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RESEARCH ARTICLE

# Neighborhood disadvantage reduces cognitive reserve independent of neuropathologic change

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## Abstract

**INTRODUCTION:** Individuals in socioeconomically disadvantaged neighborhoods exhibit increased risk for impaired cognitive function. Whether this association relates to the major dementia-related neuropathologies is unknown.

**METHODS:** This cross-sectional study included 469 autopsy cases from 2011 to 2023. The relationships between neighborhood disadvantage measured by Area Deprivation Index (ADI) percentiles categorized into tertiles, cognition evaluated by the last Mini-Mental State Examination (MMSE) scores before death, and 10 dementia-associated proteinopathies and cerebrovascular disease were assessed using regression analyses.

**RESULTS:** Higher ADI was significantly associated with lower MMSE score. This was mitigated by increasing years of education. ADI was not associated with an increase in dementia-associated neuropathologic change. Moreover, the significant association between ADI and cognition remained even after controlling for changes in major dementia-associated proteinopathies or cerebrovascular disease.

**DISCUSSION:** Neighborhood disadvantage appears to be associated with decreased cognitive reserve. This association is modified by education but is independent of the major dementia-associated neuropathologies.

KEYWORDS
Alzheimer's disease, Area Deprivation Index, cerebrovascular disease, cognitive reserve, proteinopathies, socioeconomic status

## 1 | BACKGROUND

Community-based autopsy cohorts indicate that > 90% of the attributable risk for dementia is associated with proteinopathies, namely, Alzheimer's disease neuropathologic change (ADNC), Lewy body dementia (LBD), limbic-predominant age-related TDP-43 encephalopathy (LATE), and cerebrovascular disease.[1–3] While these pathologic changes are associated with cognitive dysfunction in most

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individuals,[4,5] some individuals maintain their cognitive abilities despite considerable neuropathologic disease burden.[6–8] This discrepancy between neuropathologic burden and cognitive functions may be attributed to cognitive reserve.[9] Given the limited availability of therapeutics that target neurodegenerative disease proteinopathies,[10,11] identifying factors related to cognitive reserve could help identify preventative strategies against dementia.

Social determinants of health are non-medical factors contributing to diverse health outcomes including brain health.[12–16] Individual socioeconomic factors such as income,[17] education,[18,19] and occupation[20,21] have been linked to cognition. Contextual-level socioeconomic factors, upstream social determinants of health, have been also implicated in dementia, with neighborhood deprivation being associated with cognitive decline,[22–26] increased incidence of dementia,[27,28] and changes in hippocampal volume and cortical thickness.[22,29] Moreover, these upstream factors appear to influence cognitive abilities over and beyond individual factors,[22,23,30] emphasizing the need to better understand how neighborhood socioeconomic status affects brain health and cognition.

Little is known about the biological mechanisms underlying the association between neighborhood deprivation and cognition. Recently, a few studies found more deprived neighborhoods to be associated with differences in ADNC and cerebrovascular pathologic lesions including an increased prevalence of amyloid plaques,[31] Braak neurofibrillary tangle (NFT) stage,[32,33] and cerebral amyloid angiopathy burden,[33] suggesting that neighborhood disadvantage may directly affect specific dementia-related neuropathologies. However, it is uncertain whether the impact of neighborhood disadvantage on neuropathology consequently drives dementia due to limited availability of cognitive outcomes.[31–33]

There is a need to better understand the interrelationships among neighborhood level disadvantage, neuropathologic change, and cognition. By studying the relationships among these three components, one can differentiate whether the effect of neighborhood disadvantage on cognition is due to decreased cognitive reserve, or due to impaired brain maintenance as described in the recent framework for concepts of reserve and resilience in aging.[9] In this exploratory study, we hypothesized that neighborhood disadvantage negatively affects cognitive reserve. We used the Area Deprivation Index (ADI) as an address-based geographic metric of neighborhood disadvantage.[34,35] We report here an evaluation of demographic, clinical, and neuropathologic features in a large series of autopsy cases from a wide range of neighborhood disadvantage levels. We evaluated the presence of an association between neighborhood deprivation and cognitive function, followed by testing for associations between neighborhood disadvantage and neuropathologic measures related to dementia-associated proteinopathies (ADNC, LBD, and LATE) and cerebrovascular disease. Finally, we tested whether the effect of neighborhood disadvantage on cognition was independent of neuropathologic change as would be expected if neighborhood disadvantage is associated with lower cognitive reserve.

**RESEARCH IN CONTEXT**

1. **Systematic review**: We performed the literature review using PubMed and Google Scholar and cited relevant studies on an association between neighborhood disadvantage and cognition, as well as associations between neighborhood disadvantage and neuropathology. However, little is known about the association between neighborhood disadvantage and cognition in relation to neuropathology.
2. **Interpretation**: Neighborhood disadvantage was associated with lower cognitive ability, but this was mitigated by educational attainment. Neighborhood disadvantage was associated with a decrease in Consortium to Establish a Registry for Alzheimer's Disease score and Lewy body dementia stage but not other dementia-associated neuropathologic changes including Alzheimer's disease neuropathologic change, limbic-predominant age-related TDP-43 encephalopathy-neuropathological change and cerebrovascular pathology. Moreover, the association between neighborhood disadvantage and cognition was independent of overall changes in major dementia-associated neuropathologic changes.
3. **Future directions**: Future studies need to replicate our work in ethnically and racially diverse cohorts. To better understand relationships among neighborhood deprivation, neuropathology, and cognition, potential factors that mediate the association between neighborhood deprivation and cognition need to be evaluated.

## 2 | METHODS

### 2.1 | Study participants

The cross-sectional data on demographic, clinical, and neuropathological profiles for autopsy cases were extracted from the Integrated Neurodegenerative Disease Database (INDD) at the Center for Neurodegenerative Disease Research (CNDR) from 2011 to 2023. Of 758 autopsy cases, cases with a primary neuropathological diagnosis of rare neurodegenerative disease including amyotrophic lateral sclerosis, argyrophilic grain disease, corticobasal degeneration, frontotemporal lobar degeneration, globular glial tauopathy, Pick's disease, progressive supranuclear palsy, multiple system atrophy, Creutzfeldt–Jakob disease, and Down syndrome were excluded. Cases with incomplete neuropathological assessments or age at death before 40 years were additionally excluded. Of the remaining 483 cases, 479 cases had full addresses with 9-digit zip codes, which were then linked to corresponding ADI scores. Of these, 469 cases with available ADI scores were included in analyses.

## 2.2 | Demographics and clinical assessment

Demographic and clinical data were obtained from the INDD at CNDR. These include self-reported sex, race, ethnicity, age at onset, and years of education, and physician-reported age at death, disease duration, brain weight, and apolipoprotein E (*APOE*) ε4 allele status. For cognitive testing, the last Mini-Mental State Examination (MMSE) scores obtained before death, age at MMSE testing, and interval years from MMSE testing to death were extracted from the database.

