Title

The Impact of Sociodemographic Disadvantage on Cognitive Outcomes in Children With Newly Diagnosed Seizures and Their Unaffected Siblings Over 36 Months

Authors

Oyegbile-Chidi, Temitayo
Harvey, Danielle
Dunn, David
et al.

Publication Date

2023-11-01

DOI

10.1016/j.pediatrneurol.2023.08.028

Peer reviewed

The Impact of Sociodemographic Disadvantage on Cognitive Outcomes in Children with Newly Diagnosed Seizures and their Unaffected Siblings over 36 months

Authors: Temitayo Oyegbile-Chidi MD, PhD[1], Danielle Harvey PhD[2], David Dunn MD[3], Jana Jones PhD[4], Anna Byars PhD[5], Philip Fastenau PhD[6], Joan Austin PhD[7], Bruce Hermann PhD[4]

Abstract

The Editor's Choice article for December 2023 is "The Impact of Sociodemographic Disadvantage on Cognitive Outcomes in Children with Newly Diagnosed Seizures and their Unaffected Siblings over 36 months" by Temitayo Oyegbile-Chidi. In this research paper, the authors evaluate the long-term role of sociodemographic disadvantage on the presence of cognitive co-morbidities in new-onset epilepsy. Using a large sample size, newly diagnosed pediatric epilepsy patients along with their unaffected siblings (controls) underwent a comprehensive battery of neuropsychological tests multiple times over 36 months. Using baseline sociodemographic factors, the longitudinal relationship between a computed sociodemographic index score (SD) and cognitive/academic challenges in epilepsy was established. This critical findings of this study indicate sociodemographic disadvantage is a constant and stable predictor of cognitive and academic challenges in epilepsy. As such, a role for early intervention should be considered in disadvantaged pediatric epilepsy patients to improve overall quality of life.

Background: Accumulating evidence indicates that children with newly diagnosed epilepsy have comorbidities including cognitive challenges. Research investigating comorbidities has focused on clinical epilepsy characteristics and neurobiological/genetic correlates. The role that sociodemographic disadvantage (SD) may play has received less attention. We investigated the role of SD in cognitive status in youth with newly diagnosed epilepsy over a follow-up of 36 months to determine the degree, extent, and duration of the role of disadvantage.

Methods: A total of 289 children (six to16 years) within six weeks of their first seizure along with 167 siblings underwent comprehensive neuropsychological assessments (intelligence, language, memory, executive function, processing speed, and academic achievement) at baseline, 18 months later, and at 36 months from baseline. Baseline demographic information (race, caregiver's education, household income, and parental marital status), clinical epilepsy characteristics (age of onset, etc.), MRI and EEG information was collected.

Results: A Sociodemographic Disadvantage (SD) index was computed for each family and categorized into four groups by level of disadvantage. In children and siblings, the least disadvantaged group exhibited the highest Full-Scale IQ, neuropsychological factor scores and academic performances; whereas the most disadvantaged showed the polar opposite with the worst performances across all tests. Findings remained stable and significant over 36 months. Linear regression analyses indicated that disadvantage was a more constant and stable predictor of cognitive and academic performance over time compared to clinical epilepsy characteristics and MRI/EEG abnormalities.
Conclusions: This study indicates the strong association between sociodemographic disadvantage and cognitive/academic performance in children with newly diagnosed epilepsy and their siblings is significant and predictive of 3-year cognitive outcomes.

Author Affiliations:
1 Department of Neurology, University of California Davis, Sacramento, CA 94518, USA
2 Department of Public Health Sciences, University of California Davis, Sacramento, CA 94518, USA
3 Departments of Psychiatry and Neurology, Indiana University, Indianapolis, IN 46202, USA
4 Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI 53726, USA
5 Department of Pediatrics, Cincinnati Children's Hospital at the University of Cincinnati, Cincinnati, OH 45229, USA
6 Department of Neurology, University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA
7 Distinguished Professor Emerita, School of Nursing, Indiana University, Indianapolis, IN 46202, USA

Correspondence to: Temitayo Oyegbile-Chidi MD, PhD

Department of Neurology
University of California Davis

4860 Y Street, Sacramento CA 94518

oyegbilechidi@ucdavis.edu

Running Head: Disadvantage and Cognition in Children with Epilepsy

Keywords: Epilepsy, sociodemographic and socioeconomic disadvantage, Pediatric, Cognition, academic performance, social determinants of health

Abbreviations: SD = Sociodemographic Disadvantage, IQ = Intelligence Quotient, MRI = Magnetic Resonance Imaging, EEG = Electroencephalogram, ASM = antiseizure medication ASM, B = baseline, M18 = 18 months later, M36 = 36 months later, SD=standard deviation, FOIAS=focal onset impaired awareness seizure; CELF-3 = Clinical Evaluation of Language Fundamentals, 3rd Edition; CTOPP = Comprehensive Test of Phonological Processing, CPT-II = Conners' Continuous Performance Test, 2nd Edition; K-BIT = Kaufman Brief Intelligence Test; WISC-III = Wechsler Intelligence Scale for Children, 3rd Edition; WRAML = Wide Range Assessment of Memory and Learning; WCST = Wisconsin Card Sorting Test; EF = Executive Function/attention/construction; WJ-R = Woodcock-Johnson Revised Tests of Achievement; ANOVA = one-way analysis of variance; SPSS = Statistical Package for Social Sciences; LSD = least significant difference; SE = Standard Error

Introduction

An international literature extending over decades, consisting of population-based, community-based and clinically-based investigations, has characterized the presence and degree of abnormalities in cognition and academic underachievement in youth with epilepsy; as well as the clinical risk of developing these cognitive impairments[1–4]. Diverse aspects of cognition have been examined including metrics of general intelligence as well as specific domains of higher cognitive ability including memory, executive function, and language[5]. Interest has centered not only on the widespread risk of cognitive and academic abnormality in youth with epilepsy, but the association of this risk with numerous clinical epilepsy characteristics (e.g., age of onset, duration, etiology, seizure frequency and severity, presence and frequency of interictal electroencephalogram (EEG) abnormalities), as well as the inherent risks associated with discrete epilepsy syndromes, both generalized (e.g., idiopathic[6], childhood and juvenile absence[7], juvenile myoclonic[8]) and focal (e.g., Rolandic[9], temporal[10], frontal[11], parietal & occipital[3]). Specific epilepsy syndromes have been examined in isolation and/or contrasted to each other to gauge the relative syndrome-specific risk to cognition. Even epilepsy syndromes traditionally thought to be benign with limited cognitive and academic risk have been demonstrated to harbor cognitive and academic consequences[5,12].

Longitudinal research has examined the course of cognitive abnormalities and cognitive development over time as the timing and course of cognitive and academic problems has been a key clinical concern. In some series, cognitive abnormalities appear to remain static, but in other series problems may worsen despite of successful treatment of seizures[13]. Investigation of the timing of neurobehavioral comorbidities has led to examination of children with newly diagnosed epilepsies where cognitive and academic abnormalities have been shown to be present much earlier in the course of epilepsy than expected and in some cases to even antedate the first recognized seizure, diagnosis, and treatment of epilepsy[1–3,10,14]. The detection of abnormalities very early in the course of childhood epilepsy offers an early window for intervention.

Neuroimaging has been brought to bear to inform the neurobiological correlates of disordered cognition and academic achievement in both chronic and newly diagnosed epilepsies. The applied techniques, broad in scope, include quantitative and functional imaging of structure, connectivity and activation; as well as neurophysiological correlates including EEG and event-related potentials that indicate a significant relationship[10,15,16], which may strengthen over time[17–20]. Potential genetic contributions to cognitive, behavioral, and imaging abnormalities have also been explored through investigations of familial aggregation that include the unaffected siblings of youth with epilepsy[17–25]. The evidence thus far suggests that unaffected siblings harbor cognitive abnormalities and underlying structural brain alterations which would suggest there could indeed be a significant familial (and possibly genetic) component associated with the epilepsy syndrome. However, there are a number of reasons why unaffected siblings may have cognitive complications including but not limited to both environmental and genetic factors.

Notably, throughout this extensive literature a factor rarely examined is the role of socioeconomic and sociodemographic disadvantage. An emerging general health status literature has demonstrated the significant role of several demographic factors including race, caregiver (usually mother's) education level, marital status of the caregiver, neighborhood characteristics, and household income in different health conditions[26-28] and even amongst typically developing children[29]. These factors underlying the social determinants of health have been investigated separately and/or as an aggregate index. In epilepsy, there has been growing awareness of the impact of socioeconomic and neighborhood disadvantage on health and health-related factors on epilepsy outcomes and seizure risk[30–35], but this association has yet to be clearly characterized over time in a pediatric population . In addition, the relative contribution of sociodemographic factors compared to traditional clinical epilepsy variables is yet to be established.

