

**Neurology Publish Ahead of Print**

**DOI: 10.1212/WNL.0000000000207266**

## **Association of Neighborhood Deprivation With Cognitive and Mood Outcomes in Adults With Pharmacoresistant Temporal Lobe Epilepsy**

### **Author(s):**

Robyn M Busch, PhD<sup>1,2</sup>; Jarrod E Dalton, PhD<sup>3</sup>; Lara Jehi, MD<sup>1,2,4</sup>; Lisa Ferguson, MA<sup>1</sup>; Nikolas I Krieger, MS<sup>3</sup>; Aaron F. Struck, MD<sup>5</sup>; Bruce P Hermann, PhD<sup>5</sup>

### **Corresponding Author:**

Robyn M Busch, buschr@ccf.org

**Affiliation Information for All Authors:** 1. Epilepsy Center, Cleveland Clinic, Cleveland, OH; and 2. Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH; 3. Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH; 4. Center for Computational Life Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH; 5. Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI

### **Equal Author Contribution:**

Co-first authors: Robyn M. Busch & Jarrod E. Dalton

**Contributions:**

Robyn M Busch: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Additional contributions: literature review, database development - figure design - Jarrod E Dalton database development - Lisa Ferguson Generated ADI scores - Nikolas I Krieger figure design - Bruce P Hermann

Jarrold E Dalton: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Additional contributions: literature review, database development - Robyn M Busch figure design - database development - Lisa Ferguson Generated ADI scores - Nikolas I Krieger figure design - Bruce P Hermann

Lara Jehi: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Lisa Ferguson: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data; Additional contributions: literature review, database development - Robyn M Busch figure design - Jarrod E Dalton database development - Generated ADI scores - Nikolas I Krieger figure design - Bruce P Hermann

Nikolas I Krieger: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data; Additional contributions: literature review, database development - Robyn M Busch figure design - Jarrod E Dalton database development - Lisa Ferguson Generated ADI scores - figure design - Bruce P Hermann

Aaron F. Struck: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Bruce P Hermann: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Additional contributions: literature review, database development - Robyn M Busch figure design - Jarrod E Dalton database development - Lisa Ferguson Generated ADI scores - Nikolas I Krieger figure design

**Figure Count:1****Table Count:5**

**Search Terms:**

[ 60 ] All Epilepsy/Seizures, [ 355 ] Health disparities, [ 357 ] Structural and social determinants of health, [ 199 ] All Neuropsychology/Behavior, area deprivation / ADI

**Acknowledgment:****Study Funding:**

Primary support for this study was provided by the Cleveland Clinic Epilepsy Center.

**Disclosures:**

R.M. Busch receives support from NINDS (R01NS120976, R01NS035140, R01NS097719, R61AG069729). J.E. Dalton receives support from the NIA (R01G055480, R01AG059979) and NHLBI (R01HL153175). L. Jehi receives support from NINDS (R01NS097719) and NCATS (UL1TR002548). L. Ferguson receives support from NINDS (R01NS120976, R01NS035140, R01NS109493). A.F. Struck receives funding from Ceribell. A.F. Struck and B.P. Hermann are supported by NINDS (R01NS111022, R01NS120976, R01NS117568). None of these grants are directly related to the project reported in this manuscript.

**Preprint DOI:****Received Date:**

2022-09-22

**Accepted Date:**

2023-02-21

**Handling Editor Statement:**

Submitted and externally peer reviewed. The handling editor was Associate Editor Barbara Jobst, MD, PhD, FAAN.

## Abstract

**Background and Objectives:** Temporal lobe epilepsy (TLE) is the most common adult form of epilepsy and is associated with high risk for cognitive deficits and depressed mood. However, little is known about the role of environmental factors on cognition and mood in TLE. This cross-sectional study examined the relationship between neighborhood deprivation and neuropsychological function in adults with TLE.

**Methods:** Neuropsychological data were obtained from a clinical registry of patients with TLE and included measures of intelligence, attention, processing speed, language, executive function, visuospatial skills, verbal/visual memory, depression, and anxiety. Home addresses were used to calculate the Area Deprivation Index (ADI) for each individual, which were separated into quintiles (i.e., Quintile 1=least disadvantaged, Quintile 5=most disadvantaged). Kruskal-Wallis tests compared quintile groups on cognitive domain scores as well as mood and anxiety scores. Multivariable regression models, with and without ADI, were estimated for overall cognitive phenotype as well as for mood and anxiety scores.

**Results:** 800 patients (median age 38 years-old; 58% female) met all inclusion criteria. Effects of disadvantage (increasing ADI) were observed across nearly all measured cognitive domains as well as with significant increases in symptoms of depression and anxiety. Further, patients in more disadvantaged ADI quintiles had increased odds of a worse cognitive phenotype ( $P=0.013$ ). Patients who self-identified as members of minoritized groups were over-represented in the most disadvantaged ADI quintiles and were 2.91 (95% confidence interval, CI: 1.87–4.54) times more likely to be in a severe cognitive phenotype than non-Hispanic Whites ( $P < 0.001$ ). However, accounting for ADI attenuated this relationship, suggesting neighborhood deprivation may account for some of the relationship between race/ethnicity and cognitive phenotype (ADI-adjusted proportional odds ratio [95% CI]: 1.82 [1.37 – 2.42]).

**Discussion:** These findings highlight the importance of environmental factors and regional characteristics in neuropsychological studies of epilepsy. There are many potential mechanisms by which neighborhood disadvantage can adversely impact cognition (e.g., fewer educational opportunities, limited access to health care, food insecurity/poor nutrition, greater medical comorbidities). Future research will seek to investigate these potential mechanisms and to determine whether structural and functional alterations in the brain moderate the relationship between ADI and cognition.

