Confounders (C) include age at measurement, PCs 1–4, sex, education, smoking status, familial relatedness, neighborhood socioeconomic disadvantage, census tract population density, and census tract (model 2a/2b only)

Correlation among the neighborhood exposures

Neighborhood exposures were moderately correlated (Pearson r ranged from −0.24 to 0.99, Additional File 3: Table S2). Neighborhood socioeconomic disadvantage was positively, but weakly, correlated with unfavorable food stores without alcohol, total social engagement destinations, total popular walking destinations, and alcoholic drinking places. After adjusting for census tract population density, the correlations between neighborhood socioeconomic disadvantage and neighborhood characteristics increased in magnitude in the positive direction for all measures except fast food destinations, alcoholic drinking places, and the MRFEI measures (Additional File 3: Tables S3 and S4).

Associations between neighborhood characteristics and cognitive/WMH outcomes

Neighborhood socioeconomic disadvantage associations

Neighborhood socioeconomic disadvantage was not associated with general cognitive function or WMH either before (models 1a/1b) or after adjusting for census tract population density and census tracts as a random effect (models 2a/2b, Table 2). Furthermore, neighborhood socioeconomic disadvantage was not associated with any of the four cognitive domains (model 2a, Table 3).

Density associations

There was no association between the 12 neighborhood simple density exposures at 1-mile buffer size and cognitive/WMH outcomes either before (models 1a/1b) or after adjusting for census tract population density and census tracts as a random effect (models 2a/2b; Table 4). The associations between simple neighborhood densities per square mile for ½- and 3-mile buffer sizes and cognitive function/WMH are reported in Additional File 3: Table S5. One additional alcoholic drinking place per square mile for the 3-mile buffer size was nominally associated with a 0.71 SD (95% CI: −1.38, −0.04) decrease in general cognitive function after adjusting for census tract population density and census tracts as a random effect ($p = 0.03$; model 2a; Additional File 3: Table S5). However, after multiple testing correction, no associations were significant (all FDR $q > 0.1$).

We also tested the association between the 12 neighborhood simple density exposures examined at 1-mile

Table 1 Sample characteristics of Genetic Epidemiology Network of Arteriopathy (GENOA) African Americans ($N=542$)

	Mean (SD) or *n*%
Age at cognition measurement (years)	62.52 (7.69)
Sex	
Female	403 (74.35%)
Male	139 (25.65%)
Educational attainment	
Completed at least 4 years of college or technical/trade school	155 (28.60%)
Completed high school degree/GED	252 (46.49%)
Less than high school degree/GED	135 (24.91%)
Smoking status	
Current smoker	83 (15.31%)
Former smoker	125 (23.06%)
Never smoker	334 (61.62%)
General cognitive function	0.03 (0.99)
Delayed recall (RAVLT, number of words recalled)	6.95 (3.29)
Processing speed (DSST, number of symbols)	33.82 (13.04)
Word fluency (COWA-FAS, number of words)	29.40 (11.64)
Visual conceptual tracking (TMTA, seconds to test completion)	63.75 (35.22)
White matter hyperintensity (WMH, cm^3)[a]	9.42 (9.19)
Total intracranial volume (TIV, cm^3)[a]	1376.58 (129.81)
Neighborhood characteristics	
Neighborhood socioeconomic disadvantage	3.41 (3.46)
Fast food destination density[b]	0.75 (0.85)
Unfavorable food stores without alcohol density[b]	1.94 (1.75)
Unfavorable food stores with alcohol density[b]	1.24 (1.13)
Favorable food stores density[b]	0.22 (0.31)
Total physical activity destinations density[b]	0.34 (0.37)
Total social engagement destinations density[b]	14.37 (10.85)
Total popular walking destination density[b]	3.53 (3.13)
Alcoholic drinking places density[b]	0.36 (0.62)
Total food stores density[b]	3.34 (3.08)
MRFEI with alcohol[c]	0.10 (0.13)
MRFEI without alcohol[c]	0.12 (0.14)

Abbreviations: *RAVLT*, Rey Auditory Verbal Learning Test; *DSST*, Digit Symbol Substitution Test; *COWA-FAS*, Controlled Oral Word Association Test; *TMTA*, Trail Making Test A; *WMH*, white matter hyperintensity; *MRFEI*, Modified Retail Food Environment Index

[a] Sample size = 466

[b] Simple density measures per square mile for 1-mile buffer size

[c] Derived from simple density measures per square mile for 1-mile buffer size

buffer region with each of the four cognitive domains (model 2a; Table 5). One additional fast food destination or unfavorable food store with alcohol per square mile was nominally associated with a 0.05 (95% CI: 0.01, 0.09; $p=0.04$) and a 0.04 (95% CI: 0.00, 0.08; $p=0.04$) second increase in visual conceptual tracking score, respectively, indicating that more of these destinations was associated with better visual conceptual tracking. In addition, one additional alcohol drinking place per square mile was nominally associated with a 0.62 word (95% CI: 0.05, 1.19; $p=0.03$) increase in delayed recall score (Table 5), indicating better memory function. However, no associations were significant at FDR $q<0.1$. The associations between simple neighborhood densities per square mile for ½- and 3-mile buffer sizes and cognitive/WMH measures are reported in Additional File 3: Tables S5 and S6.