In this investigation, the role of sociodemographic disadvantage in the cognitive and academic status of youth with epilepsy is the focus. In a large cohort of children with newly diagnosed epilepsy we have 4 aims: 1) characterize the impact of disadvantage on cognition and academic achievement in youth with epilepsy, 2) consistent with contemporary interest

in familial aggregation of comorbidities, examine the impact of disadvantage on the siblings of the children with epilepsy, 3) characterize the longer term effects of disadvantage on youth with epilepsy and their siblings over three years, and 4) compare the relative explanatory power of early sociodemographic disadvantage and classic clinical seizure features for cognition and academic achievement both at baseline and over a three-year period.

Methods:

Participants:

Study participants included children with newly diagnosed seizures, their siblings as controls, and their primary caregivers in each household[36,37]. The core investigation was conducted at Indiana University and Cincinnati Children's Hospital at the University of Cincinnati. Children were recruited through electroencephalogram (EEG) laboratories, emergency departments, and pediatric neurologists in two large children's hospitals (Indianapolis and Cincinnati) and from practices of private pediatric neurologists in Indianapolis. The Cincinnati recruitment site provided the most subjects from their busy first-seizure clinic. The Indiana recruitment site recruited newly-referred children from the general epilepsy clinics. When children met the criteria, refusals were less than 10%. All children in this sample met International League Against Epilepsy criteria for epilepsy[38].

A total of 349 children with epilepsy were recruited within 6 weeks of their first recognized seizure (Mean = 35 days). Of the 349 children who agreed to participate in the study, 23 scored below 70 on screening, 11 did not provide any data, and 33 were unable to complete testing (e.g., typically scheduling/travel), for a final sample of 282[3]. There were no differences between those who completed neuropsychological testing and those who did not on age, sex, race, or socioeconomic status ($p > 0.10$). For the 36-month longitudinal analysis, 228 of the 282 children completed at least one follow-up visit.

The sibling control sample was a comparison group of 167 healthy siblings of the children with epilepsy. Only one sibling was recruited per family. For each child in the seizure group, we attempted to recruit a healthy sibling age 2–18 years (preferring ages 6+ for cognitive testing). If there were multiple siblings, the sibling that was closest in age to the child with the seizure was included in the study. When the sibling was too young (<6 years), had another chronic condition (e.g., asthma), or was too old (> 18 years), he/she was not included in the study. There was minimal difficulty recruiting siblings when siblings were available. Of the 232 eligible siblings, 50 were too young (-6 years) to complete neuropsychological testing and 35 others could not travel to the medical center for testing, resulting in 167 sibling controls.

Exclusion criteria for both children with epilepsy and siblings were: a co-morbid chronic physical disorder, intellectual disability (based on either clinic records or parent report), or seizures precipitated by an acute event (e.g., intracranial infection, metabolic derangement, and recent head injury). Children who had had two or more febrile but no afebrile seizures or who were placed on daily antiseizure medication (ASM) after a febrile seizure were also excluded. In addition, children with infantile spasms (hypsarrhythmia), electrical status epilepticus in sleep and epilepsy with continuous spike-wave during slow wave sleep were excluded from the study. Parental informed consent and child assent were obtained prior to data collection. Siblings did not have epilepsy and were not on medication that could affect mental status. The study was approved by the institutional review boards at Indiana University and Cincinnati Children's Hospital Medical Center.

Data were first collected within 6 weeks of the first recognized seizure (baseline; B) from both children with newly diagnosed epilepsy and siblings. All participants were followed prospectively and reassessed 18 months later (M18) and finally, 36 months later (M36). All data were included in the analysis regardless of the number of visits completed.

Measures

Sociodemographic Disadvantage (SD) Score - The SD score is an index based on four sociodemographic variables collected from the primary caregiver and child via structured interviews; the primary caregiver was most frequently the mother (95.8%). The four variables composing the SD are: Caregiver's education level, race (self-identified), household income, and marital status. These four variables were carefully chosen as each variable contributes significantly to disadvantage (SD) metric (See Supplemental Table 1). Based on past literature, each SD variable chosen is a relevant social determinant of health[26–28,33]. For caregiver education level and household income, those families below the mean for the sample were assigned a score of *1*, while those families at or above the mean were assigned a score of *0*. The distribution of income for this sample was nearly identical to national income statistics at the time of recruitment[39]. For race and caregiver marital status, non-white race and non-married status were each assigned a score of *1*, while white race and married status received a score of *0*. The SD score is the sum of all 4 disadvantage variables, ranging from 0-4. SD groups 3 and 4 were collapsed together due to the smaller sample sizes in each group, leading to four total groups comprising of SD0 (lowest number of disadvantages) to SD3 (highest number of disadvantages). The disadvantage assessment was conducted at the baseline (B) visit only. The Supplemental Table 2 shows the distribution of specific deprivation metrics across the SD categories, indicating that all variables chosen contribute significantly to the SD composite index.

Table 1 here

Cognitive Evaluation – All children and sibling controls completed a comprehensive neuropsychological evaluation that included standardized clinical measures of intelligence, language, immediate and delayed verbal and visual memory, executive functions, speeded fine motor dexterity, and academic achievement at baseline, M18 and M36. The specific administered tests included: Clinical Evaluation of Language Fundamentals, 3rd Edition (CELF-3)[40]; Comprehensive Test of Phonological Processing (CTOPP)[41]; Conners' Continuous Performance Test, 2nd Edition, (CPT-II)[42]; Kaufman Brief Intelligence Test (K-BIT)[43]; Coding and Symbol

Search Subtests of the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III)[44]; Wide Range Assessment of Memory and Learning (WRAML) Design Copy[45]; and the Wisconsin Card Sorting Test (WCST)[46]. Testing was administered by psychometrists who were trained, observed, and certified on the test battery and its scoring by a pediatric neuropsychologist [3].

To assess intelligence, the full-scale K-BIT IQ score was used. All youth had an IQ equal or greater than 70. In addition, each test was administered according to standardized procedures and scores were converted to age-corrected standardized scores using the best available national norms for all tests except WRAML Design Copy, which was designed by this study's research group[45]; this test was normed internally, using our own sample to generate age-corrected scores. Factor analysis of this neuropsychological test data revealed four underlying factors: (1) Language, (2) Processing Speed, (3) Executive Function/attention/construction (EF), and (4) Verbal Memory and Learning [47,48]. The Language factor consisted of measures of verbal concept formation, phonological awareness, and phonological memory. The Processing Speed factor consisted of measures assessing psychomotor speed and rapid naming. The Executive Function (EF) factor consisted of measures assessing sustained attention, problem solving, and visual-construction. The Verbal Memory and Learning factor consisted of measures of rote verbal learning and story recall. Higher factor scores indicate better neuropsychological performance[3].

Academic Achievement – All children and sibling controls were assessed using three subtests of the Woodcock-Johnson Revised Tests of Achievement (WJ-R): Letter-Word Identification, a measure of word reading; Calculation (a measure of math computation skills) and Dictation (a measure of spelling, punctuation, and syntax in writing)[49]. Standard scores for age were generated from national norms for that test.

All seizure characteristics and demographic data (e.g., caregiver's highest education level, caregiver's household income, child's age, child's sex, and child's education) were collected via structured interviews by trained research coordinators as well as psychometrists. Testing was administered by psychometrists who were trained, observed, and certified on the test battery and its scoring by a pediatric neuropsychologist[52]. Clinical seizure variables including seizure

classification, results of EEG and imaging were collected from the electronic medical record and were coded independently by study physicians blinded to the behavioral or cognitive data.

Statistical Analysis

All data obtained were collated and analyzed using the Statistical Package for Social Sciences (SPSS) software (Version 27.0, IBM, Chicago IL). Clinical epilepsy characteristics included age of onset of epilepsy, seizure burden (i.e., seizure frequency), and seizure types. One-way analysis of variance (ANOVA) tests compared SD groups on intelligence quotient (IQ), cognitive domain factor scores, and academic achievement scores each for the children with newly diagnosed epilepsy and their siblings at each time point (B, M18, M36). When the F statistic was significant, LSD post hoc comparisons were conducted among the levels of SD.

Using linear regression, we also examined which variables explained the most variance (R-squared) in IQ, cognitive domain factor scores, and academic achievement scores. Independent variables were SD, epilepsy syndrome (0=primarily generalized, 1=localization-related), EEG results (0=normal, 1=abnormal), MRI results (0=normal, 1=abnormal), age of onset of first recognized seizure, seizure frequency (number of seizures/year), and percent on first anti-seizure medication (ASM). Separate regression analyses were conducted at each time point (B, M18, M36) for each dependent (cognitive/academic) variable.

