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Abstract

Objective: This study was undertaken to determine the short-term and longer term impact of sociodemographic disadvantage on the emotional–behavioral status of youths with new onset epilepsy and their unaffected siblings at the time of diagnosis and the subsequent 3 years.

Methods: Three hundred twelve youths with newly diagnosed epilepsies and 223 unaffected siblings, aged 6–16 years, were independently assessed regarding their emotional and behavioral status by their parents and teachers at baseline, and at 18 at 36 months later; youths with seizures also completed self-report measures of depression, anxiety, and hostility at those three time points. A sociodemographic disadvantage score was computed for each family (children with newly diagnosed seizures and their siblings), and families were separated into four categories from most disadvantaged to least disadvantaged.

Results: In both children and siblings, the least disadvantaged group exhibited the lowest level of neurobehavioral problems, whereas the most disadvantaged group showed a higher level of neurobehavioral problems across all the same behavior metrics. Findings remained stable and significant across all informants (parent, teacher, child) and across all time periods (throughout the 3-year period). Furthermore, both corrected and uncorrected linear regression analyses indicated that disadvantage was a more constant and stable predictor of behavioral and emotional problems over time compared to clinical seizure characteristics and abnormalities in magnetic resonance imaging and electroencephalographic testing.

Significance: Sociodemographic disadvantage bears a strong relationship to youths with emotional and behavioral problems both at the time of diagnosis as well as prospectively. The relationship is robust and reflected in reports from multiple informants (parent, teacher, child self-report), evident in siblings as well, and possibly more explanatory than traditional clinical seizure variables.

Future studies will be needed to determine whether this disadvantage factor is modifiable with early intervention.

1 | INTRODUCTION

There is convincing evidence of elevated risk of behavioral problems, anxiety, and depression (conceptualized as *neurobehavioral comorbidities*) in youths with epilepsy compared to their peers without epilepsy.[1–4] Population- and community-based studies as well as clinical investigations have characterized the presence, degree, and clinical risk of abnormalities in emotional–behavioral and psychiatric status in youths with epilepsy, which have been the basis of numerous systematic, meta-analytic, and narrative reviews,[5–7] and have been replicated both nationally and internationally.[1–3,8–12] Diverse aspects of behavior have been examined in this population, including metrics of general behavioral risk, broadly defined as internalizing and externalizing problems, and specific symptom-based inventories of depression and anxiety, as well as formal psychiatric diagnoses.

Relatedly, the investigation of the timing of behavioral problems has led to examination of children with newly diagnosed epilepsies where behavioral abnormalities have been shown to be present much earlier in the course of epilepsy than expected and, in some cases, even antecedent to the first recognized seizure, diagnosis, and treatment of epilepsy.[13–15] This detection of abnormalities very early in the course of childhood epilepsy offers a timely window for intervention[5]; however, there are few clear indications available to predict those at higher or lower risk of developing these emotional and behavioral problems.

Over the past couple of decades, investigators have endeavored to establish predictive variables that may indicate those at higher and lower risk for emotional and behavioral problems in chronic epilepsy. Considerable research has examined the association of this risk with numerous clinical seizure characteristics (e.g., age at onset, duration, etiology, seizure frequency and severity, antiseizure medications [ASMs], presence and frequency of interictal electroencephalographic [EEG] abnormalities) as well as the inherent risks associated with discrete epilepsy syndromes, both generalized (e.g., childhood and juvenile absence, juvenile myoclonic) and focal (e.g., Rolandic, focal temporal, frontal, parietal occipital).[16–19] Specific epilepsy syndromes have been examined in isolation and/or

Key points

- Sociodemographic disadvantage is associated with neurobehavioral dysfunction in children with newly diagnosed epilepsy and unaffected siblings
- This relationship between disadvantage and neurobehavioral outcomes is evident across multiple informants (parent, teacher, child)
- This association between disadvantage and behavior remains robust and persistent over 36 months
- Disadvantage is a constant stable predictor of neurobehavioral outcomes over time when compared to clinical seizure characteristics
- Future studies will determine whether this disadvantage factor is modifiable with early intervention

contrasted to each other to gauge the relative syndrome-specific risk to behavior. The evidence indicates that poor neurobehavioral outcomes remain prevalent regardless of epilepsy syndrome or clinical seizure characteristic and frequently adversely impact school performance and quality of life.[5,20]

Additionally, potential genetic contributions to neurobehavioral complications have been explored through investigation of familial aggregation that includes the unaffected siblings of youths with epilepsy.[19,21–28] The evidence thus far suggests that unaffected siblings harbor cognitive and behavioral abnormalities, but the mechanisms of this relationship remain to be determined. In addition, research has examined the association of behavioral problems with psychosocial factors (e.g., stigma, bullying), family integrity (e.g., support, integrity), and of course underlying neurobiological markers (e.g., cortical volume, cortical thickness, diffusion parameters).[19,21–28] In the midst of this extensive literature, underinvestigated are the contributions of the social determinants of health, including socioeconomic and sociodemographic disadvantage (SD).