We also tested the associations between the 12 neighborhood kernel density exposures at ½-, 1- and 3- mile buffer sizes with cognitive function/WMH (Additional File 3: Table S7) and the cognitive domains (Additional File 3: Table S8). There were no associations between the kernel density neighborhood exposures and general

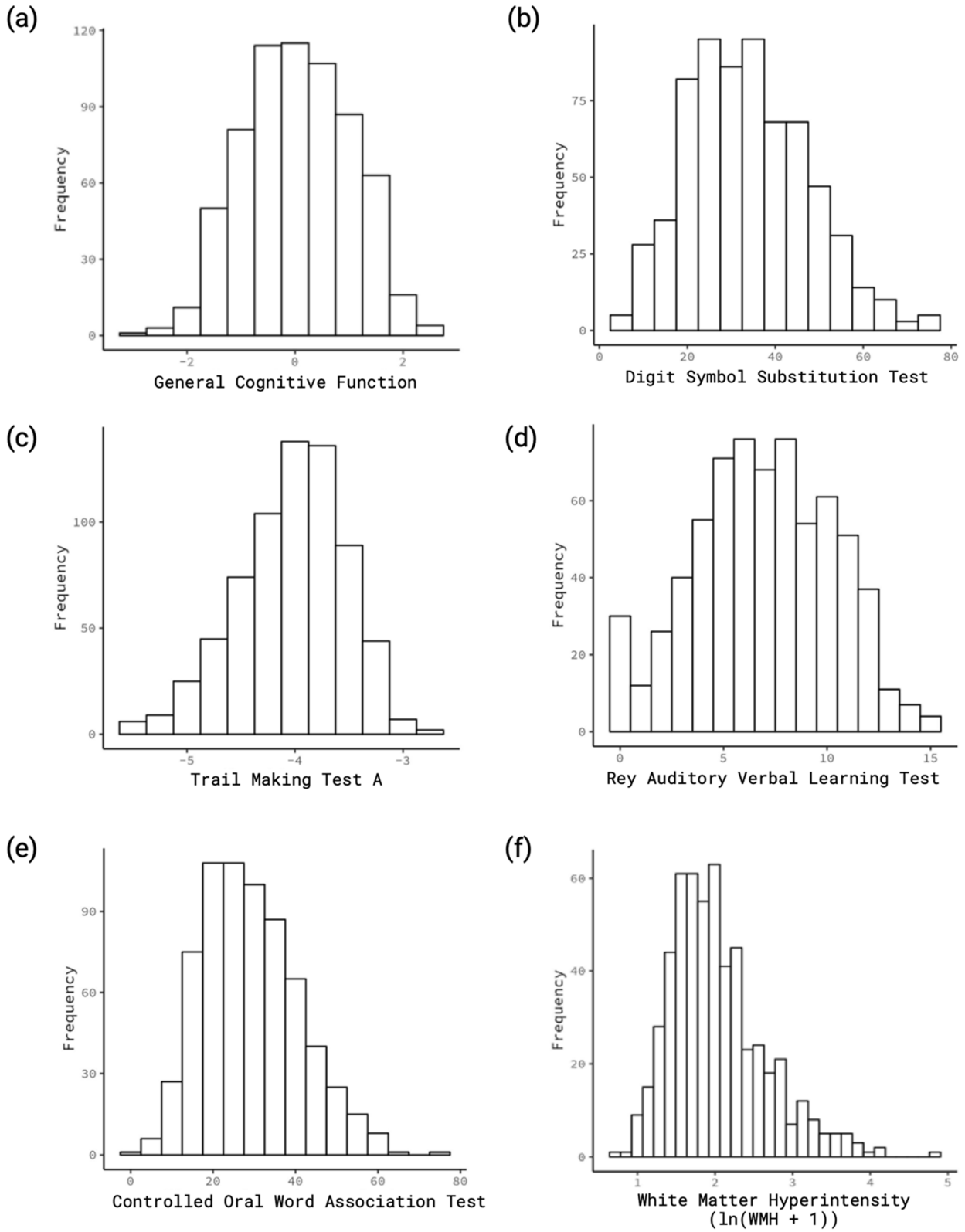

Fig. 2 Distributions of cognitive and structural brain measures. **a** General cognitive function, **b** Digit Symbol Substitution Test, **c** Trail Making Test A, **d** Rey Auditory Verbal Learning Test, **e** Controlled Oral Word Association Test, and **f** log-transformed white matter hyperintensity (ln(WMH + 1))

Table 2 Associations between neighborhood socioeconomic disadvantage and cognition/WMH

	General cognitive function ($N=477$)				White matter hyperintensity ($N=404$)			
	Model 1a		Model 2a		Model 1b		Model 2b	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Neighborhood socioeconomic disadvantage	−0.01 (−0.03, 0.01)	0.30	−0.01(−0.03, 0.01)	0.36	2.0E−3 (−0.01, 0.02)	0.83	0.01 (−0.01, 0.03)	0.28

Abbreviations: *CI* confidence interval, *WMH* white matter hyperintensity, *PC* principal component

Model 1a: cognitive function = neighborhood socioeconomic disadvantage + age at measurement + sex + PC1-4 + education + smoking status + familial relatedness (random effect)

Model 2a: cognitive function = model 1a + census tract population density + census tract (random effect)

Model 1b: WMH = model 1a + total intracranial volume

Model 2b: WMH = model 2a + total intracranial volume

* $p<0.05$

Table 3 Associations between neighborhood socioeconomic disadvantage and cognitive measures (model 2a; $N=477$)

	DSST		COWA-FAS		RAVLT		TMTA	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Neighborhood socioeconomic disadvantage	−0.01 (−0.38, 0.36)	0.95	0.02 (−0.33, 0.37)	0.92	−0.03 (−0.14, 0.09)	0.66	0.02 (−0.03, 0.00)	0.07