Results:

Sample Characteristics

Table 1B summarizes the demographic characteristics for both groups (children with seizures and siblings), clinical epilepsy characteristics in the seizure group, and family/sociodemographic characteristics for the total sample. Briefly, a total of 289 children with newly diagnosed seizures aged 6-16 years and 167 sibling controls were included in the analyses. There were no significant differences between the groups except for a trend towards lower IQ (Table 1B) (approximately 3.5 points) in the children with newly diagnosed seizures. The clinical epilepsy characteristics indicate that the children with epilepsy in this sample had an average age of onset

of epilepsy of 9.58 years of age and comprised of about 60% focal epilepsy syndromes (Table 1B). The five most frequently prescribed medications were lamotrigine, oxcarbazepine, carbamazepine, phenytoin and valproic acid. Other less commonly prescribed medications included levetiracetam, ethosuximide, zonisamide, and gabapentin. The epilepsy syndromes were divided into two groups: Generalized (motor and nonmotor) and Focal onset (focal aware and unaware with motor or nonmotor onset seizures). In this cohort, MRI abnormalities included multiple different structural abnormalities (bilateral or unilateral hippocampal atrophy/sclerosis, ventricular enlargement, volume loss, cortical dysplasias, heterotopias, angiomas, encephalomalacia, and old hemorrhages) and described in detail elsewhere[50]. The EEG abnormalities included focal and generalized epileptiform activity (localized and generalized intermittent slowing, continuous slowing, epileptiform discharges, electrographic seizures, occipital intermittent delta activity, and frontal intermittent delta activity). In this cohort, 62% evidenced epileptiform activity, 11% slow wave activity, and 1% electrographic seizures[3]. With regard to family sociodemographic characteristics, our sample was nearly identical to national statistics for the U.S. at the time of recruitment[39]. Notably, among the children with epilepsy there were no significant differences in age, sex, or education nor across a diversity of clinical epilepsy characteristics (age of onset, number of seizures; or percent of participants with specific seizure types or abnormalities on MRI and EEG) by SD group.

Sociodemographic Disadvantage (SD) Score Subgroup Characteristics

The sample was divided into four subgroups based on their SD Score. Subgroup characteristics are reported in Supplemental Table 2 & Table 2. The disadvantage assessment was conducted at the baseline visit only, with the intent to determine if initial sociodemographic disadvantage has a lasting impact over time. Families who fell into the SD-3 category were primarily of non-white ethnicity and showed the lowest levels of income, caregiver education, and married parental status, while families who fell into the SD-0 category were all of white ethnicity and showed the highest levels of income, caregiver education and married parental status (Supplemental Table 2). Notably, among the children with epilepsy there were no significant differences in child's age, child's sex, or child's education nor across a diversity of clinical epilepsy characteristics

(age of onset, number of seizures; or percent of participants with specific seizure types or abnormalities on MRI and EEG) by SD group (Table 2)

.

Table 2 here

Sociodemographic Disadvantage and Global Intellectual Ability

Both children with newly diagnosed epilepsy and their siblings have significant differences in mean intelligence quotient (IQ) based on their SD score such that families that fall in the SD-3 category show lower IQ scores compared to those who fall into the SD-0 category (See Figure 1). Furthermore, each category – SD-3, SD-2, SD-1, and SD-0 differed from the other in mean IQ levels both in children with epilepsy and siblings. In addition, these differences remained stable and significant over a 3-year period (at baseline, 18 months later, and 36 months later, see Table 3).

Figure 1 here

Sociodemographic Disadvantage and Cognitive Domains

Our data indicate that both children with epilepsy and their siblings have significant differences in cognitive domain factor scores (Language, Processing Speed, Executive Function, and Verbal Memory) based on their disadvantage score such that families that fall in the SD-3 category show lower language, processing speed, executive function, and verbal memory factor scores compared to those who fall into the SD-0 category (See Tables 3 & 4). Furthermore, each

category –SD-3, SD-2, SD-1, and SD-0 frequently differed significantly from the other in cognitive domain factor score levels both in children with epilepsy and siblings. In addition, these differences remained stable and significant over a 3-year period (baseline, 18 months later and 36 months later).

Table 3 here

Table 4 here

Sociodemographic Disadvantage and Academic Performance

Our data indicate that both children with epilepsy and their siblings have significant differences in academic performance (letter-word identification, calculation and dictation) based on their disadvantage score such that families that fall in the SD-3 category show lower letter-word identification, calculation and dictation scores compared to those who fall into the SD-0 category (See Tables 5 & 6). Furthermore, each category – SD-3, SD-2, SD-1, and SD-0 frequently differed significantly from the other in academic performance scores both in children with epilepsy and siblings. In addition, these differences remained stable and significant over a 3-year period (baseline, 18 months later and 36 months later).

Table 5 here

Table 6 here

Impact of Psychiatric Symptoms on the Relationship between Disadvantage and Global Intellectual Ability

Using a one-way ANCOVA, a focused secondary analysis assessed the potential impact of behavioral symptoms on the relationship between disadvantage and cognition. Using the Child Behavior Checklist (CBCL) Total Behavioral Problems scale as a covariate, the role of disadvantage on cognition was reassessed, specifically focusing on global intellectual ability (mean IQ). CBCL Total Behavioral Problems from each time point – B, M18, and M36 – was utilized in each analysis timepoint. The results indicate that the significant effects of disadvantage on cognition remain in spite of using CBCL as a covariate at each timepoint – Baseline - $F(3,285) = 13.05$, $p < 0.001$; M18 - $F(3,285) = 12.43$, $p < 0.001$; M36 - $F(3,285) = 12.74$, $p < 0.001$ (Figure 2). Post-hoc tests indicated that the differences across all disadvantage groups also remain significant and similar to that presented in Table 3.

Figure 2 here

Longitudinal Analysis - The Effect of Time on Disadvantage and Global Intellectual Ability

Using one-way repeated measures ANOVA, a focused secondary longitudinal analysis assessed the potential impact of disadvantage on prospective change/development of global intellectual ability (mean IQ). The results indicate no significant effect of time (within subjects) Wilks' Lambda = .999, $F(2,252)= 0.052$, $p = 0.949$ and no significant interaction between time and SD score, $F(2,252) = 0.512$, $p = 0.675$. However, there was a significant effect of disadvantage $F(3,250) = 17.96$, $p<.001$. Thus, the prospective trajectory of intellectual ability is not impacted by disadvantage, rather the impact of disadvantage is significant at baseline and persists in a static fashion from baseline to 3 years later.

Predictive Characteristics of Cognition and Academic Performance in Children with Newly Diagnosed Epilepsy

Using linear regression, we determined which factors play more significant and less significant roles in explaining the variance (R-squared) in intelligence, cognitive domain factor scores, and academic performance scores. Using the standardized beta coefficients, SD consistently served as a significant predictor of global intellectual ability, cognitive domain scores and academic performance scores, compared to age of onset, MRI/EEG findings, seizure burden, anti-seizure medication number, and seizure syndrome (see Table 7). We note here that other clinical factors such as age of onset of epilepsy and anti-seizure medications played a significant role in the regression analysis. However, none of these clinical epilepsy factors explained as much variance as disadvantage.

Table 7 here

Discussion

The goal of this investigation was to determine the contribution of social determinants of health, specifically sociodemographic disadvantage, to the neuropsychological and academic status of children with newly diagnosed epilepsy, assessing this relationship using a cross-sectional, longitudinal, and familial approach. The core findings include the following: (1) Sociodemographic disadvantage is closely associated with the neuropsychological and academic status of children with epilepsy at the onset of the disorder; (2) Sociodemographic disadvantage similarly impacts the neuropsychological and academic performance of unaffected siblings of children with epilepsy; (3) Sociodemographic disadvantage at baseline is predictive of the cognitive and academic performance of youth with epilepsy and their siblings – out to three

years after initial evaluation; and 4) Sociodemographic disadvantage accounts for more variance in the neuropsychological and academic status of children with epilepsy compared to traditional clinical epilepsy factors, documenting the clinical significance of disadvantage in this population. To our knowledge, this is the first long-term familial aggregation study assessing the role of the sociodemographic disadvantage on the cognitive and academic status of children with epilepsy and their siblings.

The sample cohort was categorized into four levels of disadvantage and neuropsychological status was reduced to four core domains (language, verbal memory, executive function, and processing speed), with additional measures of intelligence and targeted academic skills. Sociodemographic disadvantage was found to have a robust and strong impact across all cognitive/academic domains. Specifically, the least disadvantaged group exhibited the highest Full-Scale IQ, neuropsychological factor scores and academic performances; while the most disadvantaged showed the polar opposite with the worst performances across all test metrics. These were meaningful clinical differences with the low disadvantage group typically performing in the high average range and the most disadvantaged group in the low average to borderline impaired range. The overall pattern of results indicates that, at the onset of the first recognized seizure, the presence and degree of sociodemographic disadvantage plays a significant role in intellectual, cognitive and academic performance regardless of baseline clinical epilepsy characteristics (e.g., seizure burden, age of onset, or seizure syndrome). These findings corroborate prior evidence in the literature[32–35].