## Introduction

Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy and is associated with high risk for cognitive deficits and depressed mood, particularly in patients with pharmacoresistant seizures<sup>1,2</sup>. In fact, up to 80% of patients with intractable epilepsy demonstrate cognitive impairments on neuropsychological testing and up to 70% have a DSM psychiatric diagnosis, with depression and anxiety disorders among the most common<sup>1-4</sup>. These comorbidities negatively impact daily functioning and quality of life<sup>5</sup> and are reported by patients to be among the most concerning aspects of their disease<sup>6</sup>. Over decades a major focus in the neuropsychology of epilepsy has been the relationship between cognitive status and the taxonomy of epilepsy and its related clinical characteristics. In TLE, poor neuropsychological outcomes have been linked to early age at seizure onset, long duration of epilepsy, history of secondarily generalized tonic-clonic seizures, dominant-sided seizures, and etiology (presence of mesial temporal sclerosis, MTS)<sup>7</sup>. While the focus on disease-related factors is understandable, precious little is known about the impact of the social and environmental complications of epilepsy on cognition and mood in TLE. Epilepsy is more prevalent among individuals in lower (more disadvantaged) socio-economic groups, independent of social drift and other known epilepsy risk factors<sup>8-10</sup>. Further, individuals with epilepsy are more likely to live in households with the lowest annual incomes<sup>11</sup>.

In contrast, over the past decade, research on the social determinants of health has grown exponentially and suggests that social factors are a *fundamental cause* of health and disease<sup>12</sup>. The neighborhood environments in which people reside or otherwise spend their time are important contextualizers of health and longevity. Neighborhood characteristics, such as socioeconomic status and racial/ethnic composition, are associated with health disparities and

health outcomes in many chronic conditions, including epilepsy<sup>13–16</sup>. Further, factors like systemic and structural racism (e.g., housing discrimination, educational segregation, unfair lending practices, environmental injustice) and systematic inequality often force minoritized racial and ethnic groups to reside in regions with greater deprivation<sup>17</sup>. A number of studies over the past several years outside of epilepsy have shown that neighborhood deprivation is associated with brain morphology, volume, and connectivity as well as cognitive performance/decline and depressed mood<sup>18–22</sup>. However, research on the complex interactions among neighborhood deprivation, race/ethnicity, and brain health is only in its infancy.

A conceptual framework for social determinants of health in epilepsy has been proposed<sup>23</sup>, and a growing body of research has demonstrated the impact of socioeconomic and/or neighborhood deprivation on not only the incidence and prevalence of epilepsy and utilization and access to medical care, but on a number of important epilepsy outcomes including health literacy, food insecurity, stigma, pregnancy outcomes, and surgical outcomes<sup>23–25</sup>. However, despite the high prevalence of cognitive dysfunction and depressed mood in TLE and the growing awareness of the social determinant of health, very few studies have examined the relationship between socioeconomic status and neuropsychological functioning<sup>26–28</sup>, and we are not aware of any studies on the impact of neighborhood deprivation, more broadly, on cognitive and mood outcomes.

The Area Deprivation Index (ADI) was developed by Singh in 2003<sup>29</sup> and updated by Kind & Buckingham in 2018<sup>30</sup> to quantify neighborhood level socioeconomic position and includes 17 data elements derived from U.S. Census and American Community Survey data (e.g., education, employment, housing, poverty)<sup>30</sup>. High ADI scores indicate greater neighborhood deprivation. The objective of this study was to use the ADI to examine the

relationship between neighborhood deprivation and neuropsychological outcomes in adults with pharmaco-resistant TLE.

## Methods

### *Standard Protocol Approvals, Registrations, and Patient Consents*

This was a retrospective observational cohort study. All data for the study were obtained from an existing IRB-approved data registry at Cleveland Clinic. The requirement for informed consent was waived.

### *Participants*

Cases were selected from an IRB-approved neuropsychology registry for older adolescents and adults with pharmaco-resistant epilepsy who were being evaluated for epilepsy surgery at Cleveland Clinic between 1986 and 2021. Individuals were included if they met the following criteria: 1) age 16 or older, 2) history of pharmaco-resistant TLE, 3) completed a comprehensive neuropsychological evaluation as part of a pre-surgical work-up, 4) had no history of prior resective neurosurgery, and 5) available home address at or around the time of the cognitive evaluation. For those individuals who may have been assessed multiple times, data from their first neuropsychological assessment (i.e., cognitive, mood, and anxiety) was used in these analyses.

### *Assessment of Neighborhood Deprivation*

Patient addresses were extracted from the EPIC (Verona, WI) electronic health record. The R sociome package was used to estimate 2018 ADIs, nationally, at the census block group level using 5-year ACS data (2014-2018). The ADI is a standardized score ranging from 40 to 160 with a mean score of 100, with higher scores indicating greater neighborhood deprivation.

ADI percentiles were categorized into groups according to their respective quintiles of the overall ADI distribution (i.e., Quintile 1 = least disadvantaged, Quintile 5 = most disadvantaged).

### *Neuropsychological Outcomes*

All patients completed a comprehensive neuropsychological evaluation as part of a multidisciplinary work-up for potential epilepsy surgery, including measures of intelligence, attention/working memory, visuospatial processing speed, language, executive function, visuospatial skills, and verbal and visual memory (*eTable 1 in the Supplement*). Test scores within each cognitive domain were administered and scored according to the test manuals, and all scores were transformed into standard scores (mean=100, SD=15). Scores within each cognitive domain were averaged to generate a composite score for that domain. Delayed recall trials were used to generate composite scores for the verbal and visual memory domains.

Numerous studies in recent years have identified divergent cognitive and behavioral phenotypes among patients with seemingly homogenous epilepsy syndromes that relate to sociodemographic, clinical, and network characteristics<sup>31–34</sup>. In 2020, a task force was assembled by the International League Against Epilepsy and the International Neuropsychological Society to develop a consensus-based, empirically driven approach to cognitive diagnostics in epilepsy research – International Classification of Cognitive Disorders in Epilepsy (IC-CoDE) – to enhance global collaboration and facilitate big data approaches to the neuropsychology of epilepsy<sup>35,36</sup>. The IC-CoDE was used to characterize overall cognitive phenotype using a  $\leq 1.5$  SD cutoff to define cognitive impairment, across cognitive domains, for all study participants as intact, single-domain impairment, bi-domain impairment, or generalized impairment (i.e., impairment in 3 or more cognitive domains).