Abbreviations: *DSST*, Digit Symbol Substitution Test; *COWA-FAS*, Controlled Oral Word Association Test; *RAVLT*, Rey Auditory Verbal Learning Test; *TMTA*, Trail Making Test A; *CI*, confidence interval

Model 2a: neurocognitive measure = neighborhood socioeconomic disadvantage + age at measurement + sex + PC1-4 + education + smoking status + population density + familial relatedness (random effect) + census tract (random effect)

* $p<0.05$

cognitive function or WMH in models 1a/2a and 1b/2b (Additional File 3: Table S7). At the 1-mile buffer, kernel density of fast food destinations and unfavorable food stores with alcohol were both nominally associated with better visual conceptual tracking, consistent with the simple density associations; however, the association between kernel density of alcohol drinking places and delayed recall score was not. We also found that at the 1-mile buffer, kernel densities of unfavorable food stores without alcohol, total popular walking destinations, and total food stores were all nominally associated with better visual conceptual tracking as well. However, no associations were significant at FDR $q<0.1$. The associations between kernel neighborhood densities per square mile for ½- and 3-mile buffer sizes and cognitive/WMH measures are also reported in Additional File 3: Tables S7 and S8.

Mediation analysis

When the total effect of a neighborhood characteristic (simple density at 1-mile buffer) and cognitive function/WMH was significant at $p<0.05$, we conducted epigenome-wide high-dimensional mediation analysis to identify possible CpG sites that may partially mediate the relationship between the neighborhood exposure and corresponding outcome using model 2a in 477 participants with complete data. The following exposure-outcome combinations were investigated: (a) alcohol drinking places and delayed recall, (b) fast food destinations and visual conceptual tracking, and (c) unfavorable food stores with alcohol and visual conceptual tracking. Figure 3 shows quantile–quantile (QQ) plots for the 5 exposure-outcome relationships using Sobel-Comp. The p-values from Sobel-Comp test were deflated, potentially due to the large number of zero exposure-mediator (β_1) and mediator-outcome (β_3) estimates and the small sample size (Fig. 3).

Discussion

As the aging population rapidly grows, a better understanding of how the neighborhood environment may affect cognitive health is needed to mitigate the future burden of dementia in the USA. While there are studies showing the effect of individual factors, such as lifestyle, genetics and biomarkers on cognitive function, there is a need for more research on the association between neighborhood characteristics and cognitive function to date [97]. Furthermore, only a few studies have examined the potential molecular mechanisms linking neighborhood environment and cognitive health [17, 98]. To our

Table 4 Associations between simple density of neighborhood destinations per square mile for 1-mile buffer size and cognitive function/WMH

Neighborhood characteristics	General cognitive function				White matter hyperintensity			
	Model 1a ($N=542$)		Model 2a ($N=477$)		Model 1b ($N=466$)		Model 2b ($N=404$)	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Fast food destination density	−0.02 (−0.09, 0.05)	0.53	−0.03 (−0.11, 0.05)	0.39	0.03 (−0.03, 0.09)	0.23	0.04 (−0.02, 0.10)	0.25
Unfavorable food stores without alcohol density	−0.02 (−0.06, 0.02)	0.38	−0.02 (−0.06, 0.02)	0.37	0.01 (−0.02, 0.04)	0.40	0.02 (−0.02, 0.06)	0.24
Unfavorable food stores with alcohol density	−0.03 (−0.09, 0.03)	0.26	−0.05 (−0.11, 0.01)	0.14	0.02 (−0.02, 0.06)	0.26	0.03 (−0.01, 0.07)	0.25
Favorable food stores density	−0.08 (−0.28, 0.12)	0.45	−0.11 (−0.33, 0.11)	0.31	0.02 (−0.13, 0.17)	0.83	−0.01 (−0.17, 0.15)	0.84
Total physical activity destinations density	−0.07 (−0.23, 0.09)	0.36	−0.05 (−0.25, 0.15)	0.58	0.03 (−0.10, 0.16)	0.65	0.05 (−0.09, 0.19)	0.58
Total social engagement destinations density	−3.16E−03 (−0.01, 0.00)	0.29	−3.59E−03 (0.00, 0.00)	0.35	1.59E−03 (0.00, 0.01)	0.49	3.46E−03 (0.00, 0.00)	0.24
Total popular walking destination density	−3.75E−03 (−0.02, 0.02)	0.71	−2.49E−03 (−0.02, 0.02)	0.84	0.01 (−0.01, 0.03)	0.38	0.01 (−0.01, 0.03)	0.25
Alcoholic drinking places density	−0.01 (−0.11, 0.09)	0.78	0.01 (−0.11, 0.13)	0.89	1.86E−03 (−0.08, 0.08)	0.99	0.03 (−0.07, 0.13)	0.52
Total food stores density	−0.01 (−0.03, 0.01)	0.63	−3.80E−03 (−0.02, 0.02)	0.77	2.21E−03 (−0.01, 0.02)	0.78	0.01 (−0.01, 0.03)	0.37
Modified Retail Food Environment Index with alcohol	−0.10 (−0.70, 0.50)	0.73	−0.13 (−0.76, 0.50)	0.69	0.17 (−0.25, 0.59)	0.41	0.08 (−0.37, 0.53)	0.74
Modified Retail Food Environment Index without alcohol	−0.02 (−0.55, 0.51)	0.93	−0.05 (−0.62, 0.52)	0.85	0.10 (−0.28, 0.48)	0.58	0.03 (−0.40, 0.46)	0.90