## 2.3 | Neuropathology measures

Autopsy cases were examined using hematoxylin and eosin (H&E) staining and immunohistochemical staining against tau (PHF-1), amyloid beta (Aβ; NAB228) α-synuclein (Syn303), and TDP-43 (1D3) in 16 brain regions.[36] Each brain region was semi-quantitively graded for the severity of pathological lesions (0, absent; 0.5, rare; 1, mild; 2, moderate; 3, severe) and reviewed by board-certified neuropathologists (E.B.L. and J.Q.T.).[36] According to consensus criteria,[3,37–39] ten pathologies were measured, corresponding to four proteinopathies (tau, Aβ, α-synuclein, and TDP-43) and three cerebrovascular lesions (infarct, amyloid angiopathy, arteriolosclerosis). Specifically, Aβ-positive plaques, tau-positive NFTs, and neuritic plaques were evaluated to determine Thal amyloid phase (Aβ, collapsed into scores from 0 to 3 representing Thal amyloid phase 0, 1/2, 3, and 4/5), Braak NFT stage (Braak, collapsed into scores from 0 to 3 representing Braak 0, I/II, III/IV, and V/VI), Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score, and overall level of ADNC.[37] α-synuclein positive Lewy bodies and Lewy neurites were used to assign cases into those with presence versus absence of LBD (where absence of alpha-synucleinopathy or brainstem-predominant LBD was considered absent given that brainstem LBD is not associated with appreciable cognitive dysfunction[38]). 1D3-positive TDP-43 inclusions were assessed to determine the four stages of LATE neuropathological change (LATE-NC; stage 0, no LATE; stage 1, amygdala; stage 2, hippocampus; stage 3, middle frontal cortex).[3] H&E and Aβ staining were used to determine the presence/absence of large infarcts, presence/absence of moderate to high occipital cerebral amyloid angiopathy burden, and presence/absence of moderate to high arteriolosclerosis in occipital white matter.[39] In turn, these three cerebrovascular lesions were used to assign the likelihood that cerebrovascular pathology contributed to cognitive impairment in concordance with the vascular cognitive impairment neuropathology guidelines (VCING) criteria for cerebrovascular disease.[39]

## 2.4 | Neighborhood disadvantage

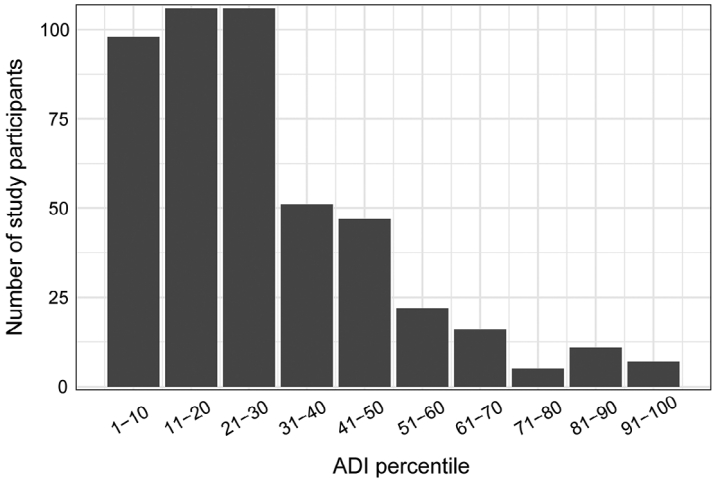
Neighborhood disadvantage was ascertained by the ADI, which was constructed from a 5-year mean of American Community Survey (ACS) data. The ADI is a composite measure of 17 indicators including poverty, employment, education, and housing conditions to generate a census-block group-level socioeconomic status metric. ADI has been validated to provide standardized neighborhood rankings by socioeconomic status and is a practical measure used for a variety of research areas.[34] In accordance with the formalized workflow,[35] we geocoded cases' residential addresses to 9-digit zip codes and then linked these to national ADI percentile rankings from 1 to 100, with higher values indicating a more disadvantaged neighborhood. In this study, 2015 ADI scores (2011–2015 ACS data) were used for autopsy cases collected from 2011 to 2015, while 2020 ADI scores (2016–2020 ACS data) were used for those collected from 2016 to 2023.

## 2.5 | Statistical analysis

Study participants were categorized into tertiles by nationally ranked ADI scores with the highest tertile (T3) indicating the most disadvantaged neighborhoods.[40,41] ADI (T1, low deprivation, reference group; T2, intermediate deprivation; T3, high deprivation) was treated as an ordinal variable. Age at death, age at onset, disease duration, brain weight, MMSE score, age at MMSE testing, interval years from MMSE testing to death, and years of education were treated as continuous variables. Thal amyloid phase, Braak stage, CERAD score, ADNC level, VCING likelihood levels, and LATE-NC stages were included as ordinal variables. LBD stages (0, no Lewy pathology or brainstem LBD, reference group; 1, amygdala-predominant, limbic/transitional, or neocortical/diffuse LBD), sex (0, female, reference group; 1, male), race (0, non-White, reference group; 1, White), ethnicity (0, Hispanic or Latino, reference group; 1, not Hispanic or Latino), *APOE* ε4 allele status (0, no *APOE* ε4 [−], reference group; 1, *APOE* ε4 [+]) were considered dichotomous variables. The presence or absence of large infarcts (0, absence, reference group; 1, presence), the severity of cerebral amyloid angiopathy in occipital lobe (0, absent to mild; 1, moderate to high), and the severity of arteriosclerosis in occipital white matter (0, absent to mild; 1, moderate to high) were also treated as dichotomous variables.

All statistical analyses were performed using R v4.3.1. We used descriptive statistics with mean ± standard deviation (SD) for continuous variables and the number of subjects (*n*) together with percentage (%) for ordinal and dichotomous variables to describe demographic, clinical, and neuropathologic characteristics of the study cohort. After detecting a significant difference in years of education across ADI tertiles, we then examined the association between ADI tertiles and MMSE score with a multivariate linear regression model with adjustment of sex, age at MMSE testing, race, years of education, and interaction terms of ADI tertiles with years of education. We next examined the association between ADI tertiles and each neuropathologic measure with a series of multivariate ordinal or binomial logistic regression models with adjustment of sex, age at death, and *APOE* ε4 allele status. Finally, we assessed the association between ADI tertiles and MMSE with a series of multivariate linear regression models with an additional adjustment for each neuropathologic measure to explore whether the association is explained by neuropathologic change. A $P$ value $< 0.05$ was set for statistical significance.

Because ADI is based on geographic areas, Moran Index ($I$) test was used to assess whether residuals from linear regression models




| ADI percentile | 1-10 | 11-20 | 21-30 | 31-40 | 41-50 | 51-60 | 61-70 | 71-80 | 81-90 | 91-100 |
|---|---|---|---|---|---|---|---|---|---|---|
| N | 98 | 106 | 106 | 51 | 47 | 22 | 16 | 5 | 11 | 7 |
| % | 20.90 | 22.60 | 22.60 | 10.87 | 10.02 | 4.69 | 3.41 | 1.07 | 2.35 | 1.49 |

**FIGURE 1** Distribution of neighborhood disadvantage by ADI in the study cohort. Bars show the number of individuals within each range of national ADI percentile rankings. The number (*N*) and proportion (%) of individuals are indicated for each bar. ADI, Area Deprivation Index.

were spatially autocorrelated.[42] The expected values of Moran *I* range from −1 to +1. Negative values close to −1 indicate that similar residuals are from uniformly dispersed areas, while positive values close to +1 indicate that similar residuals are from neighboring areas. Values close to 0 indicate that residuals are from randomly distributed areas without spatial autocorrelation. A $P$ value $< 0.05$ was set for statistical significance, with a null hypothesis of no residual spatial autocorrelation.