Finally, depression was assessed with the Beck Depression Inventory (BDI) and anxiety with the Beck Anxiety Inventory (BAI), self-report symptom inventories in which higher scores reflect greater symptoms of depression and anxiety, respectively. Raw scores were used to analyze these outcomes.

#### *Other Demographic and Clinical Variables*

Demographic variables included age, sex, race/ethnicity, and years of education. Information regarding each patient's race and ethnicity was obtained from self-report demographic data contained in their EPIC medical record. Available options for race were American Indian/Alaska Native, Asian, Black, Native Hawaiian/Pacific Islander, White, Multiracial/Multicultural, Declined, or Unavailable. Available options for ethnicity were Hispanic, Not Hispanic, Declined, or Unavailable. Clinical variables included age at seizure onset, duration of epilepsy (i.e., age at time of neuropsychological assessment minus age at seizure onset), number of ASMs, side of seizure onset, and presence/absence of mesial temporal sclerosis on MRI.

#### *Statistical Analyses*

Descriptive statistics were calculated for the overall sample and then stratified by ADI quintile using standard univariable summary statistics. Categorical variables are presented as number (percentage) and continuous variables (including continuous baseline characteristics as well as cognitive, mood, and anxiety score outcomes) with median (25<sup>th</sup>, 75<sup>th</sup> percentiles). Nonparametric Kruskal-Wallis tests were used to compare ADI quintile groups on cognitive, mood, and anxiety scores.

Cognitive phenotype was modeled as an ordinal response variable using cumulative logit models. We estimated two multivariable models for cognitive phenotype. The first model (Model

#1) included age, sex, education, minority or other race and ethnicity (vs. non-Hispanic White), age at seizure onset, duration of epilepsy, number of anti-seizure medications (ASMs), seizure side, and presence of MTS on MRI. The second model (Model #2) included these covariates as well as ADI quintile. This was done in order to compare covariate relationships in the absence and presence (respectively) of ADI effects. BDI-II and BAI scores were modeled in a similar way, with the only difference being that we used multivariable ordinary least-squares regression instead of cumulative logit regression. Effect estimates were presented as proportional odds ratio (for cognitive phenotype) or difference in means (for BDI-II and BAI scores) with Wald 95% confidence intervals and P-values. Probability distributions of cognitive phenotypes were summarized graphically by ADI, both on a univariable basis (sample proportions by group) and on a covariate-adjusted basis (adjusted means from Model 2).

We conducted a sensitivity analysis for our model of cognitive phenotype in which ADI was treated a continuous predictor (as opposed to groups defined based on quintiles). For this model, we used a quadratic effect for ADI. Analysis was implemented on a firewalled Unix server located at Cleveland Clinic, using the RStudio Integrated Development Environment<sup>37</sup>, Server Edition, Version 1.3.1093 and R statistical software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

#### *Data Availability*

The datasets analyzed in the current study are not publicly available, but further information about the datasets is available from the corresponding author on reasonable request.

### **Results**

Of 1,362 individuals with available data, a total of 800 patients met all inclusion criteria for the study. The vast majority of those not included predated institution of the electronic health

record at our hospital and, as such, did not have a home address available for calculation of the Area Deprivation Index. Of the final 800 patients included, neuropsychological testing was completed between 1990 and 2021, with the vast majority of patients (98%) completing their evaluation between 2000 and 2021. Patients were a median of 38.3 years of age (IQR: 28.3 – 47.9 years) with 12 years (IQR: 12 – 18 years) of education. The majority of participants were female (N=460; 58%) and White, non-Hispanic (N=718; 90%). Median age at seizure onset was 16 years (IQR: 8 – 27 years), and median duration of epilepsy was 17 years (IQR: 8 – 28 years). Of the 800 total patients included in the cohort, 763 had complete data on study covariates and were used in the models for cognitive phenotype. Of these, BDI-II scores were unavailable for 49, such that our models for that metric incorporated data on 714 patients. Similarly, our models for BAI included data on 360 patients for whom this outcome was assessed.

Demographic and disease characteristics of the sample are presented, by ADI quintile, in *Table 1*, and neighborhood characteristics of each ADI quintile are summarized in *eTable 2 in the Supplement*. Patients from neighborhoods in higher ADI quintiles (higher neighborhood disadvantage) were more likely to be male; were more likely to be of non-Hispanic Black, Hispanic or other race and ethnicity; had fewer years of education; and were slightly younger at seizure onset. Distributions of duration of epilepsy, number of ASMs, and seizure side were generally similar across ADI quintiles. Patients from neighborhoods in the lowest (least disadvantaged) ADI quintile had lower prevalence of MTS (38%) than patients from neighborhoods in ADI quintiles 2-5 (55%).

Summary statistics for cognitive, mood, and anxiety variables are provided in *Table 2*. Based on the Kruskal-Wallis tests, we found significant declines in all of these outcomes as a

function of increasing ADI quintile (worsening neighborhood disadvantage), with the exception of executive function, for which the relationship was marginally insignificant.

**Table 3** contains proportional odds ratios for being in a more (vs. less) severe cognitive phenotype as a function of the covariates specified above (Model #1) and additionally ADI quintile (Model #2). Prior to including ADI quintile, patients who were members of minoritized groups were nearly 3 times as likely to be in a more severe cognitive phenotype than non-Hispanic White patients (proportional odds ratio, POR, and 95% confidence interval, CI: 2.91 [1.87 – 4.54];  $P < 0.001$ ). This relationship was attenuated after the inclusion of ADI quintile in the model (Model #2 POR [95% CI]: 1.82 [1.37 – 2.42];  $P < 0.001$ ), suggesting a potential mediating effect of neighborhood deprivation on the relationship between race and ethnicity and cognitive phenotype.

