

Title: Neighborhood disadvantage reduces cognitive reserve independent of neuropathologic change

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/alz.13736](#).

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STRUCTURED 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 ten 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.

BACKGROUND

Community-based autopsy cohorts indicate that over 90% of the attributable risk for dementia is associated with proteinopathies, namely Alzheimer's disease neuropathologic change (ADNC), Lewy body disease (LBD), and limbic-predominant age-related TDP-43 encephalopathy (LATE), and cerebrovascular disease.¹⁻³ While these pathologic changes are associated with cognitive dysfunction in most 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 Alzheimer's disease neuropathologic change 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 between neighborhood level disadvantage, neuropathologic change, and cognition. By studying the relationships between 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 for 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.

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METHODS

Study participants

The cross-sectional data on demographic, clinical, and neuropathological profiles for autopsy cases were extracted from the Integrated Neurodegenerative Disease (INDD) database at the Center for Neurodegenerative Disease Research (CNDP) 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.

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 *APOE* ϵ 4 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.

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Neuropathology measures

Autopsy cases were examined using hematoxylin and eosin staining and immunohistochemical staining against tau (PHF-1), amyloid- β (NAB228) α -synuclein (Syn303), and TDP-43 (1D3) in sixteen brain regions.³⁶ Each brain region was semi-quantitatively graded for the severity of pathological lesions (0, absent; 0.5, rare; 1, mild; 2, moderate; 3, severe) and reviewed by board-certified neuropathologists (EBL and JQT).³⁶ According to consensus criteria,^{3,37-39} ten pathologies were measured, corresponding to four proteinopathies (tau, amyloid- β , α -synuclein, and TDP-43) and three cerebrovascular lesions (infarct, amyloid angiopathy, arteriolosclerosis). Specifically, amyloid- β positive plaques, tau positive neurofibrillary tangles, and neuritic plaques were evaluated to determine Thal amyloid phase (ABeta, collapsed into scores from 0 to 3 representing Thal amyloid phase 0, 1/2, 3, and 4/5), Braak neurofibrillary tangle stage (Braak, collapsed into scores from 0 to 3 representing Braak 0, I/II, III/IV, and V/VI), CERAD score, and overall level of Alzheimer's disease neuropathological change (ADNC)³⁷. α -synuclein positive Lewy bodies

and Lewy neurites were used to assign cases into those with presence versus absence of Lewy body disease (LBD where absence of alpha-synucleinopathy or brainstem-predominant Lewy body disease was considered absent given that brainstem LBD is not associated with appreciable cognitive dysfunction³⁸). ID3 positive TDP-43 inclusions were assessed to determine the four stages of limbic predominant limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC; stage 0, no LATE; stage 1, amygdala; stage 2, hippocampus; stage 3, middle frontal cortex).³ H&E and amyloid- β staining were used to determine the presence/absence of large infarcts, presence/absence of moderate to high occipital cerebral amyloid angiopathy burden, 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 VCING criteria for cerebrovascular disease³⁹.

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Neighborhood disadvantage

Neighborhood disadvantage was ascertained by the Area deprivation index (ADI) that was constructed from a 5-year mean of American Community Survey 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.

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* ϵ 4 allele status (0, no *APOE* ϵ 4 (-), reference group; 1, *APOE* ϵ 4 (+)) were considered as 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-4.3.1. We used descriptive statistics with mean $\pm$ 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* $\epsilon 4$ 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.

Considering that ADI is based on geographic areas, Moran's Index (I) test was used to assess whether residuals from linear regression models were spatially autocorrelated.⁴² The expected values of Moran's 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.

RESULTS

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.

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 the most of 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 with those 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.

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%). 230 (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 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.

Association of neighborhood disadvantage with cognition

High educational attainment likely contributes to cognitive reserve, and years of education differed across ADI tertiles ($p = .012$ 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, $\beta = -15.770$, $p = .020$) and high ADI tertiles (ADI T3 vs T1, $\beta = -19.283$, $p = .007$; Table 3) compared with 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 x Education; $\beta = 1.122$, $p = .007$; ADI T3 x Education; $\beta = 1.281$, $p = .003$; ADI T1 as the reference group; Table 3) such that higher years of education mitigated the association between neighborhood disadvantage and cognitive function.