## 3 | RESULTS

### 3.1 | Distribution of neighborhood disadvantage

National ADI percentiles for our study cohort ($n = 469$) were widely distributed with a range from 1 to 98 and a median of 23 (Figure 1). The distribution was skewed with only 18 cases (3.84%) from the top 20% most disadvantaged neighborhoods (Figure 1). When study subjects were separated into tertiles by ADI percentiles, 163 cases (34.75%) were included in the low tertile group (T1) with ADI ranging from 1 to 16; 147 (31.34%) and 159 (33.90%) cases were included in the intermediate tertile group (T2) with ADI ranging from 17 to 30 and in the high tertile group with ADI ranging from 31 to 98, respectively.

### 3.2 | Demographic and clinical characteristics of the study cohort

Demographic and clinical features of the cohort and results from univariate analyses are provided in Table 1. Within the cohort, 267 (56.93%) were male and the mean (SD) age of death was 75.85 (11.03) years. The vast majority of individuals were White ($n = 416$, 91.30%) and non-Hispanic or Latino ($n = 389$, 98.23%). The average MMSE score at the last assessment before death was 19.22, indicating cognitive impairment. The distribution of most of the demographic and clinical characteristics appeared to be similar across ADI tertiles. However, individuals who lived in high disadvantaged neighborhoods (ADI T3, ADI 31–98, $n = 125$, 80.65%) compared to those who lived in intermediate (ADI T2, ADI 17–30, $n = 139$, 95.86%) and low disadvantaged neighborhoods (ADI T1, ADI 1–16, $n = 152$, 96.82%) were less likely to be White.

### 3.3 | Neuropathologic characteristics of the study cohort

Neuropathological features of the cohort are presented in Table 2. A majority of the full cohort had the high Thal amyloid phases (4/5, $n = 261$, 55.65%), Braak stages (V/VI, $n = 216$, 46.06%), CERAD scores (score 3, $n = 222$, 47.33%), and ADNC level (high, $n = 206$, 43.92%). Two hundred thirty (49.04%) and 129 (27.51%) had amygdala predominant, transitional/limbic, or diffuse/neocortical Lewy pathology and LATE, respectively. A relatively small number of cases had a high burden of vascular lesions such as large infarcts ($n = 16$, 3.41%), moderate to severe cerebral amyloid angiopathy burden in the occipital lobe ($n = 136$, 29.00%), or moderate to severe arteriolosclerosis in the occipital white matter ($n = 75$, 15.99%). Thus, very few individuals were associated with a high likelihood that cerebrovascular pathology contributed to cognitive impairment ($n = 5$, 1.07%). Individuals from higher ADI tertiles were less likely to have higher Thal amyloid phase, Braak stage, CERAD score, ADNC level, LATE-NC stage, and VCING level and higher prevalence of amygdala predominant, transitional/limbic, or

**TABLE 1** Demographic and clinical characteristics of the study cohort stratified by ADI tertile.

| Characteristic | Overall | ADI T1 (ADI 1–16) *N* = 163 | ADI T2 (ADI 17–30) *N* = 147 | ADI T3 (ADI 31–98) *N* = 159 |
|---|---|---|---|---|
| Demographic | | | | |
| Sex – *n* (%) | | | | |
| Female | 202 (43.07) | 76 (46.63) | 54 (36.73) | 72 (45.28) |
| Male | 267 (56.93) | 87 (53.37) | 93 (63.27) | 87 (54.72) |
| Age at death, year – *n* (mean ± SD) | 469 (75.85 ± 11.03) | 163 (77.20 ± 10.50) | 147 (76.52 ± 11.30) | 159 (73.86 ± 11.10) |
| Age at onset, year – *n* (mean ± SD) | 374 (64.82 ± 10.84) | 142 (65.22 ± 10.85) | 127 (64.99 ± 10.17) | 105 (64.07 ± 11.66) |
| Disease duration, year – *n* (mean ± SD) | 374 (11.45 ± 6.09) | 142 (11.75 ± 6.19) | 127 (11.63 ± 5.94) | 105 (10.85 ± 6.14) |
| Race – *n* (%) | | | | |
| White | 416 (91.03) | 152 (96.82) | 139 (95.86) | 125 (80.65) |
| Non-White | 41 (8.97) | 5 (3.18) | 6 (4.14) | 30 (19.35) |
| Asian | 1 (0.22) | | | |
| Black or African American | 33 (7.22) | | | |
| More than one race | 7 (1.53) | | | |
| Ethnicity – *n* (%) | | | | |
| Hispanic or Latino | 7 (1.77) | 3 (2.11) | 1 (0.73) | 3 (2.56) |
| Not Hispanic or Latino | 389 (98.23) | 139 (97.89) | 136 (99.27) | 114 (97.44) |
| Brain weight, g – *n* (mean ± SD) | 468 (1221.53 ± 167.40) | 163 (1214.99 ± 168.87) | 146 (1226.66 ± 154.89) | 159 (1223.54 ± 177.47) |
| Education, year | 354 (15.86 ± 2.86) | 128 (16.41 ± 2.64) | 127 (15.76 ± 2.89) | 99 (15.29 ± 3.01) |
| *APOE* ε4 allele status – *n* (%) | | | | |
| *APOE* ε4 (+) | 228 (48.72) | 82 (50.62) | 74 (50.34) | 72 (45.28) |
| ε2/ε4 | 10 (2.14) | | | |
| ε3/ε4 | 168 (35.90) | | | |
| ε4/ε4 | 50 (10.68) | | | |
| *APOE* ε4 (–) | 240 (51.28) | 80 (49.38) | 73 (49.66) | 87 (54.72) |
| ε2/ε2 | 3 (0.64) | | | |
| ε2/ε3 | 34 (7.26) | | | |
| ε3/ε3 | 203 (43.38) | | | |
| Clinical | | | | |
| MMSE score closest to death – *n* (mean ± SD) | 323 (19.22 ± 8.63) | 114 (18.39 ± 8.62) | 117 (20.37 ± 8.08) | 92 (18.79 ± 9.22) |
| Age at MMSE, year – *n* (mean ± SD) | 312 (73.09 ± 10.88) | 109 (73.85 ± 11.00) | 113 (72.65 ± 10.68) | 90 (72.70 ± 11.04) |
| Interval from MMSE to death, year – *n* (mean ± SD) | 312 (4.84 ± 3.53) | 109 (4.61 ± 3.46) | 113 (5.02 ± 3.16) | 90 (4.88 ± 4.02) |

*Note*: Data are *n* (mean ± SD) or *n* (%). ADI T1 is the low ADI tertile group representing low disadvantaged neighborhoods. ADI T2 is the intermediate ADI tertile group representing intermediate disadvantaged neighborhoods. ADI T3 is the high ADI tertile group representing high disadvantaged neighborhoods.
Abbreviations: ADI, Area Deprivation Index; *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; SD, standard deviation; T, tertile.

diffuse/neocortical Lewy pathology, large infarct, moderate to severe burden of cerebral amyloid angiopathy in occipital lobe, and moderate to severe burden of arteriolosclerosis burden in occipital white matter.