In contrast, ADI quintile appeared not to account for racial and ethnic differences in BDI-II scores (covariate-adjusted difference [95% CI] in mean BDI-II score between the minoritized group vs. non-Hispanic White group before including ADI quintile in the model: 5.6 [3.1 – 8.1],  $P < 0.001$ ; difference [95% CI] after including ADI quintile in the model: 5.7 [3.1 – 8.4],  $P < 0.001$ ) (**Table 4**). Covariate-adjusted racial and ethnic differences in BAI scores were not statistically significant before or after including ADI quintile in the model (**Table 5**).

More disadvantaged ADI quintiles (quintiles 3-5) were generally associated with increased odds of more severe cognitive phenotypes in comparison to Quintile 1 (POR estimates ranging from 1.31 to 1.42; see **Figure 1** and “Model 2” results in **Table 3**), although the comparison of Quintile 5 to Quintile 1 was not statistically significant ( $P = 0.10$ ). Sensitivity analysis suggested a significant relationship between ADI as a continuous predictor and cognitive phenotype (Wald chi-squared test  $P = 0.013$  for the ADI effect as represented via a

quadratic curve). *eFigure 1 in the Supplement* displays covariate-adjusted phenotype probabilities as a function of (continuous) ADI from this model.

Our models suggest that higher education is associated with reduced likelihood of having more severe disease, use of additional anti-seizure medications was associated with an increased likelihood of having more severe disease, and male sex was associated with lower BAI scores, although we note that the models were not primarily designed to independently evaluate these effects and may be subject to residual confounding<sup>38</sup>.

## Discussion

Our results demonstrate a significant association between neighborhood deprivation and neuropsychological outcomes in adults with pharmacoresistant epilepsy. Notably, we observed significant declines across nearly all measured cognitive domains (e.g., attention, memory, language) as well as significant increases in symptoms of depression and anxiety as a function of increasing ADI. Further, patients in higher ADI quintiles had increased odds of having a more severe cognitive phenotype.

Drivers of the relationships between ADI and neuropsychological function are undoubtedly multifactorial and extremely complex. Neighborhood disadvantage can adversely impact cognition through many different mechanisms (e.g., fewer and less adequate educational opportunities, limited access to health care, food insecurity/poor nutrition, increased exposure to environmental pollutants and toxins, chronic stress, physical inactivity, less socialization, greater medical comorbidities)<sup>22,39</sup>. Further, recent studies outside the field of epilepsy have demonstrated strong relationships between neighborhood deprivation and neuroimaging findings, with greater abnormalities observed among individuals who live in disadvantaged areas<sup>18,19,21,40</sup>. We hypothesize that brain morphology, as assessed using various neuroimaging techniques, may

mediate the relationship between ADI and cognition in patients with epilepsy and have additional research underway to test this hypothesis. It should also be noted that epilepsy can place a significant burden on the patient and their support structure (e.g., medical expenses, adverse treatment events, employment concerns, inability to drive)<sup>41</sup>, potentially pushing them into areas with greater neighborhood deprivation. Further, there is evidence to suggest that racialized inequalities in epilepsy result in greater burden among some racial/ethnic groups compared to non-Hispanic Whites<sup>42</sup>.

Consistent with known racial disparities in the US and findings in prior ADI studies<sup>43,44</sup>, we observed an over-representation of individuals identifying as members of minoritized groups in the highest ADI quintiles. These individuals were also more likely to demonstrate a more severe cognitive phenotype than non-Hispanic Whites. Such differences in cognitive performance are commonly observed on neuropsychological measures and known to be impacted by test biases, normative issues, and societal inequities (e.g., education, adverse childhood experiences)<sup>45,46</sup>. Our observation that the strength of the relationship between race and cognitive function was in fact attenuated by inclusion of the ADI suggests that neighborhood deprivation may mediate, at least partly, the relationship between race/ethnicity and cognitive profile. Prior studies have also found neighborhood factors, such as socioeconomic position, explain more variability in cognitive test performance than race and ethnicity<sup>47</sup>, highlighting the importance of contextual factors in cognitive and behavioral functioning. Further, it is important to remain cognizant that race is a social construct, and the residual disparity observed between racial and ethnic groups in this study is likely due to uncaptured differences in the experiences of these minoritized groups rather than to intrinsic differences in biology (e.g., brain volume/function). Interestingly, recent research has suggested that social support may serve as a

buffer against volume loss and cognitive decline in minoritized groups<sup>48,49</sup>. Certainly, future research in larger, more diverse samples will be needed to disentangle the complex relationships between race/ethnicity, neighborhood disadvantage, other contextual factors and contributors to cognitive function, and neuropsychological functioning.

The study results should be considered in light of several limitations. First, ADI was measured at only one time point in adulthood (at a date close to the time of the neuropsychological evaluation) and does not account for potential neighborhood deprivation during critical periods of early development or changes in neighborhood deprivation across the lifespan. Further, we used the 2018 ADI to analyze our data which was obtained over a large time span (1990-2021). ADI data generated from a limited date range may have impacted our results to some extent. However, prior work has suggested that most neighborhoods are unlikely to change drastically, even over relatively long periods of time, and that ADI methodology is fairly robust to temporal variation<sup>29,50</sup>. But more directly, the relationship between cognition and ADI remained as described when the subset of patients seen from 2014-2018 was examined. Second, this was a cross-sectional study that examined cognition at only one point in time. Longitudinal studies will be required to examine the relationship between ADI and changes in cognition over time. Third, all patients in this study had pharmacoresistant TLE, and results may not generalize to other epilepsy subtypes or to less severe forms of epilepsy. Fourth, the vast majority of individuals in our sample (90%) self-identified as White, non-Hispanic, and most (67%) resided within the state of Ohio or surrounding states in the Midwest (20%). Further, given the relatively small number of non-White and Hispanic patients in the study, we had to aggregate all patients from minoritized groups into a single “Minority/Other” category for purposes of our statistical analyses. Future studies, in larger cohorts with greater racial and ethnic

diversity, will be required to examine potential differences between specific minoritized subgroups. Nevertheless, the vast majority of patients (91%) in our minoritized group were Black or Hispanic, groups that have been systematically disadvantaged and forced to live in more deprived areas. Finally, the measures of mood and anxiety were self-report and comparable investigations using formal psychiatric diagnoses is an important future direction.