Comparable associations were seen in the unaffected siblings of the children with epilepsy, demonstrating a strong familial aggregation effect regarding the presence or absence of an aggregation of cognitive and academic morbidity. Our data indicate that this neuropsychological aggregation has a clear relationship with measures of disadvantage. More specifically, we have shown that the presence and degree of sociodemographic disadvantage drives cognitive and academic performance in both children with epilepsy and their siblings—providing an alternative interpretation of familial associations as a potentially significantly strong predictor of cognitive function.

Another critical finding was that disadvantage rated at baseline was associated with significant persisting impact across serial evaluations out to 3 years after the baseline assessment—attesting to the strength and duration of the impact. The presence or absence of these sociodemographic factors at baseline are therefore not ephemeral and pose a lasting impact on these youth—both children with epilepsy and siblings. Notably, the epilepsy-cognition literature has often focused to a significant degree on the relations of neurocognitive problems with diverse clinical seizure variables (e.g., age of onset, duration of epilepsy, seizure frequency, number of medications, presence/absence of MRI abnormalities). However, when these clinical seizure variables were placed in direct comparison with an index of disadvantage, both at baseline and 3 years later, the explanatory power of disadvantage was evident and exceeded that of the clinical seizure variables. This suggests that disadvantage requires further consideration in this literature and should be examined in relation to other comorbidities of epilepsy (e.g., behavior), developmental factors, neurological variables, and treatment outcomes. Indeed, more recently researchers have begun to take this SD factor into consideration[30-35]. The accumulating findings continue to indicate that SD factors are very important in childhood epilepsy and contribute significantly to non-seizure outcomes. Specifically, a major key to cognitive outcomes and academic achievement is the extent and level of social deprivation.

From a clinical standpoint, our findings are easily adaptable to the clinical setting. The operational definition of disadvantage used here is clinic-friendly and easy to compute, with the potential to screen at diagnosis given its concurrent and predictive validity—opening the door for options of early intervention. Early intervention could potentially improve the long-term co-morbidities in spite of the disadvantage factor. Further studies addressing the effect of early intervention would be beneficial to gain a better understanding of the findings noted in this study.

It is important to note these findings do not negate the fact that brain structural and connectivity factors as well as the underlying epilepsy disorder play a significant role in cognition; however, our findings indicate that sociodemographic factors need to be considered as a significantly impactful factor as well. Beneficial future research would directly determine the impact of

disadvantage on neuroimaging and neurophysiological findings on cognition. In addition, our study did not assess if the impact of disadvantage as defined here is modifiable. As such, it is unknown if early intervention can reduce or thwart the impact of disadvantage on cognition in newly diagnosed epilepsy over time. Further investigation into appropriate and long-lasting interventional options would be beneficial in future studies.

This study has some limitations that should be mentioned. First, the SD score was operationally defined using a novel and easy-to-assess approach incorporating metrics known to be relevant to the social determinants of health literature. This is the first study to use this specific assessment method to evaluate disadvantage. While novel and requiring further inquiry, we believe its advantages include uncomplicated calculation even in a clinic setting, the ability of the metric to reflect the *specific circumstances* of target families of interest in a way that aggregate neighborhood indices of disadvantage may not, and its promising validity is suggested by the consistency of its relationship with metrics of cognition and academics. Nonetheless, validity and reliability remain to be more fully established for this potential research and clinical metric.

Second, evaluation of academic achievement was limited in scope. We also did not assess disorders such as dyslexia and attention deficit disorders, which can adversely affect cognitive and academic performance. Future studies examining the effect of sociodemographic disadvantage on cognition while controlling for such potential performance-related disorders would provide a more comprehensive understanding of cognitive impairment in epilepsy. Third, the specific epilepsy syndromes evaluated here were limited. We did not evaluate any epileptic encephalopathy syndromes and other disorders such as Lennox-Gastaut syndrome. As a consequence, the inferences of our findings are not generalizable to all pediatric epilepsies. Furthermore, the cause and inciting factors that precipitated the epilepsy were not assessed and may have played a role in the cognitive findings we presented. In addition, course and treatment details can vary between individuals and also over time; and can play a significant role in cognitive and academic performance. We do not have these data and could not include this information in our analyses. Future studies investigating these details in relation to disadvantage and cognition would be key to gaining a full understanding of cognitive abnormalities in

epilepsy. Fourth, it is possible that SD may change over the relatively modest span of this investigation (36 months), but the core message here is that *baseline* disadvantage in youth with epilepsy and their unaffected siblings has an impressive constant relationship with cognition and academics over time. This points to the clinical and theoretical importance of better understanding the mechanisms of effect of disadvantage and the most optimal routes of intervention. Very important for the future is an understanding of the effect of disadvantage on cognitive and brain *development*. Fifth, an important issue for future investigation is the impact of disadvantage on *cognitive development* in children with new onset epilepsy. Here we focused on the impact of disadvantage at diagnosis and demonstrated its persisting impact, detected at baseline, over the ensuing three years. But how disadvantage impacts brain and cognitive growth in youth with epilepsy remains a key question. Furthermore, prior investigations from this controlled cohort investigation have demonstrated a variety of cognitive and academic differences between the youth with new onset seizures and their unaffected sibling controls and/or the presence and predictors of change over time[3,18], but the role of disadvantage in such comparisons should be explored in the future. In addition, the current sample was not large enough to examine the contribution of specific MRI and EEG abnormalities. Our pragmatic approach of categorizing these variables as normal or abnormal may obscure important issues that deserve to be investigated in future research. Finally, in addition to the relationship between disadvantage and cognition reported here, we also recently reported a similar association between increasing disadvantage and greater behavioral problems in this cohort[51]. Given the comparable effects of deprivation on both cognition and behavior it is clear that substantial multimorbidity accrues for high disadvantage youth with a punishingly cumulative burden. Addressing the unique impact of elements of behavior problems (e.g., general externalizing or internalizing, or specific behavior problems such as ADHD or depression) will be addressed in a separate investigation.

In summary, sociodemographic disadvantage exerts a powerful impact on neuropsychological and academic performance in children with newly diagnosed epilepsy and their unaffected siblings. This strong and robust association is enduring over time and has a familial aggregation pattern. The cognitive, behavioral, and neurobiological impact of sociodemographic

disadvantage on youth with epilepsy (and their siblings) deserves further examination and inclusion in our clinical epilepsy studies.

Funding

This research was supported by the National Institute of Neurologic Disorders and Stroke (NS22416, J. Austin, P.I.). The project described was also supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860 and linked award KL2 TR001859 (T. Oyegbile-Chidi). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Competing Interests:

The authors report no competing interests.

Tables & Figures:

A.

Sociodemographic Disadvantage (SD) Categories		
	0	**1**
Caregiver's Education Level	< 12th grade	≥12th grade
Self-Identified Race	Non-white	White
Household Income	<$50-60k	≥$50-60k
Parent's Marital Status	Non-married	Married

B.

	Children with Seizures	**Siblings**
Group Characteristics		
Sample Size	289	167
Age, years (SD)	9.44 (2.6)	9.68 (3.7)
Sex M/F	158/154	108/115
IQ (SD)	100.96 (15.3)	103.58 (15.1)~
Education, years (SD)	3.79 (2.45)	3.98 (2.50)
Clinical Epilepsy Characteristics		
Age of Onset, years (SD)	9.58 (2.54)	
Seizure Frequency, per Year (SD)	43.32 (174.71)	
% With FUS (Most Common Seizure Type)	41.7% FUS	
% With Generalized Seizure Syndrome	38.6%	
% With ≥ 2 Seizure Types	8.5%	
Family Sociodemographic Characteristics		
Self-Identified Race (%White/Caucasian)	78.8% White	
Mean Household Income (SD)	$50-60k ($27.5k)	
Mean Caregiver Education, years (SD)	13.82 (2.25)	
% Married	76% married	

Table 1. A. Sociodemographic disadvantage (SD) Categories. SD ranged from 0-3 based on assigned score for each of these four variables. Each family received a *0* or *1* depending on where they fall within each category (see text for details). B. Sample Characteristics for Seizure and Sibling Groups and Family Sociodemographic Variables for Entire Sample. No significant differences between Seizure and Sibling Groups on any demographic variable. Data presented as mean (SD). SD=standard deviation, IQ=intelligence quotient, %=percent, FUS=focally unaware seizure. ~$p < 0.1$