## 3.4 | Association of neighborhood disadvantage with cognition

High educational attainment likely contributes to cognitive reserve, and years of education differed across ADI tertiles ($P = 0.012$ by analysis of variance; data not shown). Thus, we determined whether there might be an effect of years of education on the association between ADI and cognition. Indeed, while both the intermediate (ADI T2 vs. T1, $\beta = -15.770$, $P = 0.020$) and high ADI tertiles (ADI T3 vs. T1, $\beta = -19.283$, $P = 0.007$; Table 3) compared to the low ADI tertile were associated with poorer cognitive function indicated by lower MMSE scores after adjusting for sex, age at MMSE testing, race, and education, there were significant interactions between ADI tertiles and years of education (ADI T2 × education; $\beta = 1.122$, $P = 0.007$; ADI T3 × education; $\beta = 1.281$, $P = 0.003$; ADI T1 as the reference group; Table 3)

**TABLE 2** Neuropathologic characteristics of the study cohort stratified by ADI tertile.

| Characteristic | Overall | ADI T1 (ADI 1–16) *N* = 163 | ADI T2 (ADI 17–30) *N* = 147 | ADI T3 (ADI 31–98) *N* = 159 |
|---|---|---|---|---|
| Thal amyloid phase – *n* (%) | | | | |
| 0 | 52 (11.09) | 11 (6.75) | 13 (8.84) | 28 (17.61) |
| 1/2 | 75 (15.99) | 24 (14.72) | 22 (14.97) | 29 (18.24) |
| 3 | 81 (17.27) | 28 (17.18) | 23 (15.65) | 30 (18.87) |
| 4/5 | 261 (55.65) | 100 (61.35) | 89 (60.54) | 72 (45.28) |
| Braak stage – *n* (%) | | | | |
| 0 | 27 (5.76) | 8 (4.91) | 5 (3.40) | 14 (8.81) |
| I/II | 132 (28.14) | 39 (23.93) | 34 (23.13) | 59 (37.11) |
| III/IV | 94 (20.04) | 31 (19.02) | 37 (25.17) | 26 (16.35) |
| V/VI | 216 (46.06) | 85 (52.15) | 71 (48.30) | 60 (37.74) |
| CERAD score – *n* (%) | | | | |
| 0 (None) | 125 (26.65) | 29 (17.79) | 37 (25.17) | 59 (37.11) |
| 1 (Mild) | 45 (9.59) | 14 (8.59) | 9 (6.12) | 22 (13.84) |
| 2 (Moderate) | 77 (16.42) | 29 (17.79) | 29 (19.73) | 19 (11.95) |
| 3 (Severe) | 222 (47.33) | 91 (55.83) | 72 (48.98) | 59 (37.11) |
| ADNC level – *n* (%) | | | | |
| Not | 52 (11.09) | 11 (6.75) | 13 (8.84) | 28 (17.61) |
| Low | 125 (26.65) | 40 (24.54) | 32 (21.77) | 53 (33.33) |
| Intermediate | 86 (18.34) | 29 (17.79) | 38 (25.85) | 19 (11.95) |
| High | 206 (43.92) | 83 (50.92) | 64 (43.54) | 59 (37.11) |
| Lewy pathology – *n* (%) | | | | |
| No or brainstem | 239 (50.96) | 77 (47.24) | 68 (46.26) | 94 (59.12) |
| No | 198 (42.22) | | | |
| Brainstem | 41 (8.74) | | | |
| Amygdala predominant, Transitional/limbic, or diffuse/neocortical | 230 (49.04) | 86 (52.76) | 79 (53.74) | 65 (40.88) |
| Amygdala predominant | 60 (12.79) | | | |
| Transitional/limbic | 72 (15.35) | | | |
| Diffuse/neocortical | 98 (20.90) | | | |
| LATE – *n* (%) | | | | |
| No | 340 (72.49) | 108 (66.26) | 101 (68.71) | 131 (82.39) |
| Stage 1 | 24 (5.12) | 7 (4.29) | 12 (8.16) | 5 (3.14) |
| Stage 2 | 71 (15.14) | 28 (17.18) | 23 (15.65) | 20 (12.58) |
| Stage 3 | 34 (7.25) | 20 (12.27) | 11 (7.48) | 3 (1.89) |
| Large infarct – *n* (%) | | | | |
| No | 453 (96.59) | 157 (96.32) | 141 (95.92) | 155 (97.48) |
| Yes | 16 (3.41) | 6 (3.68) | 6 (4.08) | 4 (2.52) |
| Cerebral amyloid angiopathy burden in occipital lobe – *n* (%) | | | | |
| None to mild | 333 (71.00) | 105 (64.42) | 103 (70.07) | 125 (78.62) |
| Moderate to severe | 136 (29.00) | 58 (35.58) | 44 (29.93) | 34 (21.38) |
| Arteriolosclerosis burden in occipital white matter – *n* (%) | | | | |
| None to mild | 394 (84.01) | 134 (82.21) | 119 (80.95) | 141 (88.68) |
| Moderate to severe | 75 (15.99) | 29 (17.79) | 28 (19.05) | 18 (11.32) |

(Continues)

**TABLE 2** (Continued)

| Characteristic | Overall | ADI T1 (ADI 1–16) N = 163 | ADI T2 (ADI 17–30) N = 147 | ADI T3 (ADI 31–98) N = 159 |
|---|---|---|---|---|
| VCING level – *n* (%) | | | | |
| Low | 425 (90.62) | 144 (88.34) | 131 (89.12) | 150 (94.34) |
| Intermediate | 39 (8.32) | 15 (9.2) | 16 (10.88) | 8 (5.03) |
| High | 5 (1.07) | 4 (2.45) | 0 (0) | 1 (0.63) |

*Note*: Data are *n* (mean ± SD) or *n* (%). ADI T1 is the low ADI tertile group representing low disadvantaged neighborhoods. ADI T2 is the intermediate ADI tertile group representing intermediate disadvantaged neighborhoods. ADI T3 is the high ADI tertile group representing high disadvantaged neighborhoods.
Abbreviations: ADI, Area Deprivation Index; ADNC, Alzheimer's disease neuropathologic change; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; LATE, limbic-predominant age-related TDP-43 encephalopathy; SD, standard deviation; T, tertile; VCING, vascular cognitive impairment neuropathology guidelines.

**TABLE 3** Association between Area Deprivation Index and the MMSE.

| | β | SE | *P* value |
|---|---|---|---|
| ADI T2 vs. T1 | −15.770 | 6.742 | 0.020 |
| ADI T3 vs. T1 | −19.283 | 7.091 | 0.007 |
| Sex, male | 1.727 | 0.993 | 0.083 |
| Age at MMSE | 0.064 | 0.044 | 0.147 |
| Race, White | 2.343 | 2.055 | 0.255 |
| Education | −0.365 | 0.311 | 0.242 |
| ADI T2 (vs. T1) × Education | 1.122 | 0.410 | 0.007 |
| ADI T3 (vs. T1) × education | 1.281 | 0.435 | 0.003 |

*Note*: β, SE, and *P* values were determined by a multivariate linear regression model with MMSE as the dependent variable, categorized ADI (ADI T1 = low ADI tertile group representing low disadvantaged neighborhoods, reference group; ADI T2 = intermediate ADI tertile group representing intermediate disadvantaged neighborhoods; ADI T3 = high ADI tertile group representing high disadvantaged neighborhoods) as the independent variable, and sex (0 = female, reference group; 1 = male), age at MMSE, race (0 = non-White, reference group; 1 = White), years of education, and interaction terms of ADI tertiles (ADI T1 as the reference group) with years of education as covariates. $p < 0.05$ was used to determine statistical significance.
Abbreviations: ADI, Area Deprivation Index; MMSE, Mini-Mental State Examination; SE, standard error; T, tertile.

such that higher years of education mitigated the association between neighborhood disadvantage and cognitive function.