### **Conclusion**

Research in the neuropsychology of epilepsy has arguably ignored the potential impact of the social determinants of health on cognition--factors that have been hiding in plain sight for many years. Their impact on cognition appears to be pervasive and of clinical significance as ADI remains a significant predictor of neuropsychological functioning even after controlling for the clinical and seizure features of epilepsy that have for so long been the dominant interest in the field. Clearly, a realignment of research focus seems warranted with a special eye to those social factors that may be modifiable and serve to improve cognition and prevent further worsening. Interest in modifiable risk factors to improve cognition is a major focus in other disorders such as AD (e.g., diet, exercise, cognitive activities, etc.) and would represent important advances in the neuropsychology of epilepsy.

**Disclaimer:** The views expressed in this article do not necessarily represent the views of the United States Department of Agriculture, its Office of the Inspector General, or the United States of America.



**Author Contributions:**

<b>Name</b>	<b>Location</b>	<b>Contribution</b>
Robyn M. Busch	Cleveland Clinic	Conceptualization, study design, literature review, data collection, database development, data interpretation, drafted manuscript, revised manuscript for intellectual content
Jarrod E. Dalton	Cleveland Clinic	Conceptualization, study design, data generation, statistical analyses, data interpretation, drafted manuscript, figure design, revised manuscript for intellectual content
Lara Jehi	Cleveland Clinic	Conceptualization, study design, data interpretation, revised manuscript for intellectual content
Nikolas Krieger	Cleveland Clinic	Collected and interpreted data; revised manuscript for intellectual content
Lisa Ferguson	Cleveland Clinic	Data collection, database development, data interpretation, revised manuscript for intellectual content
Aaron F. Struck	University of Wisconsin, Madison	Conceptualization, study design data interpretation, revised manuscript for intellectual content
Bruce P. Hermann	University of Wisconsin, Madison	Conceptualization, study design, literature review, data interpretation, figure design, drafted manuscript, revised manuscript for intellectual content

<http://links.lww.com/WNL/C733>

## References

1. Oyegbile, T. O. *et al.* The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology* **62**, 1736–1742 (2004).
2. Zhao, F. *et al.* Neuropsychological deficits in temporal lobe epilepsy: A comprehensive review. *Ann Indian Acad Neurol* **17**, 374–382 (2014).
3. Gilliam, F. G. *et al.* Depression in epilepsy: ignoring clinical expression of neuronal network dysfunction? *Epilepsia* **45 Suppl 2**, 28–33 (2004).
4. Tsopelas, N. D., Saintfort, R. & Fricchione, G. L. The relationship of psychiatric illnesses and seizures. *Curr Psychiatry Rep* **3**, 235–242 (2001).
5. Giovagnoli, A. R. *et al.* Self-rated and assessed cognitive functions in epilepsy: impact on quality of life. *Epilepsy Res* **108**, 1461–8 (2014).
6. McAuley, J. W. *et al.* Comparing patients' and practitioners' views on epilepsy concerns: a call to address memory concerns. *Epilepsy Behav* **19**, 580–583 (2010).
7. Hermann, B. P. *et al.* Neurobehavioural comorbidities of epilepsy: towards a network-based precision taxonomy. *Nat Rev Neurol* **17**, 731–746 (2021).
8. Pickrell, W. O. *et al.* Epilepsy and deprivation, a data linkage study. *Epilepsia* **56**, 585–591 (2015).
9. Symonds, J. D. *et al.* Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. *Brain* **144**, 2879–2891 (2021).
10. Maloney, E. M., Corcoran, P., Costello, D. J. & O'Reilly, É. J. Association between social deprivation and incidence of first seizures and epilepsy: A prospective population-based cohort. *Epilepsia* **63**, 2108–2119 (2022).
11. Kobau, R. *et al.* Epilepsy surveillance among adults--19 States, Behavioral Risk Factor Surveillance System, 2005. *MMWR Surveill Summ* **57**, 1–20 (2008).
12. Link, B. & Phelan, J. Social conditions as fundamental causes of health inequalities. in *Handbook of medical sociology* 3–17 (Vanderbilt University Press, 2010).
13. Rosendale, N. Social Determinants of Health in Neurology. *Neurol Clin* **40**, 231–247 (2022).
14. Burneo, J. G. *et al.* Disparities in epilepsy: report of a systematic review by the North American Commission of the International League Against Epilepsy. *Epilepsia* **50**, 2285–2295 (2009).

15. Nathan, C. L. & Gutierrez, C. FACETS of health disparities in epilepsy surgery and gaps that need to be addressed. *Neurol Clin Pract* **8**, 340–345 (2018).
16. Tian, N., Kobau, R., Zack, M. M. & Greenlund, K. J. Barriers to and Disparities in Access to Health Care Among Adults Aged  $\geq 18$  Years with Epilepsy - United States, 2015 and 2017. *MMWR Morb Mortal Wkly Rep* **71**, 697–702 (2022).
17. Bailey, Z. D. *et al.* Structural racism and health inequities in the USA: evidence and interventions. *Lancet* **389**, 1453–1463 (2017).
18. Vargas, T., Damme, K. S. F. & Mittal, V. A. Neighborhood deprivation, prefrontal morphology and neurocognition in late childhood to early adolescence. *Neuroimage* **220**, 117086 (2020).
19. Hunt, J. F. V. *et al.* Association of Neighborhood Context, Cognitive Decline, and Cortical Change in an Unimpaired Cohort. *Neurology* **96**, e2500–e2512 (2021).
20. Richardson, R., Westley, T., Gariépy, G., Austin, N. & Nandi, A. Neighborhood socioeconomic conditions and depression: a systematic review and meta-analysis. *Soc Psychiatry Psychiatr Epidemiol* **50**, 1641–1656 (2015).
21. Botdorf, M., Dunstan, J., Sorcher, L., Dougherty, L. R. & Riggins, T. Socioeconomic disadvantage and episodic memory ability in the ABCD sample: Contributions of hippocampal subregion and subfield volumes. *Dev Cogn Neurosci* **57**, 101138 (2022).
22. Vassilaki, M. *et al.* Association of neighborhood socioeconomic disadvantage and cognitive impairment. *Alzheimers Dement* (2022) doi:10.1002/alz.12702.
23. Szaflarski, M. Social determinants of health in epilepsy. *Epilepsy Behav* **41**, 283–289 (2014).
24. Gordon, K. E. & Dooley, J. M. Food insecurity and epilepsy in a nationally representative sample. *Epilepsy Behav* **43**, 139–142 (2015).
25. Fiest, K. M., Birbeck, G. L., Jacoby, A. & Jette, N. Stigma in epilepsy. *Curr Neurol Neurosci Rep* **14**, 444 (2014).
26. Baxendale, S. & Heaney, D. Socioeconomic status, cognition, and hippocampal sclerosis. *Epilepsy Behav* **20**, 64–67 (2011).
27. Carson, J., Weir, A., Chin, R. F. & McLellan, A. Socioeconomic deprivation is an independent risk factor for behavioral problems in children with epilepsy. *Epilepsy Behav* **45**, 105–109 (2015).