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Association of neighborhood disadvantage with neuropathologic change

Compared with the low ADI tertile, the high ADI tertile but not the intermediate tertile was associated with lower ADNC level (ADI T3 vs T1; $\beta = -0.722$, 95%CI [0.316, 0.747], $p = .001$; Table 4), Thal amyloid phase (ADI T3 vs T1; $\beta = -0.647$, 95%CI [0.336, 0.815], $p = .004$; Table S1), Braak stage (ADI T3 vs T1; $\beta = -0.590$, 95%CI [0.360, 0.853], $p = .007$; Table S1), CERAD score (ADI T3 vs T1; $\beta = -0.860$, 95%CI [0.276, 0.649], $p < .001$; Table S1), LBD stage (ADI T3 vs T1; $\beta = -0.484$, 95%CI [0.393, 0.967], $p = .035$; Table 4), and LATE-NC stage (ADI T3 vs T1; $\beta = -0.807$, 95%CI [0.261, 0.763], $p = .003$;

Table 4), and lower prevalence of moderate to severe amyloid angiopathy burden in occipital lobe (ADI T3 vs T1; $\beta = -0.616$, 95%CI [0.324, 0.900], $p = .018$; Table S1) after controlling for age at death, sex, and *APOE* $\epsilon 4$ allele status. However, the high ADI tertile was not associated with changes in other pathologic measures including VCING level (ADI T3 vs T1; $\beta = -0.679$, 95%CI [0.220, 1.168], $p = .111$; Table 4), presence of large infarcts (ADI T3 vs T1; $\beta = -0.261$, 95%CI [0.210, 2.826], $p = .694$; Table S1) and moderate to high arteriosclerosis in occipital white matter (ADI T3 vs T1; $\beta = -0.428$, 95%CI [0.342, 1.241], $p = .193$; Table S1).

Association of cognition with neighborhood disadvantage and neuropathologic changes

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To explore relationships between 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, $\beta = -13.749$, $p = .015$; ADI T3 vs T1, $\beta = -16.503$, $p = .006$), LBD (ADI T2 vs T1, $\beta = -12.954$, $p = .041$; ADI T3 vs T1, $\beta = -18.107$, $p = .007$), LATE-NC stage (ADI T3 vs T1, $\beta = -13.772$, $p = .031$), or VCING level (ADI T2 vs T1, $\beta = -13.164$, $p = .038$; ADI T3 vs T1, $\beta = -18.169$, $p = .007$). As expected, neuropathologic measures were associated with lower MMSE score including ADNC level (intermediate, $\beta = -3.683$, $p = .033$; high, $\beta = -9.060$, $p < .001$; not ADNC as the reference group) and LATE-NC stage (stage 2, $\beta = -6.590$, $p < .001$; no LATE-NC as the reference group). LBD ($\beta = -0.788$, $p = .385$) and VCING level (intermediate, $\beta = 0.090$, $p = .954$; high, $\beta = -0.615$, $p = .877$; 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) and quintiles (Table S3) which revealed similar results.

Residual spatial autocorrelation in the fitted linear regression models

Given the spatial nature of ADI, we tested for spatial autocorrelation using the Moran's Index (I) test. The expected values of Moran's I were close to 0 in all models (Model 1, expected Moran's I = -3.17×10^{-3} , $p = .298$; Model 2, expected Moran's I = -3.18×10^{-3} , $p = .340$; Model 3, expected Moran's I = -3.18×10^{-3} , $p = .418$; Model 4, expected Moran's I = -3.20×10^{-3} , $p = .423$; Model 5, expected Moran's I = -3.19×10^{-3} , $p = .387$; Table S4) indicating no spatial autocorrelation in residuals for these models. These insignificant results show that our ADI regression models are correctly specified.

DISCUSSION

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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 AD and cerebrovascular pathology. Specifically, in one study, neighborhood disadvantage as assessed by ADI deciles was associated with increased odds of having amyloid- β deposits including diffuse amyloid plaques³¹ and more advanced Braak NFT stages³² 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 amyloid- β 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 when 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 with 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 towards 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 which 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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ACKNOWLEDGEMENTS

This work is supported by funding from the National Institutes of Health (Grants RF1AG065341, P01AG066597, P30AG072979, and U19AG062418). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. BK and EBL conceptualized the study, contributed to the methodology and design of the study, and drafted the manuscript. All authors were involved in data acquisition. BK and EBL performed the statistical analysis. All authors were involved in manuscript review and editing and have approved the final draft. We thank the patients and their families for contributing to our research and for participating in the brain donation program.

CONFLICT OF INTEREST STATEMENT

All other authors declare no conflicts of interest.