## 3.5 | Association of neighborhood disadvantage with neuropathologic change

Compared to the low ADI tertile, the high ADI tertile but not the intermediate tertile was associated with lower ADNC level (ADI T3 vs. T1; β = −0.722, 95% confidence interval [CI: 0.316, 0.747], *P* = 0.001; Table 4), Thal amyloid phase (ADI T3 vs. T1; β = −0.647, 95% CI [0.336, 0.815], *P* = 0.004; Table S1 in supporting information), Braak stage (ADI T3 vs. T1; β = −0.590, 95% CI [0.360, 0.853], *P* = 0.007; Table S1), CERAD score (ADI T3 vs. T1; β = −0.860, 95% CI [0.276, 0.649], *P* < 0.001; Table S1), LBD stage (ADI T3 vs. T1; β = −0.484, 95% CI [0.393, 0.967], *P* = 0.035; Table 4), and LATE-NC stage (ADI T3 vs. T1; β = −0.807, 95% CI [0.261, 0.763], *P* = 0.003; Table 4), and lower prevalence of moderate to severe amyloid angiopathy burden in occipital lobe (ADI T3 vs. T1; β = −0.616, 95% CI [0.324, 0.900], *P* = 0.018; Table S1) after controlling for age at death, sex, and *APOE* ε4 allele status. However, the high ADI tertile was not associated with changes in other pathologic measures including VCING level (ADI T3 vs. T1; β = −0.679, 95% CI [0.220, 1.168], *P* = 0.111; Table 4), presence of large infarcts (ADI T3 vs. T1; β = −0.261, 95% CI [0.210, 2.826], *P* = 0.694; Table S1), and moderate to high arteriosclerosis in occipital white matter (ADI T3 vs. T1; β = −0.428, 95% CI [0.342, 1.241], *P* = 0.193; Table S1).

## 3.6 | Association of cognition with neighborhood disadvantage and neuropathologic changes

To explore relationships among neighborhood disadvantage, neuropathology, and cognition, we estimated the association between ADI tertiles and MMSE score after separately adjusting for each pathologic measure (Table 5). There remained a significant association between higher ADI tertiles and cognitive function even when adjusting for ADNC level (ADI T2 vs. T1, β = −13.749, *P* = 0.015; ADI T3 vs. T1, β = −16.503, *P* = 0.006), LBD (ADI T2 vs. T1, β = −12.954, *P* = 0.041; ADI T3 vs. T1, β = −18.107, *P* = 0.007), LATE-NC stage (ADI T3 vs. T1, β = −13.772, *P* = 0.031), or VCING level (ADI T2 vs. T1, β = −13.164, *P* = 0.038; ADI T3 vs. T1, β = −18.169, *P* = 0.007). As expected, neuropathologic measures were associated with lower MMSE score including ADNC level (intermediate, β = −3.683, *P* = 0.033; high, β = −9.060, *P* < 0.001; not ADNC as the reference group) and LATE-NC stage (stage 2, β = −6.590, *P* < 0.001; no LATE-NC as the reference group). LBD (β = −0.788, *P* = 0.385) and VCING level (intermediate, β = 0.090, *P* = 0.954; high, β = −0.615, *P* = 0.877; low VCING as the reference group) were not significantly associated with MMSE score. To demonstrate that these results are not an artifact of subdividing the cohort into tertiles, this analysis was repeated upon dividing the cohort into quartiles (Table S2 in supporting information) and quintiles (Table S3, in supporting information), which revealed similar results.

**TABLE 4** Association between Area Deprivation Index and dementia-related proteinopathies or cerebrovascular pathology.

| | ADNC level | | | |
|---|---|---|---|---|
| | *β* | Odds ratio | 95% CI | *P* value |
| ADI T2 vs. T1 | −0.158 | 0.854 | 0.557, 1.308 | 0.468 |
| ADI T3 vs. T1 | −0.722 | 0.486 | 0.316, 0.747 | 0.001 |
| Sex, male | −0.655 | 0.519 | 0.363, 0.744 | <0.001 |
| Age at death | 0.010 | 1.010 | 0.994, 1.026 | 0.228 |
| *APOE* ε4 (+) | 1.568 | 4.797 | 3.324, 6.921 | <0.001 |
| | **LBD stage** | | | |
| | *β* | Odds ratio | 95% CI | *P* value |
| ADI T2 vs. T1 | −0.021 | 0.979 | 0.622, 1.541 | 0.927 |
| ADI T3 vs. T1 | −0.484 | 0.616 | 0.393, 0.967 | 0.035 |
| Sex, male | 0.502 | 1.652 | 1.135, 2.406 | 0.009 |
| Age at death | 0.004 | 1.004 | 0.987, 1.021 | 0.659 |
| *APOE* ε4 (+) | 0.222 | 1.248 | 0.862, 1.807 | 0.240 |
| | **LATE-NC stage** | | | |
| | *β* | Odds ratio | 95% CI | *P* value |
| ADI T2 vs. T1 | −0.179 | 0.836 | 0.513, 1.364 | 0.474 |
| ADI T3 vs. T1 | −0.807 | 0.446 | 0.261, 0.763 | 0.003 |
| Sex, male | −0.210 | 0.811 | 0.529, 1.243 | 0.336 |
| Age at death | 0.069 | 1.071 | 1.048, 1.094 | <0.001 |
| *APOE* ε4 (+) | 0.366 | 1.442 | 0.941, 2.210 | 0.093 |
| | **VCING level** | | | |
| | *β* | Odds ratio | 95% CI | *P* value |
| ADI T2 vs. T1 | −0.100 | 0.905 | 0.443, 1.848 | 0.785 |
| ADI T3 vs. T1 | −0.679 | 0.507 | 0.220, 1.168 | 0.111 |
| Sex, male | 0.052 | 1.054 | 0.554, 2.004 | 0.874 |
| Age at death | 0.037 | 1.038 | 1.006, 1.071 | 0.018 |
| *APOE* ε4 (+) | 0.291 | 1.338 | 0.708, 2.528 | 0.370 |

*Note*: *β*, odds ratio, 95% CI, and *P* values were determined by multivariate ordinal logistic regression models with ordinal ADNC level (0 = not; 1 = low; 2 = intermediate; 3 = high), ordinal LATE-NC stage (0–3), and ordinal VCING level (1 = low; 2 = intermediate; 3 = high) as dependent variables and categorized ADI (ADI T1 = low ADI tertile group representing low disadvantaged neighborhoods, reference group; ADI T2 = intermediate ADI tertile group representing intermediate disadvantaged neighborhoods; ADI T3 = high ADI tertile group representing high disadvantaged neighborhoods) as the independent variable, and a multivariate binomial logistic regression model with a dichotomously treated LBD (0 = no Lewy pathology or brainstem LBD, reference group; 1 = amygdala-predominant, transitional/limbic, or diffuse/neocortical LBD) as the dependent variable and categorized ADI (ADI T1 = low ADI tertile group representing low disadvantaged neighborhoods, reference group; ADI T2 = intermediate ADI tertile group representing intermediate disadvantaged neighborhoods; ADI T3 = high ADI tertile group representing high disadvantaged neighborhoods) as the independent variable. Sex (0 = female, reference group; 1 = male), age at death, and *APOE* ε4 status (0 = *APOE* ε4 [−], reference group; 1 = *APOE* ε4 [+]) were included as covariates in all models. $P < 0.05$ was used to determine statistical significance.