Abbreviations: *CI* confidence interval, *WMH* white matter hyperintensity, *PC* principal component

Model 1a: cognitive function = neighborhood characteristic + age at measurement + PC1-4 + sex + education + smoking status + familial relatedness (random effect)

Model 2a: cognitive function = model 1a + neighborhood socioeconomic disadvantage + census tract population density (random effect) + census tract (random effect)

Model 1b: WMH = model 1a + total intracranial volume

Model 2b: WMH = model 2a + total intracranial volume

* $p<0.05$; **$p<0.0021$ (i.e., $p<0.05$ after Bonferroni correction for 24 tests)

knowledge, this study is the first assessment of whether DNA methylation partially mediates the association between various neighborhood environment characteristics and cognitive function in AA without dementia. This cross-sectional study suggests that greater simple densities of alcohol drinking places may be associated with better memory as measured by delayed recall (RAVLT) and greater densities of fast food destination and unfavorable food stores with alcohol with better attention and processing speed as measured by visual conceptual tracking (TMTA) in cognitively normal AA. However, we did not find associations between neighborhood characteristics and WMH. We also were unable to detect mediating effects of DNA methylation on the associations between these neighborhood characteristics on cognitive function and cognitive measures in this sample. Nevertheless, our findings that neighborhood density of fast food restaurants and bars may serve as a protective resource rather than as a risk factor challenge status quo public health paradigms and are an important contribution that shows the potential utility of community and third places.

We initially expected higher densities of unfavorable food stores to be associated with worse cognitive function, suggesting that increased access to unhealthy food and drink may encourage unhealthy dietary choices that lead to lower cognitive health. Instead, we found that greater densities of alcohol drinking places, fast food, and unfavorable stores with alcohol that may encourage unhealthy dietary choices were associated with better cognitive function as measured by delayed recall and visual conceptual tracking after adjustment for population density. Considering that Jackson, MS, does not have a highly dense population (approximately 1300 people per square mile in 2010), the presence of these walking destinations may provide meeting places for community members, allowing for greater interaction and

Table 5 Associations between simple density of neighborhood destinations per square mile for 1-mile buffer size and cognitive measures (model 2a; $N = 477$)

Neighborhood characteristics	DSST		COWA-FAS		RAVLT		TMTA	
	β (95% CI)	*p*	*β* (95% CI)	*p*	*β* (95% CI)	*p*	*β* (95% CI)	*p*
Fast food destination density	−0.39 (−1.45, 0.67)	0.45	0.27 (−0.87, 1.41)	0.63	0.1 (−0.27, 0.47)	0.57	0.05 (0.01, 0.09)	**0.04***
Unfavorable food stores without alcohol density	−0.17 (−0.74, 0.40)	0.55	−0.19 (−0.80, 0.42)	0.52	0.13 (−0.07, 0.33)	0.18	0.02 (0.00, 0.04)	0.19
Unfavorable food stores with alcohol density	−0.45 (−1.29, 0.39)	0.28	−0.07 (−0.97, 0.83)	0.87	0.01 (−0.28, 0.30)	0.94	0.04 (0.00, 0.08)	**0.04***
Favorable food stores density	−1.46 (−4.36, 1.44)	0.30	0.2 (−2.90, 3.30)	0.89	−0.31 (−1.29, 0.67)	0.52	0.12 (−0.02, 0.26)	0.08
Total physical activity destinations density	−1.07 (−3.60, 1.46)	0.39	−1.18 (−3.88, 1.52)	0.37	0.44 (−0.42, 1.30)	0.30	0.05 (−0.07, 0.17)	0.38
Total social engagement destinations density	−0.06 (−0.16, 0.04)	0.26	−0.03 (−0.13, 0.07)	0.61	0.02 (−0.02, 0.06)	0.25	0.00 (0.00, 0.00)	0.36
Total popular walking destination density	−0.05 (−0.38, 0.28)	0.77	0.02 (−0.33, 0.37)	0.88	0.09 (−0.01, 0.19)	0.09	0.01 (−0.01, 0.03)	0.20
Alcoholic drinking places density	0.16 (−1.51, 1.83)	0.85	−0.93 (−2.67, 0.81)	0.28	0.62 (0.05, 1.19)	**0.03***	−3.11E−03 (−0.08, 0.08)	0.94
Total food stores density	−0.01 (−0.36, 0.34)	0.95	−0.11 (−0.48, 0.26)	0.53	0.02 (0.00, 0.04)	0.07	0.01 (−0.01, 0.03)	0.41
Modified Retail Food Environment Index with alcohol	−3.56 (−11.55, 4.43)	0.36	4.15 (−4.43, 12.73)	0.32	0.1 (−0.02, 0.22)	0.65	0.20 (−0.19, 0.59)	0.28
Modified Retail Food Environment Index without alcohol	−3.29 (−10.54, 3.96)	0.36	4.43 (−3.37, 12.23)	0.25	−0.64 (−3.48, 2.20)	0.66	0.20 (−0.13, 0.53)	0.21

Abbreviations: *DSST* Digit Symbol Substitution Test, *COWA-FAS* Controlled Oral Word Association Test, *RAVLT* Rey Auditory Verbal Learning Test, *TMTA* Trail Making Test A, *CI* confidence interval, *PC* principal component

Model 2a: neurocognitive measure = neighborhood characteristic + age at measurement + PC1-4 + sex + education + smoking status + neighborhood socioeconomic disadvantage + census tract population density + familial relatedness (random effect) + census tract (random effect)

* $p < 0.05$; ** $p < 0.001$ (i.e., $p < 0.05$ after Bonferroni correction for 48 tests)

stimulation of cognitive health, regardless of their impact on unhealthy diet and behaviors. As such, these meeting hubs may contribute to better cognitive function through increased access to community residents, neighborhood community resources, and proximal walking destinations that improve cognitive health by increasing physical activity levels, social engagement, mental health or quality of life [99].