X	SD-3 (N=29)	SD-2 (N=60)	SD-1 (N=71)	SD-0 (N=122)	P-Value
Clinical Epilepsy Characteristics					
Age, years (SD)	9.31 (2.4)	9.61 (2.6)	9.76 (2.7)	9.16 (2.5)	.491
Sex M/F	15/17	29/32	44/39	67/69	.900
Education, years (SD)	3.66 (2.4)	4.17 (2.4)	4.00 (2.5)	3.67 (2.5)	.534
Age of Onset, years (SD)	9.48 (2.6)	9.84 (2.6)	9.86 (2.7)	9.36 (2.6)	.440
Number of Seizures (SD)	34.88 (176.0)	42.48 (170.8)	39.06 (167.4)	52.84 (193.7)	.928
Most common Seizure Syndrome	FUS	FUS	FUS	FUS	NA
% Generalized Seizures	40.6%	35.5%	36.1%	29.7%	.566
# Seizure Types (% ≥ 2 seizures)	18.8%	8.3%	7.2%	8.1%	.242
MRI at baseline (% normal)	67.1%	68.8%	59.2%	76.4%	.073
EEG at baseline (% normal)	34%	26.7%	30.5%	22.9%	.331
Neurologic Exam at baseline (% normal)	90.6%	93.4%	94%	94%	.794
1st Anti-seizure medication at baseline (% on ASMs)	6.7%	13.1%	14.1%	13.1%	.763

Table 2. Clinical epilepsy characteristics for children with epilepsy by SD group. There was no significant difference in % normal MRI, EEG, exam, etc by SD score group in those with epilepsy amongst children with epilepsy during the baseline visit. Data presented as mean (SD) or percentage. SD - standard deviation, FUS – focally unaware epilepsy syndrome.

	SD-3 (N=29)	SD-2 (N=60)	SD-1 (N=71)	SD-0 (N=122)	F	P-value
	Baseline					
IQ	90.57 (2.7)	92.93 (1.9)*	100.14 (1.6)**	107.0 (1.3)***	18.86	<.001
Language	-.676 (.16)	-.485 (.12)	-.103 (.10)*	.256 (.08)**	15.06	<.001
Processing speed	-.389 (.17)	-.424 (.12)	-.049 (.10)*	.182 (.08)**	7.28	<.001
Executive Function	-.681 (.16)	-.365 (.11)	-.069 (.09)*	.109 (.07)*	9.29	<.001
Verbal Memory	-.665 (.15)	-.447 (.11)	-.044 (.09)*	.200 (.07)**	13.74	<.001
	18 Months Later					
IQ	85.17 (3.3)	95.33 (2.3)*	101.45 (1.7)**	107.44 (1.4)***	16.94	<.001
Language	-1.195 (.21)	-.396 (.14)*	-.093 (.11)*	.300 (.08)**	18.51	<.001
Processing speed	-1.065 (.22)	-.540 (.14)*	-.136 (.11)**	.233 (.06)***	14.69	<.001
Executive Function	-.738 (.20)	-.150 (.13)*	.255 (.10)**	.343 (.08)**	10.82	<.001
Verbal Memory	-1.043 (.20)	-.359 (.13)*	.003 (.10)**	.289 (.08)***	16.55	<.001
	36 Months Later					
IQ	85.33 (3.4)	95.12 (2.4)*	100.83 (1.8)*	108.08 (1.4)**	17.07	<.001
Language	-1.049 (.21)	-.425 (.16)*	.065 (.11)**	.382 (.09)***	16.25	<.001
Processing speed	-.898 (.23)	-.633 (.18)	-.096 (.13)*	.270 (.10)**	11.18	<.001
Executive Function	-.596 (.18)	.058 (.13)*	.444 (.10)**	.584 (.08)**	14.67	<.001
Verbal Memory	-1.036 (.18)	-.286 (.14)*	.137 (.10)**	.373 (.08)**	19.76	<.001

Table 3. Cognitive Domains in Children with Epilepsy Over 36 Months. In children with epilepsy, IQ and cognitive domain factor scores (Language, Processing Speed, Executive Function, and Verbal Memory) differ in all SD categories such that those who fall into the SD-3 group show significantly lower IQ and lower cognitive domain factor scores compared to those in the other SD categories. IQ and cognitive domain factor scores increase significantly and consistently as disadvantage decreases in all SD categories. In addition, this pattern remains persistent over the 36-month period. Data presented as mean (SE). F – ANOVA Statistic with degrees of freedom. For each cognitive domain, a non-starred score is significantly different from *, which is significantly different from **, which is significantly different from ***.

	SD-3 (N=18)	SD-2 (N=28)	SD-1 (N=40)	SD-0 (N=81)	F	P-value
	Baseline					
IQ	89.21 (3.0)	94.07 (2.1)	103.75 (1.8)*	109.47 (1.3)**	21.62	<.001
Language	-.712 (.19)	-.309 (.14)*	-.037 (.12)*	.509 (.08)**	17.23	<.001
Processing speed	-.301 (.20)	-.156 (.14)	.112 (.12)	.435 (.08)*	7.03	<.001
Executive Function	-.305 (.19)	-.211 (.14)	.069 (.12)	.462 (.08)*	9.02	<.001
Verbal Memory	-.625 (.18)	-.290 (.13)*	.007 (.11)*	.468 (.08)**	16.37	<.001
	18 Months later					
IQ	82.70 (3.6)	95.26 (2.6)*	105.11 (1.9)**	112.69 (1.4)***	27.14	<.001
Language	-.706 (.23)	-.095 (.17)*	.157 (.12)*	.679 (.09)**	15.11	<.001
Processing speed	-.327 (.23)	-.451 (.17)	.185 (.12)*	.576 (.09)**	12.15	<.001
Executive Function	-.800 (.22)	-.072 (.16)*	.478 (.12)**	.630 (.09)**	15.01	<.001
Verbal Memory	-.664 (.20)	-.276 (.14)	.232 (.10)*	.564 (.08)**	16.95	<.001
	36 Months Later					
IQ	88.70 (3.9)	95.28 (2.9)	104.12 (1.9)*	110.16 (1.5)**	13.41	<.001
Language	-.404 (.26)	-.136 (.19)	.255 (.13)*	.609 (.10)**	7.40	<.001
Processing speed	-.188 (.25)	-.275 (.18)	.215 (.12)*	.616 (.09)**	8.70	<.001
Executive Function	-.129 (.21)	.177 (.15)	.408 (.10)*	.692 (.08)**	6.86	<.001
Verbal Memory	-.481 (.21)	-.109 (.15)*	.181 (.10)*	.545 (.08)**	10.76	<.001

Table 4. Cognitive Domains in Siblings Over 36 Months. In siblings, IQ and cognitive domain factor scores (Language, Processing Speed, Executive Function (EF), and Verbal Memory) differ in all SD categories such that those who fall into the SD-3 group show significantly lower IQ and lower cognitive domain factor scores compared to those in the other SD categories. IQ and cognitive domain factor scores increase significantly and consistently as disadvantage decreases in all SD categories. In addition, this pattern remains persistent over the 36-month period. Data presented as mean (SE). For each cognitive domain, a non-starred score is significantly different from *, which is significantly different from **, which is significantly different from ***.

	SD-3 (N=29)	SD-2 (N=60)	SD-1 (N=71)	SD-0 (N=122)	F	P-Value
	Baseline					
Letter-Word	96.00 (3.1)	97.20 (2.2)	103.46 (1.9)*	107.79 (1.5)*	7.40	<.001
Calculation	87.00 (3.7)	93.82 (2.6)	102.49 (2.3)*	104.63 (1.7)*	8.70	<.001
Dictation	88.59 (2.9)	86.58 (2.0)	96.29 (1.8)*	98.38 (1.3)*	9.67	<.001
	18 Months Later					
Letter-Word	90.94 (3.8)	97.10 (2.6)*	103.08 (2.0)*	106.71 (1.5)**	7.08	<.001
Calculation	78.78 (5.1)	90.44 (3.5)*	96.03 (2.7)*	102.75 (2.1)**	8.02	<.001
Dictation	80.78 (3.7)	87.64 (2.5)	94.92 (2.0)*	95.73 (1.5)*	6.56	<.001
	36 Months Later					
Letter-Word	89.78 (3.9)	96.65 (2.8)	100.41 (2.1)*	104.57 (1.7)*	5.19	.002
Calculation	81.72 (5.2)	90.85 (3.8)	95.75 (2.7)*	102.46 (2.2)*	5.95	<.001
Dictation	78.78 (3.5)	84.35 (2.5)	89.92 (1.9)*	93.84 (1.5)*	7.32	<.001

Table 5. Academic Performance in Children with Epilepsy Over 36 Months. In children with epilepsy, academic performance scores (letter-word identification, calculation and dictation) differ in all SD categories such that those who fall into the SD-3 group show significantly lower academic performance scores compared to those in the other SD categories. Academic performance scores increase significantly and consistently as disadvantage decreases in all SD categories. In addition, this pattern remains persistent over the 36-month period. Data presented as mean (SE). For each academic performance score, a non-starred score is significantly different from *, which is significantly different from **, which is significantly different from ***.