Abbreviations: ADI, Area Deprivation Index; ADNC, Alzheimer's disease neuropathologic change; *APOE*, apolipoprotein E; CI, confidence interval; LATE, limbic-predominant age-related TDP-43 encephalopathy; LBD, Lewy body dementia; T, tertile; VCING, vascular cognitive impairment neuropathology guidelines.

## 3.7 | Residual spatial autocorrelation in the fitted linear regression models

Given the spatial nature of ADI, we tested for spatial autocorrelation using the Moran *I* test. The expected values of Moran *I* were close to 0 in all models (Model 1, expected Moran $I = -3.17 \times 10^{-3}$, $P = 0.298$; Model 2, expected Moran $I = -3.18 \times 10^{-3}$, $P = 0.340$; Model 3, expected Moran $I = -3.18 \times 10^{-3}$, $P = 0.418$; Model 4, expected Moran $I = -3.20 \times 10^{-3}$, $P = 0.423$; Model 5, expected Moran $I = -3.19 \times 10^{-3}$, $P = 0.387$; Table S4 in supporting information)

**TABLE 5** Association of area deprivation index and dementia-related proteinopathies or cerebrovascular pathology with the MMSE.

| | β | SE | *P* value |
|---|---|---|---|
| ADI T2 vs. T1 | −13.749 | 5.626 | 0.015 |
| ADI T3 vs. T1 | −16.503 | 5.911 | 0.006 |
| ADNC, low | −0.963 | 1.705 | 0.573 |
| ADNC, intermediate | −3.683 | 1.715 | 0.033 |
| ADNC, high | −9.060 | 1.557 | <0.001 |
| Sex, male | 1.356 | 0.853 | 0.113 |
| Age at MMSE | 0.066 | 0.039 | 0.090 |
| Interval from MMSE to death | 0.802 | 0.118 | <0.001 |
| Race, White | 0.104 | 1.725 | 0.952 |
| Education | −0.341 | 0.260 | 0.191 |
| ADI T2 (vs. T1) × education | 0.960 | 0.342 | 0.005 |
| ADI T3 (vs. T1) × education | 1.068 | 0.363 | 0.003 |
| | β | SE | *P* value |
| ADI T2 vs. T1 | −12.954 | 6.314 | 0.041 |
| ADI T3 vs. T1 | −18.107 | 6.625 | 0.007 |
| LBD stage | −0.788 | 0.905 | 0.385 |
| Sex, male | 2.858 | 0.949 | 0.003 |
| Age at MMSE | 0.130 | 0.042 | 0.002 |
| Interval from MMSE to death | 0.884 | 0.131 | <0.001 |
| Race, White | 1.866 | 1.922 | 0.332 |
| Education | −0.254 | 0.291 | 0.384 |
| ADI T2 (vs. T1) × education | 0.925 | 0.384 | 0.017 |
| ADI T3 (vs. T1) × education | 1.196 | 0.406 | 0.003 |
| | β | SE | *P* value |
| ADI T2 vs. T1 | −9.253 | 6.046 | 0.127 |
| ADI T3 vs. T1 | −13.772 | 6.368 | 0.031 |
| LATE-NC, stage 1 | −3.198 | 1.848 | 0.085 |
| LATE-NC, stage 2 | −6.590 | 1.130 | <0.001 |
| LATE-NC, stage 3 | −2.872 | 1.637 | 0.080 |
| Sex, male | 2.622 | 0.893 | 0.004 |
| Age at MMSE | 0.187 | 0.042 | <0.001 |
| Interval from MMSE to death | 0.990 | 0.127 | <0.001 |
| Race, White | 2.063 | 1.826 | 0.260 |
| Education | −0.205 | 0.278 | 0.460 |
| ADI T2 (vs. T1) × education | 0.697 | 0.368 | 0.059 |
| ADI T3 (vs. T1) × education | 0.911 | 0.391 | 0.020 |
| | β | SE | *P* value |
| ADI T2 vs. T1 | −13.164 | 6.332 | 0.038 |
| ADI T3 vs. T1 | −18.169 | 6.651 | 0.007 |
| VCING, intermediate | 0.090 | 1.554 | 0.954 |
| VCING, high | −0.615 | 3.977 | 0.877 |
| Sex, male | 2.736 | 0.944 | 0.004 |
| Age at MMSE | 0.134 | 0.042 | 0.002 |
| Interval from MMSE to death | 0.886 | 0.132 | <0.001 |
| Race, White | 1.970 | 1.968 | 0.317 |
| Education | −0.263 | 0.293 | 0.370 |
| ADI T2 (vs. T1) × education | 0.937 | 0.386 | 0.016 |
| ADI T3 (vs. T1) × education | 1.201 | 0.408 | 0.003 |

*Note*: β , SE, and *P* values were determined by multivariate linear regression models with MMSE as the dependent variable, categorized ADI (ADI T1 = low ADI tertile group representing low disadvantaged neighborhoods, reference group; ADI T2 = intermediate ADI tertile group representing intermediate disadvantaged neighborhoods; ADI T3 = high ADI tertile group representing high disadvantaged neighborhoods) and ordinal ADNC level (0 = not, reference group; 1 = low; 2 = intermediate; 3 = high), dichotomously treated LBD (0 = no Lewy pathology or brainstem LBD, reference group; 1 = amygdala-predominant, transitional/limbic, or diffuse/neocortical LBD), ordinal LATE-NC stage (0–3, 0 as the reference group), or ordinal VCING level (1 = low, reference group; 2 = intermediate; 3 = high) as independent variables. Sex (0 = female, reference group; 1 = male), age at MMSE, interval years from MMSE to death, race (0 = non-White, reference group; 1 = White), years of education, and interaction terms of ADI tertiles (ADI T1 as the reference group) with years of education were included as covariates in all models. $P < 0.05$ was used to determine statistical significance.

Abbreviations: ADI, Area Deprivation Index; ADNC, Alzheimer's disease neuropathologic change; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy-neuropathologic change; LBD, Lewy body dementia; MMSE, Mini-Mental State Examination; SE, standard error; T, tertile; VCING, vascular cognitive impairment neuropathology guidelines.

indicating no spatial autocorrelation in residuals for these models. These insignificant results show that our ADI regression models are correctly specified.

## 4 | DISCUSSION

In this relatively large, cross-sectional, autopsy cohort, we sought to determine whether the association between neighborhood disadvantage and cognition can be attributed to a decrease in cognitive reserve, independent of dementia-associated neuropathologic change. We observed that higher neighborhood disadvantage was associated with lower cognitive ability after adjusting for confounding factors, consistent with previous reports linking neighborhood socioeconomic status and cognition.[22,23,26,27,43] Importantly, neighborhood-level education attainment data is one domain included in the calculation of ADI.[34] Interestingly, educational attainment modified the relationship between ADI and cognition such that higher educational attainment mitigated the association between ADI. As educational attainment is thought to increase cognitive reserve, the fact that the association between ADI and cognition was mitigated by education suggests that

neighborhood disadvantage also affects cognitive reserve. Moreover, if replicated in other independent cohorts, this interaction between education and neighborhood disadvantage suggests that educational programs may potentially mitigate the deleterious effects of neighborhood disadvantage.

Neighborhood disadvantage has been proposed as being related to cognitive reserve.[44,45] We found that higher ADI did not appear to be associated with higher neuropathologic burden. Indeed, higher ADI was associated with overall lower neuropathologic burden of dementia-associated proteinopathies and cerebrovascular disease including lower Thal amyloid phase, Braak stage, CERAD score, ADNC level, LBD stage, and LATE-NC stage and lower prevalence of moderate to severe amyloid angiopathy burden in occipital lobe and not associated with changes in VCING level and prevalence of large infarct and moderate to severe arteriolosclerosis burden in occipital white matter.