To date, results from previous studies examining similar characteristics of the neighborhood environment and cognitive function have been mixed. In the Chicago Health and Aging Project (CHAP), increasing densities of social and walking destinations such as community centers were associated with slower cognitive decline [100], yet a study in the Multi-Ethnic Study of Atherosclerosis (MESA) showed an inverse association between these same measures and cognitive function and most noticeably in individuals of non-white race [101]. Also, closer access to community resources has been associated with better cognitive function in NHW, but worse cognitive function in AA [102], while other studies showed no association between the presence of neighborhood built environment characteristics, such as recreation centers and institutional resources (e.g., libraries, schools and community centers) and cognitive function [100, 102, 103]. In our study, the plausible mechanisms and direction or presence of neighborhood-cognitive function association may depend on the neighborhood characteristic and cognitive domain being studied, and more than one mechanism may be at play.

Different underlying mechanisms of neighborhood environment on cognitive function have been examined to understand how interventions can prevent dementia onset. In MESA, increasing social destination density, walking destination density, and intersection density were associated with worse cognitive function, and increasing proportion of land dedicated to retail was associated with better processing speed [104]. While we did not observe similar patterns among simple densities, we did observe greater kernel densities of total popular walking destinations per square mile (for ½- and 1-mile buffer sizes) were associated with higher visual conceptual tracking and greater kernel densities of total social engagement destinations per square mile (½-mile buffer) were associated with higher delayed recall. Access to a safe and walkable neighborhood environment may help older adults age in place and delay the onset of cognitive impairment and decline prior to dementia [103, 105, 106]. In addition, the positive relationship between proportion of land dedicated to retail