A growing 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.[29–33] Within the field of pediatrics, the role of SD in health care outcomes has been well established among disorders such as asthma, diabetes, COVID-19, sleep health, and autism.[34–41] In the field of epilepsy, there has been growing awareness of the impact of socioeconomic and neighborhood disadvantage on health and health-related factors in epilepsy.[42–47] In addition, SD may play a role in psychiatric outcomes of children with epilepsy, as children from poor families and from single-parent homes have a significantly higher risk of developing a psychiatric disorder compared to their less disadvantaged peers with epilepsy,[48] suggesting that lower socioeconomic status may be an independent factor associated with poor behavioral outcomes in youths with epilepsy. These findings, although insightful, do not compare the impact of disadvantage to the impact of traditional clinical epilepsy characteristics on neurobehavioral outcomes in this population. Furthermore, the extent, robustness, and stability of the role of SD on neurobehavioral outcomes over time has yet to be fully characterized. These current gaps in the epilepsy disparities literature are yet to be explored and are the focus of this investigation.

This study examines the role of disadvantage in the emotional–behavioral status of youths with seizures. In a large cohort of children with newly diagnosed seizures, we pursued four aims: (1) to characterize the impact of disadvantage on neurobehavioral status in youths with seizures as assessed by multiple informants (parents, teachers, and children) using multiple assessment tools; (2) consistent with contemporary interest in the familial aggregation of comorbidities, to examine the impact of disadvantage on the behavioral status of the unaffected siblings of the youths with seizures; (3) to characterize the longer term effects of disadvantage on behavior in youths with seizures and their siblings over 3 years; and (4) to compare the relative explanatory power of disadvantage and classic clinical seizure features on neurobehavioral status in children with newly diagnosed epilepsy both at baseline and over time.

2 | MATERIALS AND METHODS

2.1 | Participants

Study participants included children with newly diagnosed seizures, their siblings as controls, and their primary caregivers in each household.[13,49] The core investigation was conducted at Indiana University and Cincinnati Children's Hospital at the University of Cincinnati. A total of 312 children were recruited within 6 weeks of their first recognized seizure (mean = 35 days). Children were recruited through 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. Seizure type and epileptic syndrome were classified by board-certified child neurologists using International League Against Epilepsy criteria[50,51] following review of all relevant information available at the evaluation of the first recognized seizure. The sibling control sample was a comparison group of 223 healthy siblings of the children with seizures. Only one sibling was recruited per family.

Exclusion criteria for both children with seizures and siblings were a comorbid 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 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 seizures and siblings. All participants were followed prospectively and reassessed 18 months later (M18) and finally, 36 months later (M36). For children with seizures, the attrition rate was 10% over the first 18 months of the investigation and another 5% over the second 18 months. All data were included in the analysis regardless of the number of visits completed.

2.2 | Measures

2.2.1 | SD score

The SD score is an index based on four sociodemographic variables collected from the primary caregiver, 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 the disadvantage (SD) metric (see Tables 1, S1). Based on past literature, each SD variable chosen is a relevant social determinant of health.[29–36,42–48] For caregiver education level and household income, those families below the mean for the sample were assigned a score of 1, whereas 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.[52] For race and caregiver marital status, non-White race and nonmarried status were each assigned a score of 1, whereas White race and married status received a score of 0. The SD score is the sum of all four disadvantage variables, ranging 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 SD0 (lowest number of disadvantages) to SD3 (highest number of disadvantages). The disadvantage assessment was conducted at the B visit only.

2.2.2 | Behavioral evaluation

Four instruments were used to assess emotional and behavioral concerns: (1) Child Behavior Checklist (CBCL), completed by parents; (2) Teacher Report Form (TRF), completed by teachers; (3) Children's Depression Inventory (CDI-2); and (4) Multiple Affect Adjective Check List (MAACL).[53–55] The CDI-2 and MAACL are completed by the child. Relevant details follow below.