	SD-3 (N=18)	SD-2 (N=28)	SD-1 (N=40)	SD-0 (N=81)	F	P-Value
Baseline						
Letter-Word	92.07 (3.6)	94.89 (2.6)*	101.83 (2.2)**	108.15 (1.5)***	10.17	<.001
Calculation	86.00 (4.0)	91.57 (2.8)	102.95 (2.4)*	109.63 (1.7)**	16.75	<.001
Dictation	84.93 (3.2)	89.71 (2.3)*	92.40 (1.9)*	99.35 (1.4)**	9.14	<.001
18 Months Later						
Letter-Word	94.50 (4.2)	94.58 (3.1)	100.51 (2.2)	108.09 (1.6)*	7.66	<.001
Calculation	87.10 (5.2)	89.79 (3.8)	105.03 (2.7)*	111.69 (2.0)**	13.05	<.001
Dictation	82.90 (4.6)	85.53 (3.3)	90.89 (2.4)	100.62 (1.8)*	9.38	<.001
36 Months Later						
Letter-Word	96.70 (4.8)	96.17 (3.6)	104.74 (2.3)*	107.03 (1.9)*	3.30	.022
Calculation	83.20 (6.1)	91.67 (4.5)	100.43 (3.0)*	109.34 (2.3)**	8.32	<.001
Dictation	87.70 (4.3)	86.67 (3.2)	91.17 (2.1)	99.19 (1.7)*	6.40	<.001

Table 6. Academic Performance in Siblings Over 36 Months. In siblings, academic performance scores (letter-word identification, calculation and dictation) differ in all SD categories such that those who fell into the SD-3 group show significantly lower academic performance scores compared to those in the other SD categories. Academic performance scores increase significantly and consistently as disadvantage decreases in all SD categories. In addition, this pattern remains persistent over the 36-month period. Data presented as mean (SE). For each academic performance score, a non-starred score is significantly different from *, which is significantly different from **, which is significantly different from ***.

	Variance (R^2)	Model P-value	SD (β)	Seizure Syndrome (β)	EEG Result (β)	MRI Result (β)	Age of Onset (β)	Seizure Burden (β)	ASM Number (β)
				Baseline					
IQ	22.3%	<.001	.427**	.115	.027	-.011	.106	.033	.093
Cognitive Domains									
Language	19.2%	<.001	.402**	.133	.083	-.042	.083	.039	.034
Processing speed	12.7%	<.001	.275**	.096	.193*	.028	-.016	.044	.005
Executive Function	35.8%	<.001	.333**	.082	.048	.032	.502**	.025	.020
Verbal Memory	19.3%	<.001	.398**	.049	.097	.004	.163*	.017	.054
Academic Performance									
Letter-Word	9.8%	.003	.273**	.129	.039	-.037	.021	.025	.031
Calculation	13.0%	<.001	.295**	.157*	.005	-.056	.110	.034	.040
Dictation	16.0%	<.001	.287**	.093	.059	-.051	-.200**	.003	.000
				18 Months Later					
IQ	21.6%	<.001	.426**	.069	-.035	-.080	.076	.040	.100
Cognitive Domains									
Language	24.8%	<.001	.431**	.129	.086	-.025	.036	.039	.139*
Processing speed	19.7%	<.001	.407**	.053	.124	.054	.026	.034	.058
Executive Function	24.0%	<.001	.322**	.063	.017	-.020	.326**	.025	.136*
Verbal Memory	22.1%	<.001	.413**	.053	.085	.016	.043	.051	.153*
Academic Performance									
Letter-Word	12.3%	<.001	.281**	.114	.063	-.012	-.045	.017	.131
Calculation	14.3%	<.001	.292**	.088	.078	-.063	.117	.081	.144*
Dictation	13.1%	<.001	.254**	.099	-.050	-.058	-.129*	.019	.100
				36 Months Later					
IQ	24.0%	<.001	.438**	.150	.044	.035	.005	.109	.085
Cognitive Domains									
Language	26.1%	<.001	.447**	.176*	.037	.029	.098	.078	.099
Processing speed	18.1%	<.001	.364**	.070	.167*	.039	-.011	.070	.044
Executive Function	24.6%	<.001	.408**	.054	.041	-.008	.205*	.063	.138*
Verbal Memory	26.4%	<.001	.465**	.082	.072	.026	.047	.038	.110
Academic Performance									
Letter-Word	10.3%	.019	.270**	.110	-.003	.031	.095	.036	.075
Calculation	12.7%	.003	.276**	.075	-.024	-.041	.146*	.128	.092
Dictation	13.2%	.002	.303**	.151	-.018	.022	-.039	.071	.082

Table 7. Linear Regression models Over 36 Months. This table indicates the amount of variability explained by the model (R-squared), significance of the model (model p-value) and best predictors of IQ, cognitive domains and academic performance in children with epilepsy (Standardized ß Coefficients). Throughout the 36-month period, disadvantage score (SD) remains significant and impactful, while age of onset of epilepsy, MRI/EEG findings, seizure burden,

anti-seizure medication number, and seizure syndrome show less impact in comparison amongst the models. *p<0.05, **p<0.001.

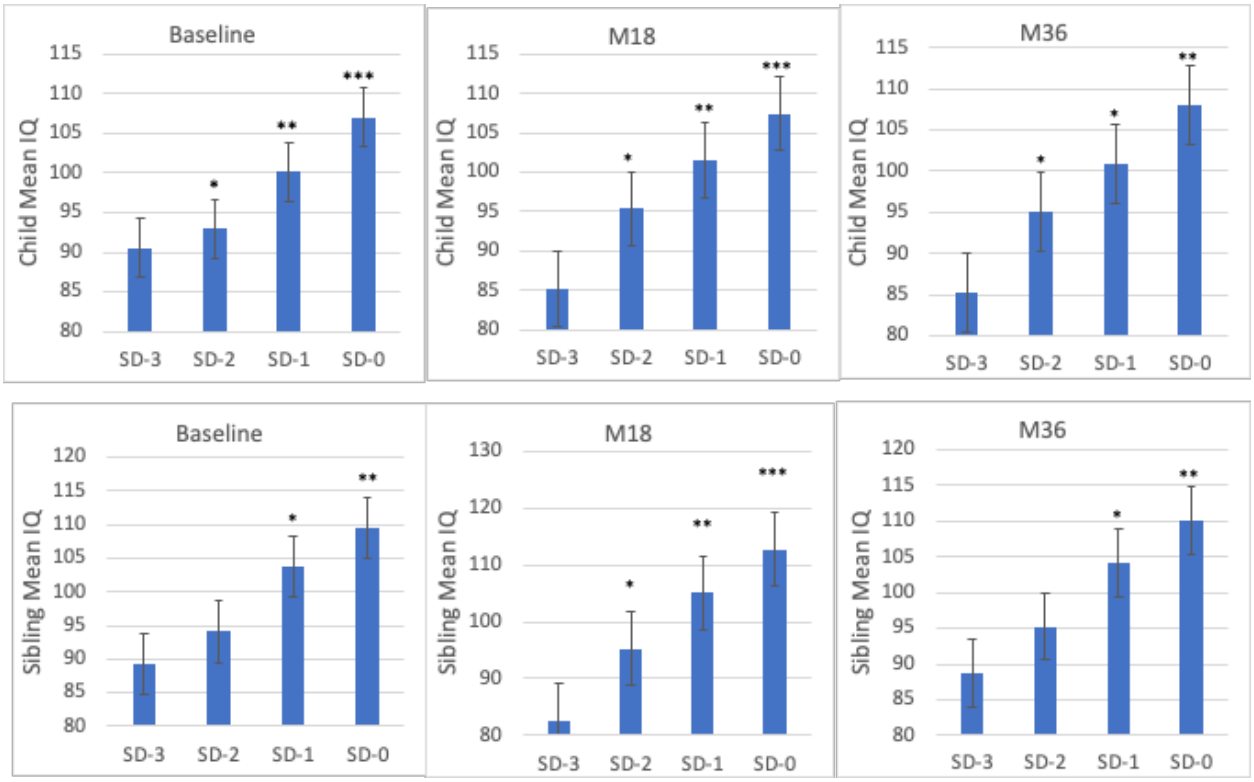

Figure 1. Mean IQ Scores for children with epilepsy and their siblings, by SD Score and Time Point. SD=Sociodemographic Disadvantage Score. In both groups, mean IQ differs between at least SD-3 and SD-0 at all time points such that families who fall into the SD4 group show significantly lower IQ compared to those in the other SD categories. Mean IQ increases significantly and consistently as sociodemographic disadvantage decreases in all SD categories. In addition, this pattern remains persistent over the 36-month period. The non-starred bar is

significantly different from *, which is significantly different from **, which is significantly different from ***.