These support the theoretical possibility that neighborhood disadvantage is associated with a change in cognitive reserve independent of neuropathologic changes. However, our findings are inconsistent with previous studies, in which higher ADI was associated with an increase in Alzheimer's disease and cerebrovascular pathology. Specifically, in one study, neighborhood disadvantage as assessed by ADI deciles was associated with increased odds of having A$\beta$ deposits including diffuse amyloid plaques[31] and more advanced Braak NFT stages[32] when covarying for age at death, sex, and year of death. These inconsistent findings may be, in part, due to different covariates between two studies. Moreover, we chose a more stringent cutoff to define the presence of A$\beta$ pathology as diffuse amyloid plaques are not generally associated with cognitive dysfunction. A second study from the Brains for Dementia Research study found associations between area deprivation (indices of multiple deprivation) and both Braak stage and CERAD score comparing the top versus bottom quintiles but not between other intermediate quintiles where there appeared to sometimes be the opposite, albeit insignificant, relationship.[33] Moreover, that autopsy cohort did not appear to exhibit an overall effect of area deprivation on cognition. In contrast with these two studies, we here examined the relationship between categorized tertiles of neighborhood disadvantage, various neuropathologic measures, and cognition to specifically ask whether the relationship between neighborhood disadvantage and cognition relates to dementia-associated neuropathologic change. Our results suggest that the highest tertile of ADI is associated with an increased risk of dementia independent of major dementia-associated proteinopathies such as ADNC, LBD, and LATE and cerebrovascular disease as assessed by VCING, compared to the lowest tertile of ADI. Moreover, the intermediate tertile of ADI was also associated with poorer cognitive function independent of ADNC, LBD, and VCING. Thus, neighborhood deprivation appears to exert its effects on cognition by lowering cognitive reserve, and not by affecting brain maintenance.

A strength of our study is that we analyzed a relatively large number of comprehensively characterized autopsy cases with harmonized demographic, clinical, and neuropathology data. Furthermore, we tested for residual spatial autocorrelation to ensure that the reported linear regression models were implemented appropriately. However, there are some limitations to our study. First, a large proportion of study cases were White and/or non-Hispanic or Latino and so the effects of neighborhood disadvantage on minoritized populations cannot be ascertained here. Second, although we categorized our study cohort into tertiles by ADI scores and therefore each categorized group included the similar number of study subjects, this cohort is skewed toward highly educated individuals from low ADI neighborhoods, which has the potential to distort the estimated association coefficients. Third, we used a cross-sectional design with ADI linked to their latest address. Ongoing efforts to obtain lifetime exposure data including lifetime ADI may reveal stronger effects of neighborhood deprivation on neuropathology and cognition. Fourth, many subjects in our autopsy cohort were historically obtained through research protocols that excluded vascular dementia. Thus, caution is recommended in interpreting whether neighborhood deprivation affects cerebrovascular disease given the very low rates of severe cerebrovascular disease in this cohort. Finally, due to the retrospective nature of this study, we did not have the data to test other potential mediating factors related to cardiovascular risk and lifestyle factors that may explain neighborhood effects on dementia.[46–48] Considering these limitations, replication studies are warranted to verify our findings.

In conclusion, neighborhood disadvantage is a risk factor for dementia that appears to be modulated by high educational attainment. Moreover, the relationship between neighborhood disadvantage and cognition is independent of the major dementia-related neuropathologies, consistent with the hypothesis that neighborhood factors affect cognitive reserve. Thus, improving resources for deprived areas with, for example, educational resources may have positive effects in preserving cognition.

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## CONFLICT OF INTEREST STATEMENT

All other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

## CONSENT STATEMENT

Participants from neurodegenerative research programs at the University of Pennsylvania provided written consent before participating in this study, and consent was obtained from next-of-kin prior to autopsy.

