Association of Racial Residential Segregation Throughout Young Adulthood and Cognitive Performance in Middle-aged Participants in the CARDIA Study

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IMPORTANCE Neighborhood-level residential segregation is implicated as a determinant for poor health outcomes in black individuals, but it is unclear whether this association extends to cognitive aging, especially in midlife.

OBJECTIVE To examine the association between cumulative exposure to residential segregation during 25 years of young adulthood among black individuals and cognitive performance in midlife.

DESIGN, SETTING, AND PARTICIPANTS The ongoing prospective cohort Coronary Artery Risk Development in Young Adults (CARDIA) Study recruited 5115 black and white participants aged 18 to 30 years from 4 field centers at the University of Alabama, Birmingham; University of Minnesota, Minneapolis; Northwestern University, Chicago, Illinois; and Kaiser Permanente, Oakland, California. Data were acquired from February 1985 to May 2011. Among the surviving CARDIA cohort, 3671 (71.8%) attended examination year 25 of the study in 2010, when cognition was measured, and 3008 (81.9%) of those completed the cognitive assessments. To account for time-varying confounding and differential censoring, marginal structural models using inverse probability weighting were applied. Data were analyzed from April 16 to July 20, 2019.

MAIN OUTCOMES AND MEASURES Racial residential segregation was measured using the Getis-Ord Gi* statistic, and the mean cumulative exposure to segregation was calculated across 6 follow-up visits from baseline to year 25 of the study, then categorized into high, medium, and low segregation. Cognitive function was measured at year 25 of the study, using the Digit Symbol Substitution Test (DSST), Stroop color test (reverse coded), and Rey Auditory Verbal Learning Test. To facilitate comparison of estimates, z scores were calculated for all cognitive tests.

RESULTS A total of 1568 black participants with available cognition data were included in the analysis. At baseline, participants had a mean (SD) age of 25 (4) years and consisted of 936 women (59.7%). Greater cumulative exposure to segregated neighborhoods was associated with a worse DSST z score (for high segregation, $\beta = -0.37$ [95% CI, $-0.61$ to $-0.13$]; for medium segregation, $\beta = -0.25$ [95% CI, $-0.51$ to 0.002]) relative to exposure to low segregation.

CONCLUSIONS AND RELEVANCE In this cohort study, exposure to residential segregation throughout young adulthood was associated with worse processing speed among black participants as early as in midlife. This association may potentially explain black-white disparities in dementia risk at older age.

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Several studies have reported disparities in cognitive performance,\textsuperscript{1-3} risk of dementia,\textsuperscript{1,4-6} and markers of brain aging\textsuperscript{7-9} between non-Hispanic black and white older adults in the United States, largely attributed to structural racism.\textsuperscript{10} In particular, neighborhood-level racial residential segregation continues to persist despite the passage of the Fair Housing Act of 1968\textsuperscript{11} and has been associated with many adverse health outcomes.\textsuperscript{10,12,13} Furthermore, residential segregation has been associated with worse built environment,\textsuperscript{13} psychosocial factors,\textsuperscript{14} educational quality,\textsuperscript{15} health behaviors,\textsuperscript{16} environmental exposures,\textsuperscript{17} and cardiometabolic disease,\textsuperscript{18-20} all of which may contribute to cognitive and brain aging.\textsuperscript{21-27} The association between racial residential segregation and cardiometabolic health factors, such as obesity and elevated blood pressure, is a particularly salient and clinically translatable pathway, because cardiometabolic health is a major risk factor for cognitive decline and brain aging.\textsuperscript{28} Educational quality is another important pathway owing to its association with cognitive reserve and dementia risk.\textsuperscript{27,29} However, literature examining the association of racial residential segregation with cognitive function is sparse.

Growing evidence suggests that maintaining cognitive function is a lifelong process and that several of the most important risk factors may begin earlier in the life course.\textsuperscript{30-32} Therefore, we examined the association between cumulative exposure to residential segregation during 25 years of young adulthood and cognitive performance in middle-aged black adults who are members of the Coronary Artery Risk Development in Young Adults (CARDIA) study.