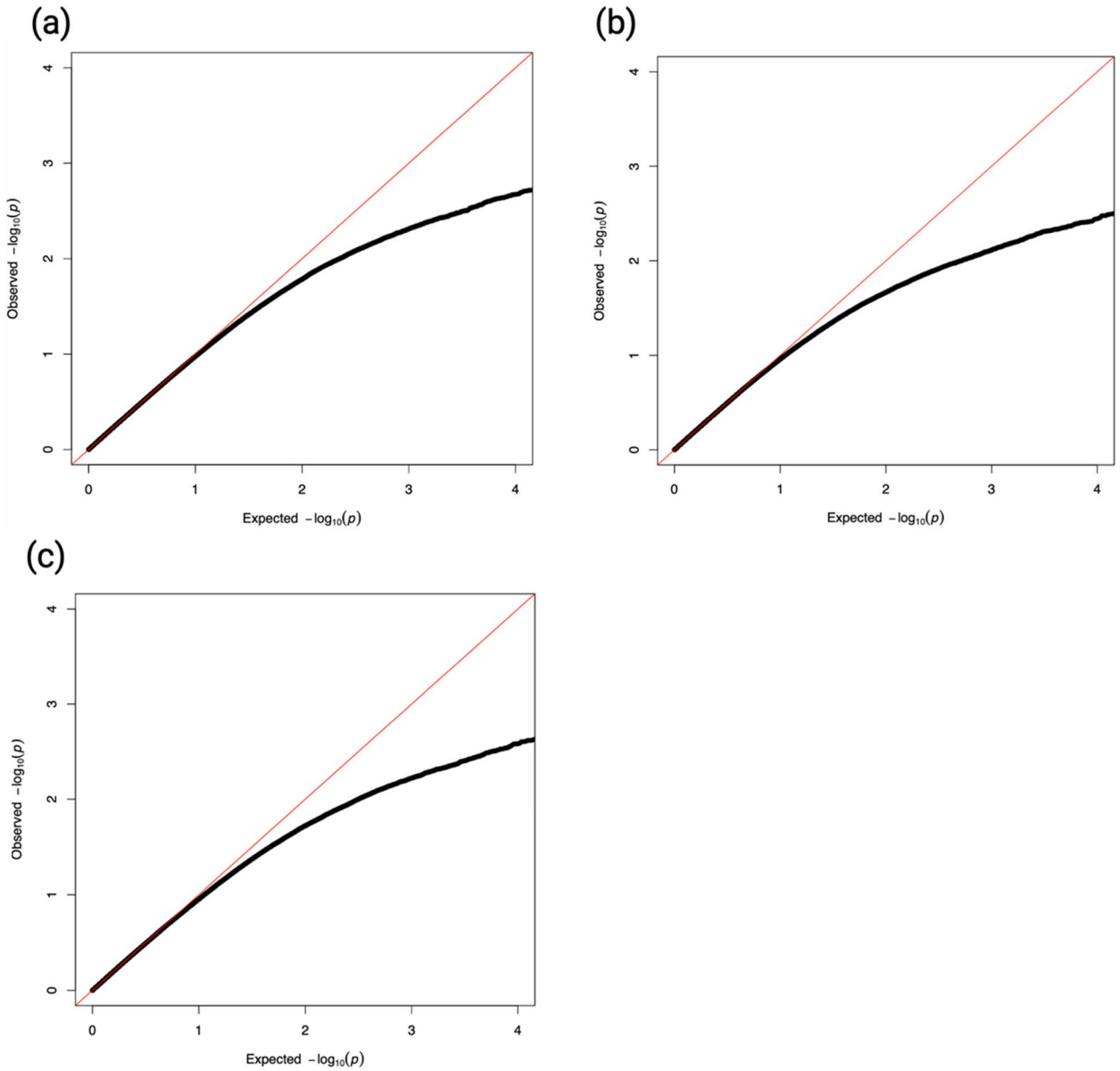

Fig. 3 Quantile–quantile (QQ) plots for the epigenetic mediation of the associations between neighborhood characteristics and cognitive function. QQ plots for the Sobel-Comp mediation hypothesis testing method with $N = 477$ observations. The exposures are simple densities per square mile for 1-mile buffer sizes, the outcomes are neurocognitive measures, and the mediators are 857,121 CpG sites. The exposure–outcome models tested are as follows: **a** alcohol drinking places density—RAVLT, **b** fast food destination density—TMTA, and **c** unfavorable food stores (with alcohol) density—TMTA. Mediation models are adjusted for age, sex, education, smoking status, first four principal components, neighborhood socioeconomic disadvantage, and census tract population density, with family and census tracts as random effects

and processing speed may be explained by increased utilitarian physical activity and social engagement or increased cognitive stimulation that contributes to the cognitive reserve [103]. Also, fast food outlets and local retail food environments may play a role in providing social and community engagement, connectedness, emotional support, and cognitive stimulation for older adults outside of more formal or age-graded settings such as doctor's office, church, or senior center [107, 108].

Other studies have found inverse relationships between neighborhood destinations (such as retail stores) and cognitive function that may be related to cognitive overload among older adults due to stress from greater number of destination choices or navigation of traffic. It is possible that highly dense areas

consisting of social and walking destinations and street intersections have increased vehicular pollutant exposure due to decreased distances to busy roadways and decreased air ventilation created by buildings [109]. Airborne pollutants have been associated with worse cognitive function and brain structure in older adults [109]. Neighborhood factors such as low SES, high racial segregation, and unhealthy diet and lifestyle habits may increase susceptibility to cognitive decline and dementia [24–32]. These mixed results from other studies may be affected by residual confounding from unmeasured factors. Thus, additional research on the many confounders and mechanisms related to the relationship between the neighborhood environment and cognitive function is necessary.

In addition, we found correlations between favorable and unfavorable destinations, even after adjusting for population density, which may further illuminate our findings in the context of cognitive health and behaviors. For example, greater densities of fast food destinations were associated with greater densities of favorable food stores, physical activity destinations, and MRFEI (the proportion of favorable food stores to total food stores), even after adjusting for population density. These correlations in Jackson may be attributed to a complex interplay of socioeconomic, urban planning, cultural, historical, and policy-related factors and confounders. Furthermore, socioeconomic disparities often lead to variations in access to health-promoting resources, with neighborhoods of lower SES facing limited access to healthy options and an increased prevalence of unhealthy alternatives. The availability of favorable food stores may reflect the demand from residents, according to their purchasing power, who can afford healthier options. To account for this discrepancy, we adjusted for neighborhood socioeconomic disadvantage in our associations. The city's urban planning, historical development (e.g., redlining and discriminatory housing practices in the past), and government policies may play crucial roles in shaping the distribution of health-related destinations. Another possibility is that areas with higher commercial zoning may attract both fast food establishments and favorable food stores, creating clusters of businesses in certain neighborhoods. Additionally, cultural preferences and consumer demand influence the types of businesses and amenities in specific neighborhoods. For example, the high correlation between favorable and unfavorable food store density may be due to a micro-cultural artifact at play in Jackson that encourages increased densities of fast food in Black neighborhoods [110]. This micro-culture, which results from shared race/ethnicity, beliefs, styles, skills, and habits of residents of a particular area, may disfavor physical activity and other healthy behaviors, even in the presence of features that allow for them [111, 112].

To date, the relationships between neighborhood disadvantage markers and health outcomes in AA have been mixed. Multiple theories have been proposed to describe minority communities that have been historically oppressed and their reliance on community-specific, and often non-institutional, resources [113]. For example, the "weathering" hypothesis of racial inequality proposes that Black individuals endure early health deterioration due to cumulative economic and social disadvantages across the life course [114]. As such, multiple and chronic stressors may result in wear and tear on health from an increased "allostatic load." Another theory of "cognitive reserve" proposes that other cognitive attributes may compensate for cognitive health in the case that other faculties (e.g., brain tissue integrity) are weakened [115]. Lastly, based on Marginalized-Related Diminished Returns (MDRs), there may be no innate or neurobiological explanation for observed racial disparities; instead, adverse social factors (e.g., structural racism, segregated schools, poor education and social disparities such as unsafe neighborhoods) may prevent Black communities (across socioeconomic levels) from securing tangible gains from their higher educational attainment [116–118]. To that end, it is important to consider the effects of structural racism, social stratification, Jim Crow, redlining and racial segregation on Black communities when considering cognitive aging and other health disparities. In this study, results are mixed; however, they present the possibility that third places and gathering spaces among community may be important for the overall cognitive health of AA. As such, while genetic factors may play some role in explaining racial disparities in health between AA and EA, social factors may be more important [119, 120]. Effective efforts and interventions to reduce chronic stressors and improve health treatments would not only focus on the individual but must also seek to alter the social, economic, and political structures that cause disease in vulnerable populations [119]. Further research is warranted at the intersection of race, SES, and cognitive health, as the racial disparities in the effects of risk and protective factors for dementia has been understudied [57].