28. Hohmann, L., Holtkamp, M., Oltmanns, F. & Bengner, T. Associations of individual and structural socioeconomic status with cognition and mental distress in pharmaco-resistant focal epilepsy. *Epilepsy Behav* **116**, 107726 (2021).
29. Singh, G. K. Area deprivation and widening inequalities in US mortality, 1969-1998. *Am J Public Health* **93**, 1137–1143 (2003).
30. Kind, A. J. H. & Buckingham, W. R. Making Neighborhood-Disadvantage Metrics Accessible - The Neighborhood Atlas. *N Engl J Med* **378**, 2456–2458 (2018).
31. Hermann, B., Seidenberg, M., Lee, E.-J., Chan, F. & Rutecki, P. Cognitive phenotypes in temporal lobe epilepsy. *J Int Neuropsychol Soc* **13**, 12–20 (2007).
32. Hermann, B. P., Struck, A. F., Dabbs, K., Seidenberg, M. & Jones, J. E. Behavioral phenotypes of temporal lobe epilepsy. *Epilepsia Open* **6**, 369–380 (2021).
33. Hermann, B. P. *et al.* Behavioral phenotypes of childhood idiopathic epilepsies. *Epilepsia* **61**, 1427–1437 (2020).
34. Hermann, B. *et al.* Network, clinical and sociodemographic features of cognitive phenotypes in temporal lobe epilepsy. *Neuroimage Clin* **27**, 102341 (2020).
35. Norman, M. *et al.* Addressing neuropsychological diagnostics in adults with epilepsy: Introducing the International Classification of Cognitive Disorders in Epilepsy: The IC CODE Initiative. *Epilepsia Open* **6**, 266–275 (2021).
36. McDonald, C. R. *et al.* Development and application of the International Classification of Cognitive Disorders in Epilepsy (IC-CoDE): Initial results from a multi-center study of adults with temporal lobe epilepsy. *Neuropsychology* (2022) doi:10.1037/neu0000792.
37. RStudio Team, Others. RStudio: integrated development for R. in *RStudio: integrated development for R* 14 (RStudio, Inc., 2015).
38. Westreich, D. & Greenland, S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. *Am J Epidemiol* **177**, 292–298 (2013).
39. Vassilaki, M., Petersen, R. C. & Vemuri, P. Area Deprivation Index as a Surrogate of Resilience in Aging and Dementia. *Front Psychol* **13**, 930415 (2022).
40. Hunt, J. F. V. *et al.* Association of Neighborhood-Level Disadvantage With Cerebral and Hippocampal Volume. *JAMA Neurol* **77**, 451–460 (2020).
41. Ioannou, P. *et al.* The burden of epilepsy and unmet need in people with focal seizures. *Brain Behav* **12**, e2589 (2022).

42. Szaflarski, M. Racialized Inequities in Epilepsy Burden and Treatment. *Neurol Clin* **40**, 821–830 (2022).
43. Webb, E. K. *et al.* Neighborhood disadvantage is associated with stable deficits in neurocognitive functioning in traumatically-injured adults. *Health Place* **67**, 102493 (2021).
44. Kind, A. J. H. *et al.* Neighborhood Socioeconomic Disadvantage and 30-Day Rehospitalization: A Retrospective Cohort Study. *Ann Intern Med* **161**, 765 (2014).
45. Pedraza, O. & Mungas, D. Measurement in cross-cultural neuropsychology. *Neuropsychol Rev* **18**, 184–193 (2008).
46. Rivera Mindt, M., Byrd, D., Saez, P. & Manly, J. Increasing Culturally Competent Neuropsychological Services for Ethnic Minority Populations: A Call to Action. *The Clinical Neuropsychologist* **24**, 429–453 (2010).
47. Moore, T. M. *et al.* Characterizing social environment's association with neurocognition using census and crime data linked to the Philadelphia Neurodevelopmental Cohort. *Psychol. Med.* **46**, 599–610 (2016).
48. Bygrave, D. C. *et al.* The Role of Race in Relations of Social Support to Hippocampal Volumes Among Older Adults. *Res Aging* **44**, 205–214 (2022).
49. Sims, R. C., Levy, S.-A., Mwendwa, D. T., Callender, C. O. & Campbell, A. L. The influence of functional social support on executive functioning in middle-aged African Americans. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* **18**, 414–431 (2011).
50. Bensken, W. P. *et al.* Health Status and Chronic Disease Burden of the Homeless Population: An Analysis of Two Decades of Multi-Institutional Electronic Medical Records. *J Health Care Poor Underserved* **32**, 1619–1634 (2021).