## REFERENCES

1. Mehta RI, Schneider JA. Neuropathology of the common forms of dementia. *Clin Geriatr Med*. 2023;39(1):91-107. doi:10.1016/j.cger.2022.07.005
2. Schneider JA. Neuropathology of dementia disorders. *Continuum*. 2022;28(3):834-851. doi:10.1212/con.0000000000001137
3. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*. 2019;142(6):1503-1527. doi:10.1093/brain/awz099
4. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol*. 2012;71(5):362-381. doi:10.1097/NEN.0b013e31825018f7
5. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet*. 2001;357(9251):169-175. doi:10.1016/s0140-6736(00)03589-3
6. Bennett DA, Wilson RS, Boyle PA, Buchman AS, Schneider JA. Relation of neuropathology to cognition in persons without cognitive impairment. *Ann Neurol*. 2012;72(4):599-609. doi:10.1002/ana.23654
7. Ahangari N, Fischer CE, Schweizer TA, Munoz DG. Cognitive resilience and severe Alzheimer's disease neuropathology. *Aging Brain*. 2023;3:100065. doi:10.1016/j.nbas.2023.100065
8. Zhang M, Ganz AB, Rohde S, et al. Resilience and resistance to the accumulation of amyloid plaques and neurofibrillary tangles in centenarians: An age-continuous perspective. *Alzheimers Dement*. 2023;19(7):2831-2841. doi:10.1002/alz.12899
9. Stern Y, Albert M, Barnes CA, Cabeza R, Pascual-Leone A, Rapp PR. A framework for concepts of reserve and resilience in aging. *Neurobiol Aging*. 2023;124:100-103. doi:10.1016/j.neurobiolaging.2022.10.015
10. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol*. 2022;79(1):13-21. doi:10.1001/jamaneurol.2021.4161
11. Golde TE. Disease-modifying therapies for Alzheimer's disease: more questions than answers. *Neurotherapeutics*. 2022;19(1):209-227. doi:10.1007/s13311-022-01201-2
12. Kind AJ, Jencks S, Brock J, et al. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. *Ann Intern Med*. 2014;161(11):765-774. doi:10.7326/m13-2946
13. Alegría M, NeMoyer A, Falgàs Bagué I, Wang Y, Alvarez K. Social determinants of mental health: where we are and where we need to go. *Curr Psychiatry Rep*. 2018;20(11):95. doi:10.1007/s11920-018-0969-9
14. Jilani MH, Javed Z, Yahya T, et al. Social determinants of health and cardiovascular disease: current state and future directions towards healthcare equity. *Curr Atheroscler Rep*. 2021;23(9):55. doi:10.1007/s11883-021-00949-w
15. Walker RJ, Smalls BL, Campbell JA, Strom Williams JL, Egede LE. Impact of social determinants of health on outcomes for type 2 diabetes: a systematic review. *Endocrine*. 2014;47(1):29-48. doi:10.1007/s12020-014-0195-0
16. Röhr S, Pabst A, Baber R, et al. Social determinants and lifestyle factors for brain health: implications for risk reduction of cognitive decline and dementia. *Sci Rep*. 2022;12(1):12965. doi:10.1038/s41598-022-16771-6
17. Basu R. Effects of education and income on cognitive functioning among Indians aged 50 years and older: evidence from the Study on Global Ageing and Adult Health (SAGE) Wave 1 (2007-2010). *WHO South East Asia J Public Health*. 2013;2(3):156-164. doi:10.4103/2224-3151.206762
18. Hayes-Larson E, Ikesu R, Fong J, et al. Association of education with dementia incidence stratified by ethnicity and nativity in a cohort of older Asian American individuals. *JAMA Netw Open*. 2023;6(3):e231661. doi:10.1001/jamanetworkopen.2023.1661
19. Ramos J, Chowdhury AR, Caywood LJ, et al. Lower levels of education are associated with cognitive impairment in the old order Amish. *J Alzheimers Dis*. 2021;79(1):451-458. doi:10.3233/jad-200909
20. Sörman DE, Hansson P, Pritschke I, Ljungberg JK. Complexity of primary lifetime occupation and cognitive processing. *Front Psychol*. 2019;10:1861. doi:10.3389/fpsyg.2019.01861
21. Huang LY, Hu HY, Wang ZT, et al. Association of occupational factors and dementia or cognitive impairment: a systematic review and meta-analysis. *J Alzheimers Dis*. 2020;78(1):217-227. doi:10.3233/jad-200605
22. Hunt JFV, Vogt NM, Jonaitis EM, et al. Association of neighborhood context, cognitive decline, and cortical change in an unimpaired cohort. *Neurology*. 2021;96(20):e2500-e2512. doi:10.1212/wnl.0000000000011918
23. Zuelsdorff M, Larson JL, Hunt JFV, et al. The Area Deprivation Index: a novel tool for harmonizable risk assessment in Alzheimer's disease research. *Alzheimers Dement (N Y)*. 2020;6(1):e12039. doi:10.1002/trc2.12039
24. Wörn J, Ellwardt L, Aartsen M, Huisman M. Cognitive functioning among Dutch older adults: do neighborhood socioeconomic status and urbanity matter? *Soc Sci Med*. 2017;187:29-38. doi:10.1016/j.socscimed.2017.05.052
25. Besser LM, McDonald NC, Song Y, Kukull WA, Rodriguez DA. Neighborhood environment and cognition in older adults: a systematic review. *Am J Prev Med*. 2017;53(2):241-251. doi:10.1016/j.amepre.2017.02.013
26. Vassilaki M, Aakre JA, Castillo A, et al. Association of neighborhood socioeconomic disadvantage and cognitive impairment. *Alzheimers Dement*. 2022;19(3):761-770. doi:10.1002/alz.12702
27. Becerril A, Pfoh ER, Hashmi AZ, et al. Racial, ethnic and neighborhood socioeconomic differences in incidence of dementia: a regional retrospective cohort study. *J Am Geriatr Soc*. 2023;71(8):2406-2418. doi:10.1111/jgs.18322
28. Mobley TM, Shaw C, Hayes-Larson E, et al. Neighborhood disadvantage and dementia incidence in a cohort of Asian American and non-Latino White older adults in Northern California. *Alzheimers Dement*. 2023;19(1):296-306. doi:10.1002/alz.12660
29. Hunt JFV, Buckingham W, Kim AJ, et al. Association of neighborhood-level disadvantage with cerebral and hippocampal volume. *JAMA Neurol*. 2020;77(4):451-460. doi:10.1001/jamaneurol.2019.4501
30. Rosso AL, Flatt JD, Carlson MC, et al. Neighborhood socioeconomic status and cognitive function in late life. *Am J Epidemiol*. 2016;183(12):1088-1097. doi:10.1093/aje/kwv337
31. Powell WR, Buckingham WR, Larson JL, et al. Association of neighborhood-level disadvantage with Alzheimer disease neuropathology. *JAMA Netw Open*. 2020;3(6):e207559. doi:10.1001/jamanetworkopen.2020.7559
32. Powell WR, Zuelsdorff M, Keller SA, et al. Association of neighborhood-level disadvantage with neurofibrillary tangles on neuropathological tissue assessment. *JAMA Network Open*. 2022;5(4):e228966-e228966. doi:10.1001/jamanetworkopen.2022.8966
33. Hamilton CA, Matthews FE, Erskine D, Attems J, Thomas AJ. Neurodegenerative brain changes are associated with area deprivation in the United Kingdom: findings from the brains for dementia research study. *Acta Neuropathol Commun*. 2021;9(1):198. doi:10.1186/s40478-021-01301-8

34. Kind AJH, Buckingham WR. Making neighborhood-disadvantage metrics accessible - the neighborhood atlas. *N Engl J Med*. 2018;378(26):2456-2458. doi:10.1056/NEJMp1802313
35. University of Wisconsin School of Medicine Public Health. 2019 Area Deprivation Index v3.1. Accessed September 23, 2022. https://www.neighborhoodatlas.medicine.wisc.edu/
36. Toledo JB, Van Deerlin VM, Lee EB, et al. A platform for discovery: the University of Pennsylvania integrated neurodegenerative disease biobank. *Alzheimers Dement*. 2014;10(4):477-484.e1. doi:10.1016/j.jalz.2013.06.003
37. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol*. 2012;123(1):1-11. doi:10.1007/s00401-011-0910-3
38. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. *Neurology*. 2017;89(1):88-100. doi:10.1212/wnl.0000000000004058
39. Skrobot OA, Attems J, Esiri M, et al. Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment. *Brain*. 2016;139(11):2957-2969. doi:10.1093/brain/aww214
40. Banwell E, Collaco JM, Oates GR, et al. Area deprivation and respiratory morbidities in children with bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2022;57(9):2053-2059. doi:10.1002/ppul.25969
41. Goitia JJ, Jr., Phan DQ, Schweis F, et al. Neighborhood resources and racial/ethnic differences in survival after myocardial infarction. *J Am Coll Cardiol*. 2021;78(6):632-633. doi:10.1016/j.jacc.2021.06.007
42. Chen Y. Spatial autocorrelation approaches to testing residuals from least squares regression. *PLoS ONE*. 2016;11(1):e0146865. doi:10.1371/journal.pone.0146865
43. Pase MP, Rowsthorn E, Cavuoto MG, et al. Association of neighborhood-level socioeconomic measures with cognition and dementia risk in Australian adults. *JAMA Netw Open*. 2022;5(3):e224071. doi:10.1001/jamanetworkopen.2022.4071
44. Vassilaki M, Petersen RC, Vemuri P. Area Deprivation Index as a surrogate of resilience in aging and dementia. *Front Psychol*. 2022;13:930415. doi:10.3389/fpsyg.2022.930415
45. Clarke PJ, Ailshire JA, House JS, et al. Cognitive function in the community setting: the neighbourhood as a source of 'cognitive reserve'? *J Epidemiol Community Health*. 2012;66(8):730-736. doi:10.1136/jech.2010.128116
46. Deckers K, Cadar D, van Boxtel MPJ, Verhey FRJ, Steptoe A, Köhler S. Modifiable risk factors explain socioeconomic inequalities in dementia risk: evidence from a population-based prospective cohort study. *J Alzheimers Dis*. 2019;71(2):549-557. doi:10.3233/jad-190541
47. Röhr S, Pabst A, Baber R, et al. Socioeconomic inequalities in cognitive functioning only to a small extent attributable to modifiable health and lifestyle factors in individuals without dementia. *J Alzheimers Dis*. 2022;90(4):1523-1534. doi:10.3233/jad-220474
48. Heger IS, Deckers K, Schram MT, et al. Associations of the Lifestyle for Brain Health Index with structural brain changes and cognition: results from the Maastricht study. *Neurology*. 2021;97(13):e1300-e1312. doi:10.1212/wnl.0000000000012572

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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