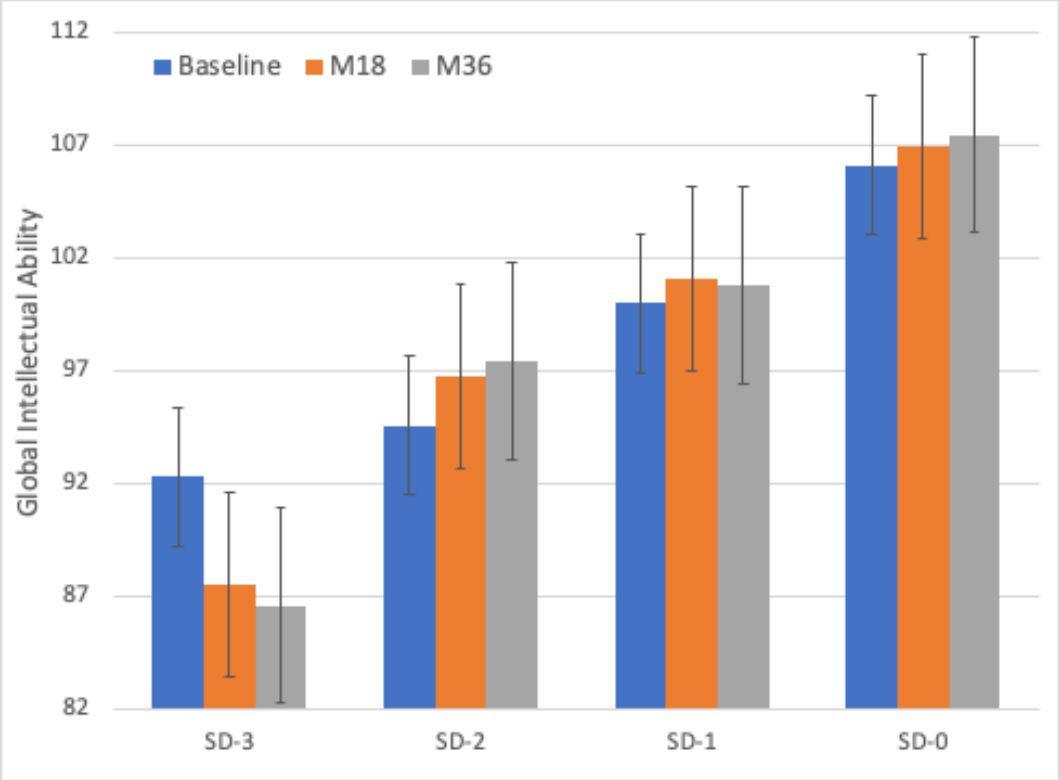

Figure 2. Global Intellectual Ability (Mean IQ) Scores for children with epilepsy by SD Score and Time Point, **using CBCL total behavioral problems as a covariate**. SD=Sociodemographic Disadvantage Score. Mean IQ differs between at least SD-3 and SD-0 at all time points such that children with epilepsy who fall into the SD4 group show significantly lower IQ compared to those in the other SD categories. Mean IQ increases significantly and consistently as sociodemographic disadvantage decreases in all SD categories. In addition, this pattern remains persistent over the 36-month period.

Supplementary material

Supplemental Table 1: Association of individual SD metrics with total SD score

	Disadvantage Score	Marital Status	Income	Mother's Education	Race
Disadvantage Score	1	-.313**	.785**	.351**	.610**
Marital Status		1	-.254**	-.115*	-.083
Income			1	.440**	.255**
Mother's Education				1	.080
Race					1

**p<0.001

Supplemental Table 2: Distribution of disadvantage metrics across disadvantage groups X	**SD-3 (N=29)**	**SD-2 (N=60)**	**SD-1 (N=71)**	**SD-0 (N=122)**	**P-Value**
Sociodemographic Disadvantage Score Characteristics					
Self-Identified Race (%White/Caucasian)	9.4%	80.3%	88%	100%	<.001
Household Income (% >$50-60k)	0%	4.9%	21.7%	100%	<.001
Caregiver Education (%>12th grade)	62.5%	80.3%	97.6%	100%	<.001
% Married	12.5%	34.4%	92.8%	100%	<.001

REFERENCES:

1. Hermann B, Jones J, Sheth R, Dow C, Koehn M, Seidenberg M. Children with new-onset epilepsy: neuropsychological status and brain structure. *Brain J Neurol*. 2006;129(Pt 10):2609-2619. doi:10.1093/brain/awl196

2. Oyegbile TO, VanMeter JW, Motamedi GK, Bell WL, Gaillard WD, Hermann BP. Default mode network deactivation in pediatric temporal lobe epilepsy: Relationship to a working memory task and executive function tests. *Epilepsy Behav EB*. 2019;94:124-130. doi:10.1016/j.yebeh.2019.02.031

3. Fastenau PS, Johnson CS, Perkins SM, et al. Neuropsychological status at seizure onset in children. *Neurology*. 2009;73(7):526-534. doi:10.1212/WNL.0b013e3181b23551

4. Berg AT, Langfitt JT, Testa FM, et al. Global cognitive function in children with epilepsy: A community-based study. *Epilepsia*. 2008;49(4):608-614. doi:10.1111/j.1528-1167.2007.01461.x

5. Oyegbile-Chidi T, Harvey D, Eisner J, et al. The Relationship Between Sleep, Cognition and Behavior in Children With Newly-Diagnosed Epilepsy Over 36 Months. *Front Neurol*. 2022;13:903137. doi:10.3389/fneur.2022.903137

6. Loughman A, Bowden SC, D'Souza W. Cognitive functioning in idiopathic generalised epilepsies: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2014;43:20-34. doi:10.1016/j.neubiorev.2014.02.012

7. Cheng D, Yan X, Gao Z, Xu K, Zhou X, Chen Q. Neurocognitive Profiles in Childhood Absence Epilepsy. *J Child Neurol*. 2017;32(1):46-52. doi:10.1177/0883073816668465

8. Almane DN, Jones JE, McMillan T, et al. The Timing, Nature, and Range of Neurobehavioral Comorbidities in Juvenile Myoclonic Epilepsy. *Pediatr Neurol*. 2019;101:47-52. doi:10.1016/j.pediatrneurol.2019.03.011

9. Danielsson J, Petermann F. Cognitive deficits in children with benign rolandic epilepsy of childhood or rolandic discharges: a study of children between 4 and 7 years of age with and without seizures compared with healthy controls. *Epilepsy Behav EB*. 2009;16(4):646-651. doi:10.1016/j.yebeh.2009.08.012

10. Oyegbile TO, VanMeter JW, Motamedi G, et al. Executive dysfunction is associated with an altered executive control network in pediatric temporal lobe epilepsy. *Epilepsy Behav EB*. 2018;86:145-152. doi:10.1016/j.yebeh.2018.04.022

11. Braakman HMH, Vaessen MJ, Hofman PAM, et al. Cognitive and behavioral complications of frontal lobe epilepsy in children: a review of the literature. *Epilepsia*. 2011;52(5):849-856. doi:10.1111/j.1528-1167.2011.03057.x

12. Cheng D, Yan X, Gao Z, Xu K, Zhou X, Chen Q. Common and Distinctive Patterns of Cognitive Dysfunction in Children With Benign Epilepsy Syndromes. *Pediatr Neurol*. 2017;72:36-41.e1. doi:10.1016/j.pediatrneurol.2016.12.005

13. Oyegbile TO, Dow C, Jones J, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology*. 2004;62(10):1736-1742. doi:10.1212/01.wnl.0000125186.04867.34

14. Hermann BP, Jones JE, Jackson DC, Seidenberg M. Starting at the beginning: the neuropsychological status of children with new-onset epilepsies. *Epileptic Disord Int Epilepsy J Videotape*. 2012;14(1):12-21. doi:10.1684/epd.2012.0483

15. Myatchin I, Mennes M, Wouters H, Stiers P, Lagae L. Working memory in children with epilepsy: an event-related potentials study. *Epilepsy Res*. 2009;86(2-3):183-190. doi:10.1016/j.eplepsyres.2009.06.004

16. Rzezak P, Valente KD, Duchowny MS. Temporal lobe epilepsy in children: executive and mnestic impairments. *Epilepsy Behav EB*. 2014;31:117-122. doi:10.1016/j.yebeh.2013.12.005