CONSENT STATEMENT

Participants from neurodegenerative research programs at the University of Pennsylvania provided written consent before participating in this study.

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KEYWORDS

area deprivation index, socioeconomic status, cognitive reserve, Alzheimer's disease, proteinopathies, cerebrovascular disease

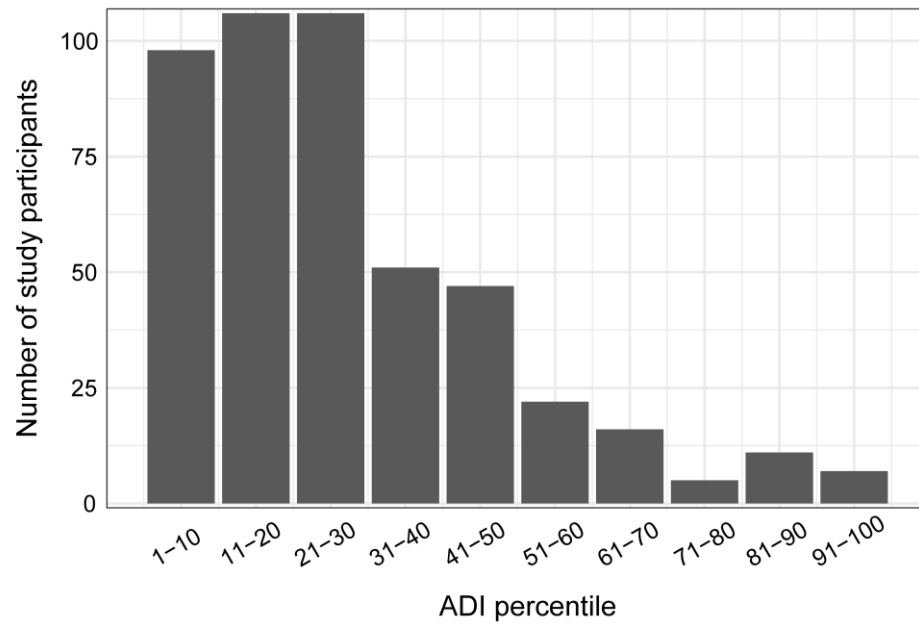


FIGURE 1. Distribution of neighborhood disadvantage by Area Deprivation Index (ADI) in the study cohort

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.

TABLE 1. Demographic and clinical characteristics of the study cohort stratified by area deprivation index (ADI) tertile

		ADI T1 (ADI	ADI T2 (ADI	ADI T3 (ADI
Characteristic	Overall	1-16)	17- 30)	31-98)
		N=163	N=147	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, yr - n (mean	469 (75.85 ±	163 (77.20 ±	147 (76.52 ±	159 (73.86 ±
± SD)	11.03)	10.50)	11.30)	11.10)
Age at onset, yr - n (mean	374 (64.82 ±	142 (65.22 ±	127 (64.99 ±	105 (64.07 ±
± SD)	10.84)	10.85)	10.17)	11.66)
Disease duration, yr - n	374 (11.45 ±	142 (11.75 ±	127 (11.63 ±	105 (10.85 ±
(mean ± SD)	6.09)	6.19)	5.94)	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	33 (7.22)			
American				
More than One	7 (1.53)			
Race				
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 $\pm$ SD)	468 (1221.53 $\pm$ 167.40)	163 (1214.99 $\pm$ 168.87)	146 (1226.66 $\pm$ 154.89)	159 (1223.54 $\pm$ 177.47)
Education, yr	354 (15.86 $\pm$ 2.86)	128 (16.41 $\pm$ 2.64)	127 (15.76 $\pm$ 2.89)	99 (15.29 $\pm$ 3.01)
<i>APOE</i> ϵ 4 allele status - n (%)				
<i>APOE</i> ϵ 4 (+)	228 (48.72)	82 (50.62)	74 (50.34)	72 (45.28)
ϵ 2/ ϵ 4	10 (2.14)			
ϵ 3/ ϵ 4	168 (35.90)			
ϵ 4/ ϵ 4	50 (10.68)			
<i>APOE</i> ϵ 4 (-)	240 (51.28)	80 (49.38)	73 (49.66)	87 (54.72)
ϵ 2/ ϵ 2	3 (0.64)			
ϵ 2/ ϵ 3	34 (7.26)			
ϵ 3/ ϵ 3	203 (43.38)			
Clinical				
MMSE score closest to death - n (mean $\pm$ SD)	323 (19.22 $\pm$ 8.63)	114 (18.39 $\pm$ 8.62)	117 (20.37 $\pm$ 8.08)	92 (18.79 $\pm$ 9.22)
Age at MMSE, yr - n (mean $\pm$ SD)	312 (73.09 $\pm$ 10.88)	109 (73.85 $\pm$ 11.00)	113 (72.65 $\pm$ 10.68)	90 (72.70 $\pm$ 11.04)