**Methods**

**Source Population and Analytic Sample**

The CARDIA study is an ongoing, multicenter, prospective cohort study that focuses on the development and determinants of subclinical and clinical cardiovascular disease. Recruitment methods have previously been described.\textsuperscript{33} Briefly, starting in 1985, 5115 black and white participants aged 18 to 30 years were recruited from 4 field centers: the University of Alabama at Birmingham; University of Minnesota, Minneapolis; Northwestern University, Chicago, Illinois; and Kaiser Permanente, Oakland, California. Within each center, recruitment was balanced by sex, age, and educational level. The institutional review board at each field site and supporting sites approved the study. At each visit, participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

In 2010, cognitive testing was added to the CARDIA cohort 25-year follow-up examination. Race was self-reported, and race categories (white and black) were defined by CARDIA investigators. Given that racial residential segregation is distinctively experienced by black individuals in the United States, we restricted our analytical sample to participants who self-identified as black (n = 2636). We then excluded persons who were missing the cognitive battery (n = 1068). Our final analytical sample included 1568 black participants who had available cognitive data. A comparison of black participants who were included vs excluded from the final analytical sample is presented in eTable 1 in the Supplement.

**Exposure of Interest: Racial Residential Segregation**

**From 1985 to 2010**

Neighborhood-level residential segregation is represented by the Getis and Ord local G* statistic, as previously described.\textsuperscript{35,34} Briefly, the G* statistic is a widely accepted measure of relative racial composition of one’s neighborhood compared with the larger metropolitan area. The G* statistic was calculated for black racial composition. The calculation of the G* statistic has been previously described in detail in a supplemental methods section by Kershaw et al.\textsuperscript{19} Briefly, CARDIA participants’ geocoded addresses were linked to tract-level census data at each of the available CARDIA visits (1985-1986, 1992-1993, 1995-1996, 2000-2001, 2005-2006, and 2010-2011). The proportion of black residents in one’s census tract was then compared with the mean proportion of black residents in the surrounding metropolitan area or county, with a spatial weight included to account for racial composition of each tract compared with neighboring tracts. The G* statistic produces a z score representing the number of SDs that the racial composition of one’s census tract is from the greater surrounding metropolitan area.

We created a measure of cumulative exposure to racial residential segregation, the exposure of interest, by calculating the mean G* statistic for each person across the follow-up period. We then categorized exposure to racial residential segregation as high (G* > 1.96), medium (G* range, 0-1.96), and low (G* < 0), based on critical z score values at the 5% significance level (95% CI).\textsuperscript{20} The higher the G* statistic, the greater the representation of black residents in the census tract compared with the larger metropolitan area. A description of the mean G* statistic at each time point is presented in eTable 2 in the Supplement.

**Primary Outcome of interest: Cognitive Performance in 2010**

Cognitive testing in the CARDIA study has been previously described.\textsuperscript{31} In brief, cognitive performance was measured...
using 3 different tests representing distinct domains of cognition. The Digit Symbol Substitution Test (DSST) is a subtest of the Wechsler Adult Intelligence Scale and measures performance on a speed test (range, 0-133 points). The interference score on the Stroop color test (executive skills) measures the additional amount of processing needed to respond to one stimulus while suppressing another. The test was scored by seconds needed to spell out color words printed in a different color plus number of errors. Stroop scores were reverse coded such that greater scores indicated better performance. The Rey Auditory Verbal Learning Test (RAVLT) measures verbal memory and assesses the ability to memorize and retrieve words (range, 0-15 points). All 3 cognitive measures were treated as continuous. Furthermore, given that the cognitive tests have different value ranges, each test was $z$ scored based on the sample mean and SD at the time of cognitive testing to facilitate comparison of estimates. Higher $z$ scores indicate better performance.

**Covariates**

The covariates chosen for this analysis were based on prior literature regarding factors that act as both possible confounders and mediators of the segregation-cognition association. Covariate data were measured at each examination, except sex (male or female) and field center, which were collected at baseline. Data on age, marital status (married vs not), years of education, physical activity (in standardized units based on duration and intensity), income (based on income categories, ranging from <5000 to >10000), and mean alcohol consumption (in milliliters per day) were self-reported in response to validated standardized questionnaires administered by trained research associates. Smoking status (current smoking vs not) questionnaires were self-administered. Body mass index was calculated using measured weight in kilograms divided by height in meters squared. Blood pressure was measured 3 times at 1-minute intervals, and systolic blood pressure was calculated as the mean of the last 2 measures. Fasting glucose level was measured using the hexokinase UV method by American BioScience Laboratories, Van Nuys, California, and subsequently, samples were analyzed using the hexokinase-glucose-6-phosphate dehydrogenase method by Linco Research, St Louis, Missouri, as previously described. Depressive symptoms were measured using the Center for Epidemiologic Studies-Depressive Scale (20-item version).