2.3 | CBCL and TRF

The CBCL was completed by a caregiver/parent to measure each child's and sibling's behavior problems during the past 6 months, with the test administered at B, M18, and M36. Details of this instrument are provided elsewhere.[54] Briefly, the CBCL has 118 items describing behaviors that are rated using 3-point scales of 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true).[54] Three summary scores from the CBCL were used including *T*-scores for total behavior problems, total internalizing problems, and total externalizing problems, all normed for age and sex. For the children with seizures, parents were specifically instructed to exclude any behaviors that might have represented actual seizure activity or any behaviors that occurred immediately prior to, or after, a seizure. The TRF was completed by each child's teacher based on the child's behavior within the past 2 months at B (to assess baseline emotional–behavioral status and affect), and again at the M18 and M36 time periods (18 and 36 months following the child's first seizure).[54,56,57] Details of this instrument are also provided elsewhere.[54,56,57] The

TRF was completed by one teacher only (primary teacher) per time period, who usually was a different primary teacher at each time period. Like the CBCL, each item was rated on a 3-point scale and scores were computed for the three broadband scales: Total Behavior Problems, Internalizing Problems, and Externalizing Problems.

Both the CBCL and TRF have been used extensively in children with epilepsy and have been found to be reliable and valid in the pediatric epilepsy population.[18,21,58,59] Many past studies have relied primarily upon parents to rate their child's behavior problems.[13,60] Making use of both the CBCL and TRF provides insight into informant consistency and lends credence to the reliability of the behavior problems of the child as seen in multiple different settings (school and home primarily).

Of note, both CBCL and TRF data were collected for the children with newly diagnosed seizures, whereas CBCL data only was collected for siblings.

2.4 | Children's Depression Inventory

The CDI-2 is a self-report questionnaire for children and adolescents designed to identify symptoms of depression appropriate for developmental age.[55,61] The CDI-2 instrument has been utilized extensively in the pediatric epilepsy population.[62,63] The children with seizures completed this measure at B, M18, and M36.

2.5 | Multiple Affect Adjective Check List

The MAACL measures both positive and negative affect as a trait and/or state form, and can be used in the diagnosis and treatment of mood disorders. It has been extensively used, well validated, and internally reliable, shows good sensitivity to transient stressful conditions,[64] and has been used to investigate children with epilepsy.[65] The children with seizures completed the MAACL anxiety and hostility subtest measures at B, M18, and M36.

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.[66] Clinical seizure variables including seizure classification and 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.

2.6 | Statistical analysis

All data obtained were collated and analyzed using Statistical Package for Social Sciences software (version 27.0, IBM). Clinical seizure characteristics included were age at onset of seizures, seizure burden (i.e., seizure frequency), and seizure syndrome.[67,68] One-way analysis of variance tests compared SD groups on each behavioral measure assessed in the children with newly diagnosed seizures and their siblings at each time point (B, M18, M36). When the *F* statistic was significant, Tukey honest significant post hoc comparisons were conducted among the levels of SD.

Using linear regression, we examined the variance explained by the variables of interest across the dependent measures (R^2). Independent variables were SD, epilepsy syndrome (0 = primarily generalized, 1 = localization-related), EEG results (0 = normal, 1 = abnormal), magnetic resonance imaging (MRI) results (0 = normal, 1 = abnormal), age at onset of first recognized seizure, seizure frequency (number of seizures/year), and number of ASMs. Separate regression analyses were conducted at each time point (B, M18, M36) for each dependent (behavioral) variable. Corrected and uncorrected regression findings are presented. Corrections, presented as *k* significant findings, were conducted via false discovery rate analyses incorporating all studied regression models.

3 | RESULTS

3.1 | Sample characteristics

Tables 1–3 summarizes demographic characteristics for both groups (children with seizures and siblings), clinical seizure characteristics in the seizure group, and family/sociodemographic characteristics for the total sample (Table 1). Briefly, a total of 312 children with newly diagnosed seizures aged 6–16 years and 223 sibling controls

TABLE 1 SD categories.

Family/mother SD category	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	Nonmarried	Married

Note: SD ranged 0–4 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).

Abbreviation: SD, sociodemographic disadvantage.

TABLE 2 Sample characteristics for seizure and sibling groups and family sociodemographic variables for entire sample.

Characteristic	Children with seizures	Siblings
Child characteristics		
Sample size	312	223
Age, years (StD)	9.44 (2.6)	9.68 (3.7)
Sex, M/F	158/154	108/115
IQ (StD)	100.96 (15.3)	103.58 (15.1)
Education, years (StD)	3.79 (2.45)	3.98 (2.50)
Self-identified race (% White)	77.2	68.2
Clinical epilepsy characteristics		
Age at onset, years (StD)	9.58 (2.54)	–
Seizure frequency, per year (StD)	43.32 (174.71)	–
% with FUS (most common seizure type)	41.7	–
% with generalized seizure syndrome	38.6	–
% with ≥2 seizure types	8.5	–
Family/mother sociodemographic characteristics		
Self-identified race (% White)	78.8	
Mean household income (StD)	$50–60k ($27.5k)	
Mean caregiver education, years (StD)	13.82 (2.25)	
% married	76	

Note: No significant differences were found between seizure and sibling groups on any demographic variable. Data presented as mean (StD) unless otherwise indicated.