**Table 1. Demographic and clinical information stratified by ADI quintile**

Variable	Quintile 1 N = 124 <sup>1</sup>	Quintile 2 N = 181 <sup>1</sup>	Quintile 3 N = 206 <sup>1</sup>	Quintile 4 N = 172 <sup>1</sup>	Quintile 5 N = 117 <sup>1</sup>
<b>Age</b>	37 (24.5, 48)	41.3 (29.3, 50.9)	39 (28.6, 47.7)	38.1 (30.4, 46.1)	36.3 (27.7, 45.8)
<b>Sex</b>					
Female	73 (59%)	102 (56%)	126 (61%)	101 (59%)	58 (50%)
Male	51 (41%)	79 (44%)	80 (39%)	71 (41%)	59 (50%)
<b>Race/Ethnicity</b>					
Non-Hispanic White	119 (96%)	173 (96%)	197 (96%)	154 (90%)	75 (64%)
Non-Hispanic Black	4 (3.2%)	4 (2.2%)	6 (2.9%)	9 (5.2%)	37 (32%)
Hispanic	1 (0.8%)	2 (1.1%)	1 (0.5%)	7 (4.1%)	4 (3.4%)
All Others	0 (0%)	2 (1.1%)	2 (1%)	2 (1.2%)	1 (0.9%)
<b>Education</b>	14 (12, 16)	13 (12, 16)	12 (12, 15)	12 (12, 14)	12 (11, 13)
<b>Age at Seizure Onset</b>	18 (9, 28)	18 (8, 30)	16 (8, 26.8)	16 (7, 25)	16 (8, 26)
<b>Duration of Epilepsy</b>	13 (5, 24)	18 (7, 30)	17 (8, 28)	18.5 (10, 30.5)	15 (8, 26.8)
<b>Number of ASMs</b>					
0	2 (1.6%)	1 (0.6%)	1 (0.5%)	0 (0%)	1 (0.9%)
1	20 (16%)	33 (18%)	25 (12%)	34 (20%)	18 (16%)
2	74 (60%)	99 (55%)	117 (57%)	103 (60%)	68 (59%)
3	25 (20%)	40 (22%)	49 (24%)	29 (17%)	24 (21%)
4	3 (2.4%)	6 (3.3%)	13 (6.3%)	6 (3.5%)	5 (4.3%)
<b>Seizure Side</b>					
Dominant	59 (48%)	83 (46%)	110 (53%)	81 (47%)	61 (52%)
Nondominant	52 (42%)	77 (43%)	83 (40%)	79 (46%)	48 (41%)
Undetermined	13 (10%)	21 (12%)	13 (6.3%)	12 (7%)	8 (6.8%)
<b>MTS</b>					
MTS	47 (38%)	93 (51%)	122 (59%)	93 (54%)	61 (52%)
No MTS	77 (62%)	88 (49%)	84 (41%)	79 (46%)	56 (48%)

<sup>1</sup>Values are reported as median (interquartile range) or number (percentage); Quintile 1=least disadvantaged, Quintile 5=most disadvantaged; Abbreviations: ASMs=anti-seizure medications; MTS=mesial temporal sclerosis

**Table 2. Cognitive, mood, and anxiety scores stratified by ADI quintile**

Variable	Quintile 1 N = 124 <sup>1</sup>	Quintile 2 N = 181 <sup>1</sup>	Quintile 3 N = 206 <sup>1</sup>	Quintile 4 N = 172 <sup>1</sup>	Quintile 5 N = 117 <sup>1</sup>	P-Value
<b>Full Scale IQ</b>	100 (93, 107)	94 (87, 101)	92 (84, 101)	89 (80, 100)	86 (77, 96)	<b>&lt;0.001<sup>2</sup></b>
<b>Attention</b>	95 (88, 103)	92 (87, 100)	92 (85, 100)	90 (83, 100)	85 (78, 95)	<b>&lt;0.001<sup>2</sup></b>
<b>Processing Speed</b>	99 (89, 105)	96 (86, 103)	94 (85, 101)	93 (84, 100)	90 (77, 99)	<b>&lt;0.001<sup>2</sup></b>
<b>Language</b>	84 (73, 96)	82 (70, 93)	77 (68, 86)	77 (66, 90)	76 (66, 88)	<b>&lt;0.001<sup>2</sup></b>
<b>Executive Function</b>	95 (82, 104)	92 (84, 103)	90 (81, 100)	90 (78, 104)	89 (76, 100)	0.052 <sup>2</sup>
<b>Visuospatial Skills</b>	102 (93, 109)	98 (88, 105)	97 (88, 105)	97 (88, 105)	89 (80, 100)	<b>&lt;0.001<sup>2</sup></b>
<b>Delayed Verbal Memory</b>	95 (86, 103)	91 (80, 98)	89 (77, 98)	90 (78, 100)	87 (80, 98)	<b>0.020<sup>2</sup></b>
<b>Delayed Visual Memory</b>	93 (85, 105)	93 (83, 103)	88 (80, 98)	90 (83, 100)	88 (80, 98)	<b>&lt;0.001<sup>2</sup></b>
<b>Depression<sup>3</sup></b>	8 (4, 13)	11 (5.2, 18)	12 (6, 18)	12 (7, 20)	12 (5, 20)	<b>0.007<sup>2</sup></b>
<b>Anxiety<sup>3</sup></b>	6 (4, 12)	8 (4, 15)	9 (4, 16)	11 (5, 24)	11 (7, 22)	<b>0.001<sup>2</sup></b>
<b>Cognitive Phenotype</b>						<b>0.006<sup>4</sup></b>
<b>Intact</b>	79 (64%)	103 (57%)	93 (45%)	81 (47%)	47 (40%)	
<b>Single Domain</b>	27 (22%)	41 (23%)	54 (26%)	41 (24%)	31 (26%)	
<b>Bi-Domain</b>	9 (7.3%)	26 (14%)	32 (16%)	28 (16%)	18 (15%)	
<b>Generalized</b>	9 (7.3%)	11 (6.1%)	27 (13%)	22 (13%)	21 (18%)	

<sup>1</sup>Values are reported as median (interquartile range) or n (%); Cognitive domain scores are reported as standard scores (mean=100, SD=15)