**Statistical Analysis**

Data were analyzed from April 16 to July 20, 2019. First, we summarized baseline characteristics of our sample stratified by cumulative racial residential segregation status (low, medium, or high) using frequencies and column percentages for categorical variables, means and SDs for normally distributed variables, and medians and interquartile range for non-normally distributed variables. Next, we examined the association of cumulative exposure of racial residential segregation (1985-2010) with cognition in 2010. Given the longitudinal nature of the study spanning 25 years and the repeated measures of racial residential segregation and covariates, we pos-
Participants are from the Coronary Artery Risk Development in Young Adults study. Unmeasured confounders and lines from time-varying confounders to censoring at study times (T) are not diagrammed here for clarity. Time-varying confounders are lagged by T−1. Health status variables include physical activity, smoking status, body mass index, systolic blood pressure, fasting glucose level, depressive symptoms, and alcohol consumption. Dotted lines indicate censoring at each time.

Table 1. Sample Characteristics at Baseline Stratified by Cumulative Racial Residential Segregation Category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Racial residential segregation category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High (n = 1286)</td>
</tr>
<tr>
<td>Sociodemographic</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>24 (4)</td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Income, median (IQR), $1000</td>
<td>21 (14-43)</td>
</tr>
<tr>
<td>Married, No. (%)</td>
<td>268 (20.8)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>781 (60.7)</td>
</tr>
<tr>
<td>Clinical risk factors</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>111 (11)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)b</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Fasting glucose level, mean (SD), mg/dL</td>
<td>81 (11)</td>
</tr>
<tr>
<td>CES-D score, median (IQR)c</td>
<td>10 (6-17)</td>
</tr>
<tr>
<td>Health behaviors</td>
<td></td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>396 (30.8)</td>
</tr>
<tr>
<td>Total physical activity, median (IQR), exercise units</td>
<td>290 (144-500)</td>
</tr>
<tr>
<td>Mean alcohol consumption, median (IQR), mL</td>
<td>2 (0-11)</td>
</tr>
</tbody>
</table>

Abbreviations: CES-D, Center for Epidemiologic Studies–Depressive Scale; IQR, interquartile range. SI conversion factor: To convert glucose level to millimoles per liter, multiply by 0.055.

a Includes 1568 participants at baseline (1985). Data are from the 1985-2010 Coronary Artery Risk Development in Young Adults study.
b Calculated as weight in kilograms divided by height in meters squared.
c Scores range from 0 to 60, with higher scores indicating greater number of depressive symptoms.
Table 2. Association Between Cumulative Exposure to Racial Residential Segregation Throughout Young Adulthood and Midlife Cognitive Functiona

<table>
<thead>
<tr>
<th>Racial residential segregation</th>
<th>Cognitive measure, β (95% CI)</th>
<th>Stroop color test</th>
<th>RAVLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>−0.37 (−0.61 to −0.13)</td>
<td>−0.16 (−0.46 to 0.13)</td>
<td>−0.13 (−0.37 to 0.11)</td>
</tr>
<tr>
<td>Medium</td>
<td>−0.25 (−0.51 to 0.0002)</td>
<td>−0.07 (−0.38 to 0.24)</td>
<td>−0.07 (−0.33 to 0.18)</td>
</tr>
<tr>
<td>Low</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Abbreviations: DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test.