17. Aronu AE, Iloeje SO. Behavioral problems of siblings of epileptic children in Enugu. *Niger J Clin Pract*. 2011;14(2):132-136. doi:10.4103/1119-3077.84000

18. Dunn DW, Johnson CS, Perkins SM, et al. Academic problems in children with seizures: relationships with neuropsychological functioning and family variables during the 3 years after onset. *Epilepsy Behav EB*. 2010;19(3):455-461. doi:10.1016/j.yebeh.2010.08.023

19. Whelan CD, Alhusaini S, O'Hanlon E, et al. White matter alterations in patients with MRI-negative temporal lobe epilepsy and their asymptomatic siblings. *Epilepsia*. 2015;56(10):1551-1561. doi:10.1111/epi.13103

20. Alhusaini S, Whelan CD, Doherty CP, Delanty N, Fitzsimons M, Cavalleri GL. Temporal Cortex Morphology in Mesial Temporal Lobe Epilepsy Patients and Their Asymptomatic Siblings. *Cereb Cortex N Y N 1991*. 2016;26(3):1234-1241. doi:10.1093/cercor/bhu315

21. Almane DN, Zhao Q, Rathouz PJ, et al. Contribution of Family Relatedness to Neurobehavioral Comorbidities in Idiopathic Childhood Epilepsies. *J Int Neuropsychol Soc JINS*. 2018;24(7):653-661. doi:10.1017/S1355617718000243

22. Levav M, Mirsky AF, Herault J, Xiong L, Amir N, Andermann E. Familial association of neuropsychological traits in patients with generalized and partial seizure disorders. *J Clin Exp Neuropsychol*. 2002;24(3):311-326. doi:10.1076/jcen.24.3.311.985

23. Hesdorffer DC, Caplan R, Berg AT. Familial clustering of epilepsy and behavioral disorders: evidence for a shared genetic basis. *Epilepsia*. 2012;53(2):301-307. doi:10.1111/j.1528-1167.2011.03351.x

24. Badawy RAB, Vogrin SJ, Lai A, Cook MJ. Capturing the epileptic trait: cortical excitability measures in patients and their unaffected siblings. *Brain J Neurol*. 2013;136(Pt 4):1177-1191. doi:10.1093/brain/awt047

25. Wandschneider B, Centeno M, Vollmar C, et al. Motor co-activation in siblings of patients with juvenile myoclonic epilepsy: an imaging endophenotype? *Brain J Neurol*. 2014;137(Pt 9):2469-2479. doi:10.1093/brain/awu175

26. Ajilore O, Thames AD. The fire this time: The stress of racism, inflammation and COVID-19. *Brain Behav Immun*. 2020;88:66-67. doi:10.1016/j.bbi.2020.06.003

27. Rosendale N. Social Determinants of Health in Neurology. *Neurol Clin*. 2022;40(1):231-247. doi:10.1016/j.ncl.2021.08.012

28. 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

29. Burneo-Garcés C, Cruz-Quintana F, Pérez-García M, Fernández-Alcántara M, Fasfous A, Pérez-Marfil MN. Interaction between Socioeconomic Status and Cognitive Development in Children Aged 7, 9, and 11 Years: A Cross-Sectional Study. *Dev Neuropsychol*. 2019;44(1):1-16. doi:10.1080/87565641.2018.1554662

30. Morgan CL, Ahmed Z, Kerr MP. Social deprivation and prevalence of epilepsy and associated health usage. *J Neurol Neurosurg Psychiatry*. 2000;69(1):13-17. doi:10.1136/jnnp.69.1.13

31. Puka K, Rubinger L, Chan C, Smith ML, Widjaja E. Predictors of intellectual functioning after epilepsy surgery in childhood: The role of socioeconomic status. *Epilepsy Behav EB*. 2016;62:35-39. doi:10.1016/j.yebeh.2016.06.023

32. Carson J, Weir A, Chin RF, McLellan A. Socioeconomic deprivation is an independent risk factor for behavioral problems in children with epilepsy. *Epilepsy Behav EB*. 2015;45:105-109. doi:10.1016/j.yebeh.2015.03.009

33. Geerts A, Brouwer O, van Donselaar C, et al. Health perception and socioeconomic status following childhood-onset epilepsy: the Dutch study of epilepsy in childhood. *Epilepsia*. 2011;52(12):2192-2202. doi:10.1111/j.1528-1167.2011.03294.x

34. Camfield C, Camfield P, Smith B. Poor versus rich children with epilepsy have the same clinical course and remission rates but a less favorable social outcome: A population-based study with 25 years of follow-up. *Epilepsia*. 2016;57(11):1826-1833. doi:10.1111/epi.13576

35. Huber R, Weber P. Is there a relationship between socioeconomic factors and prevalence, adherence and outcome in childhood epilepsy? A systematic scoping review. *Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc*. 2022;38:1-6. doi:10.1016/j.ejpn.2022.01.021

36. Austin JK, Dunn DW, Caffrey HM, Perkins SM, Harezlak J, Rose DF. Recurrent seizures and behavior problems in children with first recognized seizures: a prospective study. *Epilepsia*. 2002;43(12):1564-1573. doi:10.1046/j.1528-1157.2002.26002.x

37. Austin JK, Dunn DW, Johnson CS, Perkins SM. Behavioral issues involving children and adolescents with epilepsy and the impact of their families: recent research data. *Epilepsy Behav EB*. 2004;5 Suppl 3:S33-41. doi:10.1016/j.yebeh.2004.06.014

38. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482. doi:10.1111/epi.12550

39. DeNavas-Walt C, Cleveland, R. U.S. Census Bureau, Current Population Reports, P60-218, Money Income in the United States: 2001, U.S. Government Printing Office, Washington, DC, 2002. https://www2.census.gov/library/publications/2002/demo/p60-218.pdf

40. Coret M, Mccrimmon A. Test Review: Wiig, E. H., Semel, E., & Secord, W. A. (2013). Clinical Evaluation of Language Fundamentals-Fifth Edition (CELF-5). *J Psychoeduc Assess*. 2015;33:495-500. doi:10.1177/0734282914557616

41. Wagner R, Togesen J, Rashotte C. Comprehensive test of phonological processing. Pro-Ed; Austin TX: 1999.

42. Conners' Continuous Performance Test II (CPT II). Statistics Solutions. Accessed November 14, 2021. https://www.statisticssolutions.com/free-resources/directory-of-survey-instruments/conners-continuous-performance-test-ii-cpt-ii/

43. Kaufman AS, Kaufman NL. Kaufman brief intelligence test. American Guidance Service; Circle Pines, MN: 1990.

44. Wechsler D. Wechsler intelligence scale for children. 3rd edition. The Psychological Corporation; San Antonio, TX: 1991.

45. Lopez W, Byars A, Fastenau PS, Pederson S, Minnich H. Design Copy Trial for the Wide Range Assessment of Memory and Learning. Journal of the International Neuropsychological Society, 2006;12(S1):35-36.

46. Heaton RK, Cheleune GJ, Talley JL, Kay GG, Curtiss G. Wisconsin card sorting test. Psychological Assessment Resources; Odessa, FL: 1993.

47. Byars AW, Byars KC, Johnson CS, et al. THE RELATIONSHIP BETWEEN SLEEP PROBLEMS AND NEUROPSYCHOLOGICAL FUNCTIONING IN CHILDREN WITH FIRST RECOGNIZED SEIZURES. *Epilepsy Behav EB*. 2008;13(4):607-613. doi:10.1016/j.yebeh.2008.07.009

48. Baum KT, Byars AW, deGrauw TJ, et al. The Effect of Temperament and Neuropsychological Functioning on Behavior Problems in Children with New-Onset Seizures. *Epilepsy Behav EB*. 2010;17(4):467-473. doi:10.1016/j.yebeh.2010.01.010

49. Woodcock RW, Johnson MB. Woodcock–Johnson Psycho-Educational Test Battery-Revised. Allen, TX: DLM Teaching Resources; 1989.

50. Kalnin AJ, Fastenau PS, deGrauw TJ, et al. Magnetic resonance imaging findings in children with a first recognized seizure. *Pediatr Neurol*. 2008;39(6):404-414. doi:10.1016/j.pediatrneurol.2008.08.008

51. Oyegbile-Chidi T, Harvey D, Jones J, et al. Impact of sociodemographic disadvantage on neurobehavioral outcomes in children with newly diagnosed seizures and their unaffected siblings over 36 months. *Epilepsia*. In press. doi:10.1111/epi.17672

52. Byars AW, deGrauw TJ, Johnson CS, Fastenau PS, Perkins SM, Egelhoff JC, et al. The association of MRI findings and neuropsychological functioning after the first recognized seizure. Epilepsia 2007;48:1067-74.