Interval from MMSE to death, yr - n (mean $\pm$ SD)	312 (4.84 $\pm$ 3.53)	109 (4.61 $\pm$ 3.46)	113 (5.02 $\pm$ 3.16)	90 (4.88 $\pm$ 4.02)
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Abbreviations: SD, standard deviation; ADI, Area Deprivation Index; T, tertile; MMSE,

Mini-Mental State Examination; *APOE*, apolipoprotein E.

Data are n (mean $\pm$ 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.

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TABLE 2. Neuropathologic characteristics of the study cohort stratified by area deprivation index (ADI) tertile

Characteristic	Overall	ADI T1 (ADI	ADI T2 (ADI	ADI T3 (ADI
		1-16)	17-30)	31-98)
		N=163	N=147	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 (%)					
Author Manuscript	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)			

Author Manuscript	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)
	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)

Abbreviations: ADI, Area Deprivation Index; T, tertile; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; ADNC, Alzheimer's disease neuropathologic change; LATE, limbic-predominant age-related TDP-43 encephalopathy; VCING, vascular cognitive impairment neuropathology guidelines.

Data are n (mean $\pm$ 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.

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TABLE 3. Association between area deprivation index and the Mini-Mental State Examination (MMSE)

	β	SE	<i>P</i> 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) x Education	1.122	0.410	0.007
ADI T3 (vs T1) x Education	1.281	0.435	0.003

Abbreviations: SE, standard error; MMSE, Mini-Mental State Examination; ADI, Area Deprivation Index; T, tertile.

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.

TABLE 4. Association between area deprivation index and dementia-related proteinopathies or cerebrovascular pathology

	ADNC level			
	β	Odds Ratio	95% CI	<i>P</i> 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
<i>APOE</i> ϵ 4 (+)	1.568	4.797	3.324, 6.921	< 0.001

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	LBD stage			
	β	Odds Ratio	95% CI	<i>P</i> 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
<i>APOE</i> ϵ 4 (+)	0.222	1.248	0.862, 1.807	0.240

	LATE-NC stage			
	β	Odds Ratio	95% CI	<i>P</i> 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
<i>APOE</i> ε4 (+)	0.366	1.442	0.941, 2.210	0.093

VCING level				
	β	Odds Ratio	95% CI	<i>P</i> 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
<i>APOE</i> ε4 (+)	0.291	1.338	0.708, 2.528	0.370

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

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* ϵ 4 status (0 = *APOE* ϵ 4 (-), reference group; 1 = *APOE* ϵ 4 (+)) were included as covariates in all models. $P < 0.05$ was used to determine statistical significance.

TABLE 5. Association of area deprivation index and dementia-related proteinopathies or cerebrovascular pathology with the Mini-Mental State Examination (MMSE)

		β	SE	<i>P</i> value
Author Manuscript	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) x Education	0.960	0.342	0.005
	ADI T3 (vs T1) x Education	1.068	0.363	0.003
		β	SE	<i>P</i> 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) x Education	0.925	0.384	0.017
	ADI T3 (vs T1) x Education	1.196	0.406	0.003
<hr/>				
		β	SE	<i>P</i> value
<hr/>				
	ADI T2 vs T1	-9.253	6.046	0.127
	ADI T3 vs T1	-13.772	6.368	0.031
	LATE-NC, stage1	-3.198	1.848	0.085
	LATE-NC, stage2	-6.590	1.130	<0.001
	LATE-NC, stage3	-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) x Education	0.697	0.368	0.059
	ADI T3 (vs T1) x Education	0.911	0.391	0.020
<hr/>				
		β	SE	<i>P</i> value
<hr/>				
	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) x Education	0.937	0.386	0.016
ADI T3 (vs T1) x Education	1.201	0.408	0.003

Abbreviations: SE, standard error; ADI, area deprivation index; T, tertile; MMSE, mini-mental state examination; ADNC, Alzheimer's disease neuropathologic change; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; VCING, vascular cognitive impairment neuropathology guidelines.

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.