Considering that the neighborhood context has the potential to influence cognitive function, it is important to clarify the potential biological mechanisms linking neighborhood characteristics and cognitive function to shed light on the etiology and causal mechanisms driving health disparities. DNA methylation may help us better understand the pathways that mediate or interact with the environment and cognitive function. Previous studies have shown that the neighborhood context affects DNA methylation, even after adjusting for individual- level

factors and that DNA methylation patterns in stress and inflammatory pathways may be responsive to interventions [38]. EWAS have also found multiple CpGs related to neurodegeneration associated with cognitive function [40, 41]. Considering these factors and that past studies have found CpGs mediating the relationship between neighborhood socioeconomic disadvantage and various CVD risk factors [44–46], which are potential upstream factors of cognitive function and dementia, we expected to detect mediating CpG sites in the associations between neighborhood characteristics and cognitive function/WMH.

One reason that we may not have observed epigenetic mediation is because genetic factors may play a smaller role in cognitive function for AA than NHW. For example, the strongest risk factor for dementia, *APOE* epsilon 4, has a weaker effect in AA than Whites [121, 122]. Perhaps neighborhood factors also impact cognitive function through pathways outside of genetic changes. A second reason could be the choice of mediation model implemented. Sobel-Comp [96] is a more powerful extension of high-dimensional mediation hypothesis testing (HDMT) [123] that is preferred when almost all exposure-mediator and mediator-outcome associations are equal to 0 (π_{00} is close to 1), and there are almost no non-zero exposure-mediator or mediator-outcome associations (π_{01} and π_{10} are close to 0). One limitation is that Sobel-Comp is conservative under these conditions, compared to other high-dimensional mediation methods such as JT-Comp [124]; however, Sobel-Comp has the advantages of using the correct mixture reference distribution for Sobel's test statistic, maintaining a false positive rate (FPR) close to the nominal level, and it yielding larger true positive rates (TPRs). In this study, Sobel-Comp was the appropriate method because π_{00} was bounded away from 1 for all associations tested, but we did not detect significant mediation effects due to a potentially large number of zero exposure-mediator (β_1) and mediator-outcome (β_3) estimates, deflated p-values, and small sample size. In addition, DNA methylation levels of proximal CpGs in the same biological pathways may be correlated, resulting in properties that are not desirable for TPR and FPR [77]. When there are correlated mediators, single-mediator hypothesis testing methods like Sobel-Comp are unable to fully account for all the mediator-outcome confounders affected by the exposure (also known as co-mediators), thus reducing the power to detect mediating CpGs and potentially biasing our effect estimates [46, 125–127]. While it is possible to jointly model multiple mediators using the Bayesian high-dimensional mediation method [128] and its use may have reduced the multiple testing burden and increased the power to detect independent effects, this method is computationally heavy and only a few thousand mediators would have been evaluated simultaneously [128–130]. Evaluating our mediation analysis models to account for multiple correlated mediators are of interest for future analysis. Our results may indicate that methylation is not a critical component of the mediating pathway between neighborhood exposures and cognitive/WMH outcomes.

Our observed associations should also be considered with caution due to the limited statistical power inherent in our sample. The small sample size may have restricted our ability to detect the total effects between neighborhood characteristics and cognitive/WMH outcomes that could exist within the population. In addition, although our total effect associations allowed us to begin to characterize the relationships between neighborhood factors and cognitive function, findings did not reach statistical significance when accounting for multiple testing using FDR, which could be attributed to small sample size and power. Research using AA samples with larger sample sizes is needed to better understand how neighborhood characteristics are related to cognitive/WMH outcomes in AA populations.

Our study also had other limitations. Our findings may be affected by residual confounding by unmeasured variables, increased exposure to factors including air pollution, potential for chance social interactions, crime, physical disability, discrimination, and structural racism that may be due to increased walking in the neighborhood which influences cognitive function, or factors related to study design (e.g., cross-sectional nature, bias due to loss-to-follow-up, or bias due to refusal of blood draw). Notably, GENOA is a unique example in that it was initially established to recruit hypertensive sibships. As such, participants were already actively engaging with the University of Mississippi for their medical care and part of a research knowledgeable community that was more likely to trust doctors and be a part of the medical system. In addition, participants were accessing family resources for their hypertension status and other potential comorbidities, indicating that the cohort is possibly sicker than those in the general population. As such, our cohort may have intrinsic selection bias to the nature of those living in the area and having agreed to be a part of the GENOA study. Moreover, we did not investigate the important ways in which air pollution, structural racism and stress are mediators on the pathways of specific neighborhood-cognitive function/WMH associations. Also, further longitudinal and life-course studies that explore mediation pathways between early-life, mid-life, and late-life neighborhood, methylation, and cognitive function/WMH measures are needed. In this study, neighborhood characteristics were based on current

home addresses, and we did not take into account that earlier or longer-term neighborhood exposures may be important for late-life cognitive function/WMH.