<sup>2</sup>Kruskal-Wallis test

<sup>3</sup>Depression and anxiety scores are reported as raw scores

<sup>4</sup>Pearson Chi-squared test

**Table 3. Proportional Odds Ratios for More Severe Cognitive Phenotypes**

	Model 1			Model 2		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	0.83	0.51, 1.35	0.4	0.91	0.68, 1.21	0.5
Sex (male)	0.79	0.59, 1.04	0.093	0.87	0.74, 1.03	0.12
Education	0.84	0.79, 0.89	<b>&lt;0.001</b>	0.90	0.87, 0.94	<b>&lt;0.001</b>
Minority/Other Race	2.91	1.87, 4.54	<b>&lt;0.001</b>	1.82	1.37, 2.42	<b>&lt;0.001</b>
Age at Seizure Onset	1.19	0.73, 1.93	0.5	1.09	0.82, 1.46	0.5
Duration of Epilepsy	1.19	0.74, 1.94	0.5	1.10	0.82, 1.46	0.5
Number of ASMs	1.69	1.40, 2.05	<b>&lt;0.001</b>	1.36	1.21, 1.52	<b>&lt;0.001</b>
Seizure Side						
Non-dominant	0.99	0.74, 1.32	>0.9	0.98	0.82, 1.16	0.8
Undetermined	1.11	0.65, 1.86	0.7	1.08	0.79, 1.47	0.6
MTS (no MTS)	0.72	0.54, 0.97	<b>0.031</b>	0.84	0.71, 1.01	0.058
ADI Quintile						
Quintile 1				—	—	—
Quintile 2				1.11	0.84, 1.47	0.5
Quintile 3				1.42	1.08, 1.87	<b>0.012</b>
Quintile 4				1.36	1.02, 1.81	<b>0.035</b>
Quintile 5				1.31	0.95, 1.81	0.1

Proportional odds ratios reflect the (relative) odds of being in a more severe phenotype category (vs. less severe): intact cognition < single domain < bi-domain < generalized

Abbreviations: OR=odds ratio; CI=confidence interval



**Table 4. Linear Models of Depression Based on BDI-II Score**

	Model 1			Model 2		
	Beta	95% CI	p-value	Beta	95% CI	p-value
Age	-0.67	-3.2, 1.8	0.6	-0.78	-3.3, 1.7	0.5
Sex (male)	-1.8	-3.3, -0.4	<b>0.013</b>	-1.8	-3.3, -0.4	<b>0.014</b>
Education	-0.21	-0.5, 0.1	0.2	-0.12	-0.4, 0.2	0.5
Minority/Other Race	5.6	3.1, 8.1	<b>&lt;0.001</b>	5.7	3.1, 8.4	<b>&lt;0.001</b>
Age at Seizure Onset	0.72	-1.8, 3.2	0.6	0.83	-1.6, 3.3	0.5
Duration of Epilepsy	0.66	-1.8, 3.1	0.6	0.77	-1.7, 3.2	0.5
Number of ASMs	0.23	-0.7, 1.2	0.6	0.21	-0.7, 1.2	0.7
Seizure Side						
Non-dominant	-0.06	-1.6, 1.4	>0.9	-0.06	-1.6, 1.4	>0.9
Undetermined	3.4	0.7, 6.2	<b>0.014</b>	3.6	0.9, 6.3	<b>0.010</b>
MTS (no MTS)	-0.27	-1.8, 1.3	0.7	-0.16	-1.7, 1.4	0.8
ADI Quintile						
Quintile 1				--	--	--
Quintile 2				2.0	-0.3, 4.4	0.091
Quintile 3				2.8	0.5, 5.2	<b>0.019</b>
Quintile 4				4.1	1.7, 6.6	<b>&lt;0.001</b>
Quintile 5				1.6	-1.3, 4.4	0.3

Abbreviations: BDI-II=Beck Depression Inventory – Second Edition; CI=confidence interval; ASMs=anti-seizure medications; MTS=mesial temporal sclerosis

**Table 5. Linear Models of Anxiety Based on BAI Score**

	Model 1			Model 2		
	Beta	95% CI	p-value	Beta	95% CI	p-value
Age	1.9	-1.9, 5.7	0.3	1.9	-1.9, 5.6	0.3
Sex (male)	-2.8	-5.0, -0.5	<b>0.017</b>	-3.0	-5.2, -0.8	<b>0.007</b>
Education	-0.4	-0.9, 0.1	0.13	-0.1	-0.6, 0.4	0.8
Minority/Other Race	1.8	-1.6, 5.2	0.3	-1.0	-4.7, 2.7	0.6
Age at Seizure Onset	-1.9	-5.7, 1.9	0.3	-1.9	-5.6, 1.9	0.3
Duration of Epilepsy	-1.8	-5.6, 2.0	0.3	-1.9	-5.6, 1.9	0.3
Number of ASMs	1.0	-0.4, 2.4	0.2	0.8	-0.6, 2.2	0.2
Seizure Side						
Non-dominant	1.3	-1.1, 3.6	0.3	1.2	-1.1, 3.5	0.3
Undetermined	3.6	-0.4, 7.6	0.079	3.6	-0.3, 7.6	0.071
MTS (no MTS)	1.5	-0.9, 3.9	0.2	1.7	-0.7, 4.0	0.2
ADI Quintile						
Quintile 1				—	—	
Quintile 2				3.8	0.3, 7.3	<b>0.033</b>
Quintile 3				4.0	0.5, 7.5	<b>0.027</b>
Quintile 4				7.3	3.6, 11	<b>&lt;0.001</b>
Quintile 5				8.8	4.2, 13	<b>&lt;0.001</b>

Abbreviations: BAI=Beck Anxiety Inventory; CI=confidence interval; ASMs=anti-seizure medications; MTS=mesial temporal sclerosis

## Figure Legends

**Figure 1. Phenotype Probabilities by ADI Quintile.** (A) Unadjusted model, (B) Covariate-adjusted model controlling for age, sex, education, race, age at seizure onset, duration of epilepsy, number of ASMs, seizure side, MTS, and ADI quintile.