a Includes 1568 participants at baseline (1985). Midlife cognition was measured in 2010 in the 1985-2010 Coronary Artery Risk Development in Young Adults study. Estimates are from marginal structural models. Cognitive scores are calculated as z scores to facilitate comparison across estimates, and Stroop scores were additionally reverse coded. Marginal structural models were adjusted for baseline age, visit, examination center, sex, and baseline years of education. Estimates are summarized across results from 10 multiply imputed data sets.
metabolic disease,18-20 and subsequently, these factors have been associated with cognitive decline in older populations.21-26 Because many of these factors represent vascular disease or are known to influence vascular disease risk, these data are consistent with our findings with the measure of processing speed (DSST), which is associated with cerebrovascular injury.55 We posit that the association of racial residential segregation with cognitive performance is mediated by complex downstream pathways influencing both contextual risk factors and individual social, psychological, and health-related conditions. Future studies should examine the extent to which these factors mediate this association to identify the most effective targets for intervention. To enhance translation to the clinic, future work should also consider how intervention on these proximal risk factors in late life may mitigate the risk of earlier life exposure to racial residential segregation on cognitive health.

In this study, we used marginal structural models to account for time-varying confounding and differential censoring across the study period. Assessing the validity of estimates from this model requires a thorough evaluation of several assumptions. First, although the exchangeability assumption cannot be tested pragmatically, we included the most important determinants of segregation and cognitive performance based on previous literature. Second, the consistency assumption is more difficult to fulfill in the context of social exposures.56 We defined segregation using the Gi* statistic and subsequent categorization, which captures the clustering dimension of residential segregation. However, measures of other dimensions of segregation may not yield the same associations observed herein. The possible violation of this assumption is further concerning, given other evidence showing that racial residential segregation operationalized by measures other than the Gi* statistic is not associated with cognition.42,43 Furthermore, segregation status is not as well-defined an intervention as other more explicitly defined exposures, such as medication use. Considering the manipulability criterion also aids in assessment of this assumption57; in other words, interventions to treat segregation may occur in many different ways, including policy-level interventions, natural phenomena, and changes in economic or social factors. Residual segregation as we have defined it in this study likely does not meet this criterion; however, future work can aim to examine other definitions of segregation as well as examine downstream, well-defined exposures. Finally, we examined the positivity assumption graphically and did not observe any obvious violations.

Strengths and Limitations
This study has several strengths. First, we leveraged a unique data set with repeated measures of health and social factors across early adulthood in black participants, and this allowed us to examine our associations of interest accounting for time-varying confounding and differential censoring. Second, studies examining racial residential segregation in the context of cognitive function are limited, and thus our findings contribute to an important yet sparse literature.

Several limitations to this work are worth noting. First, although we attempted to account for time-varying confounding using inverse probability of treatment weights and marginal structural models, we caution about the causality of the findings. Future studies are warranted to replicate our findings in other cohorts. Second, although inverse probability weighting is a powerful method for accounting for time-varying confounding and potential bias due to attrition, it is limited by the specification of the model, and the inverse probability weight estimator can be unstable if cell sizes are small. Third, cognition was examined at only 1 point, but next steps should include examining cognitive trajectories and dementia incidence. We examined different domains of cognitive function, but both validity and reliability can be strengthened by having data on a more thorough neuropsychological battery.58 Fourth, although there are several hypothesized pathways through which racial residential segregation may influence cognitive function, we were not able to identify specific mechanisms in this study. Future studies using analytical approaches, such as structural equation modeling, are needed to better elucidate these pathways. Fifth, although we used census tracts to approximate neighborhood level segregation, previous research in multiple population-based epidemiological studies have shown high correlations (range, 0.85-0.96) between neighborhood indicators measured at the block group and census tract levels.59 In addition, because the Gi* statistic is a spatial autocorrelation measure, it reflects the composition of the tract in which the participant lives and neighboring tracts, thus accounting for some uncertainty involved in using census tracts as proxies for neighborhoods. In addition, our measure of segregation is the result of people who may have changed their neighborhood of residence as well as changes in the racial composition of the neighborhoods over time.19 Separating one from the other is beyond the scope of this analysis, and as such our analysis focused on the overall measure of racial composition.

Conclusions
Taken together, these data suggest that exposure to racial residential segregation during young adulthood is associated with worse cognitive function as early as midlife. Interventions targeting mediating pathways of this association may help attenuate the risk of cognitive impairment in black residents of segregated neighborhoods. More importantly, our findings suggest that policies that address segregation and the uneven distribution of resources, such as the Health in All Policies,60 may be beneficial for reducing inequities in cognitive performance.