Our study also has notable strengths. To our knowledge, this study is the first to examine the role of DNA methylation in mediating the relationships between neighborhood characteristics and cognitive function/WMH in a cohort of older adults without diagnosed dementia. Our study was also conducted in AA, an understudied population with a higher prevalence of dementia [131, 132] and higher conferred risk of cognitive decline and dementia from neighborhood environment compared to EA [133]. Additionally, with rich cognitive and WMH measures, we were able to assess associations with multiple cognitive domains, general cognitive function, and a risk factor for VaD. We were also able to adjust for neighborhood socioeconomic disadvantage to control for the influence of income, education, employment, and other SES indicators that might independently affect cognitive health. We also controlled for confounding by census tract population density because it could influence the availability of stores and cognitive outcomes. High-density urban areas may have greater access to stores and services, and low-density rural areas may have lower access to these destinations. Both densities may affect cognitive health, so adjusting for population density ensures that our results are not skewed by these population differences and are more accurate. Also, we utilized a powerful high dimensional mediation method that reduced the likelihood of false positives. Lastly, our primary analysis used 1-mile density buffers around participants' homes, which provide more precise spatial representation of neighborhoods than administrative boundaries and may more accurately reflect nearby places and distances that an older adult would walk.

Conclusions

In the present study, we found that destination density had small but notable effects on several domains of cognitive function in AA without dementia. However, we detected no significant mediating effects of DNA methylation on these associations. Upon further examination of the potential pathways between the neighborhood environment and cognitive function, we may develop potential behavioral, infrastructural, and pharmaceutical interventions to allow aging in place and healthy brain aging in older adults, especially marginal populations that are most at risk.

Abbreviations

AA	African American
AD	Alzheimer's disease
COWA-FAS	Controlled Oral Word Association Test
CpG	Cytosine-phosphate-guanine
DAG	Directed acyclic graph
DNAm	DNA methylation
DSST	Digit Symbol Substitution Test
EA	European Americans
EWAS	Epigenome-wide association study
FDR	False discovery rate
FLAIR	Fluid-attenuated inversion recovery
FUPC	First unrotated principal component
GENOA	Genetic Epidemiology Network of Arteriopathy
GMBI	Genetics of Microangiopathic Brain Injury
MCI	Mild cognitive impairment
MMSE	Mini Mental State Exam
MRI	Magnetic resonance imaging
NHW	Non-Hispanic whites
PC	Principal component
PCA	Principal component analysis
RA	Risk allele
RAF	Risk allele frequency
RAVLT	Rey Auditory Verbal Learning Test
SCWT	Stroop Color-Word Test
SD	Standard deviation
SES	Socioeconomic status
SVD	Small vessel disease
TMTA	Trail Making Test A
VaD	Vascular dementia
WMH	White matter hyperintensity

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03845-7.

Additional File 1: Fig. S1. Flow diagram illustrating sample sizes for neighborhood density and neighborhood socioeconomic disadvantage analyses for cognitive measures in GENOA AA. Fig. S2. Flow diagram illustrating sample sizes for neighborhood density and neighborhood socioeconomic disadvantage analyses for white matter hyperintensity in GENOA AA.

Additional File 2: Supplementary Methods

Additional File 3: Table S1. Pearson's correlations among the cognitive/WMH outcomes ($N = 466$). Table S2. Pearson's correlations among neighborhood socioeconomic disadvantage and neighborhood simple density measures per square mile for 1-mile buffer size ($N = 542$). Table S3. Associations among neighborhood socioeconomic disadvantage and neighborhood simple density measures per square mile for 1-mile buffer size after adjusting for census tract population density ($N = 542$). Table S4. Pearson's correlations among neighborhood socioeconomic disadvantage and simple and kernel densities per square mile for 1-mile buffer size. Table S5. Associations between simple density of neighborhood destinations per square mile for ½-, 1- and 3- mile buffer sizes and cognitive function/WMH. Table S6. Associations between simple density of neighborhood destinations per square mile for ½-, 1- and 3- mile buffer sizes and cognitive measures ($N = 477$). Table S7. Associations between kernel density of neighborhood destinations per square mile for ½-, 1- and 3- mile buffer sizes and cognitive function/WMH. Table S8. Associations between kernel density of neighborhood destinations per square mile for ½-, 1- and 3- mile buffer sizes and cognitive measures ($N = 477$).

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Authors' contributions

Conceptualization, D.L.C., J.A.S.; methodology, D.L.C., J.A.S., L.T., X.Z., K.L.M., F.F., A.V.D.R.; software, formal analysis, and investigation, D.L.C., J.D., L.O., S.M.R., L.T.; resources, F.F., A.V.D.R., T.H.M., S.L.R.K.; writing—original draft preparation, D.L.C., J.A.S.; writing—review and editing, D.L.C., S.M.R., W.Z., T.H.M., S.L.R.K., K.B., X.Z., J.A.S.; visualization, D.L.C.; supervision, J.A.S.; funding acquisition, J.A.S. All authors read and approved the final manuscript.

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Data availability
The phenotype data used in the current study are available upon reasonable request to J.A.S. and S.L.R.K. and with a completed data use agreement (DUA). Genotype data are available from the Database of Genotypes and Phenotypes (dbGaP): *Genetic Epidemiology Network of Arteriopathy (GENOA)*, accession number: phs001238.v2.p1, https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001238.v2.p1, released 08/08/2018. Methylation data are available from the Gene Expression Omnibus (GEO): *Methylation data from stored peripheral blood leukocytes from African American participants in the GENOA study*, accession number: GSE210256, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE210256, released 08/04/2022. Due to IRB restriction, mapping of the sample IDs between genotype data (dbGaP) and methylation data (GEO) cannot be provided publicly but is available upon written request to J.A.S. and S.L.R.K.

Declarations

Ethics approval and consent to participate
This study was approved by the Health Sciences and Behavioral Sciences Institutional Review Board at the University of Michigan (HUM00113791). Written informed consent was obtained from all participants.

Consent for publication
All authors have read and agreed to the published version of the manuscript.

Competing interests
The authors declare no competing interests.

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