Abbreviations: F, female; FUS, focally unaware seizure; IQ, intelligence quotient; M, male; StD, standard deviation.

were included in the analyses. There were no significant differences between the groups except for a trend toward lower intelligence quotient (Table 2; approximately 3.5 points, $p < .1$) in the children with newly diagnosed seizures. The clinical seizure characteristics indicate that the children with seizures in this sample had an average age at onset of seizures of 9.58 years and approximately 60% of the seizure group was comprised of focal epilepsy syndromes (Table 2). The five most frequently prescribed ASMs 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: primary generalized (generalized tonic–clonic, absence, and myoclonic

TABLE 3 Clinical epilepsy characteristics for children with epilepsy by SD group.

Characteristic	SD-3, $n=32$	SD-2, $n=61$	SD-1, $n=83$	SD-0, $n=136$	p
Clinical epilepsy characteristics					
Child's age, years (StD)	9.31 (2.4)	9.61 (2.6)	9.76 (2.7)	9.16 (2.5)	.491
Child's sex, M/F	15/17	29/32	44/39	67/69	.900
Child's education, years (StD)	3.66 (2.4)	4.17 (2.4)	4.00 (2.5)	3.67 (2.5)	.534
Age at onset, years (StD)	9.48 (2.6)	9.84 (2.6)	9.86 (2.7)	9.36 (2.6)	.440
Number of seizures (StD)	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
% with ≥2 seizure types	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
% on ASMs at baseline	6.7%	13.1%	14.1%	13.1%	.763

Note: There was no significant difference in percent normal MRI, EEG, examination, et cetera by SD score group in those with epilepsy among children with epilepsy during the baseline visit. Data are presented as mean (StD) or percentage.

Abbreviations: F, female; FUS, focally unaware epilepsy syndrome; M, male; NA, not available; SD, sociodemographic disadvantage; StD, standard deviation.

TABLE 4 Neurobehavior in children with seizures over 36 months.

Neurobehavior	SD-3, $n=32$	SD-2, $n=61$	SD-1, $n=83$	SD-0, $n=136$	$F_{3,\,308}$	p
Baseline						
Internalizing	59.56 (2.0)	59.56 (1.4)	55.51 (1.2)*	53.28 (.9)**	5.97	<.001
Externalizing	57.53 (1.9)	55.51 (1.4)	51.95 (1.2)*	50.13 (.9)*	6.23	<.001
Total	60.53 (2.0)	59.46 (1.4)	55.13 (1.2)*	52.48 (.9)*	8.05	<.001
TRF internalizing	60.97 (1.8)	57.20 (1.3)	53.87 (1.1)*	51.02 (.9)**	10.68	<.001
TRF externalizing	60.38 (1.8)	55.81 (1.2)*	50.46 (1.1)**	50.17 (.8)**	12.86	<.001
TRF total	63.28 (1.9)	58.66 (1.3)*	53.32 (1.2)**	51.09 (.9)**	15.36	<.001
18 months later						
Internalizing	58.46 (2.1)	53.58 (1.5)	50.74 (1.3)*	49.82 (1.0)*	5.41	.001
Externalizing	56.82 (2.0)	53.87 (1.4)	51.20 (1.2)	49.15 (.9)*	5.55	.001
Total	59.54 (2.2)	55.29 (1.6)	51.46 (1.3)*	49.72 (1.0)*	7.14	<.001
TRF internalizing	56.00 (1.8)	57.29 (1.4)	54.12 (1.1)	50.67 (.9)*	6.47	<.001
TRF externalizing	59.86 (1.7)	53.96 (1.3)*	49.60 (1.0)**	49.48 (.8)**	12.94	<.001
TRF total	61.24 (1.8)	57.35 (1.4)	53.23 (1.1)*	50.85 (.9)*	11.86	<.001
36 months later						
Internalizing	53.20 (2.1)	54.57 (1.5)	50.36 (1.2)	49.04 (1.0)*	3.55	.015
Externalizing	53.92 (2.1)	53.43 (1.5)	50.33 (1.2)	46.67 (1.0)*	6.82	<.001
Total	55.80 (2.2)	55.15 (1.6)	50.36 (1.3)*	47.83 (1.0)*	7.15	<.001
TRF internalizing	57.40 (2.2)	56.14 (1.5)	53.61 (1.2)	50.78 (.9)*	4.72	.003
TRF externalizing	55.85 (1.9)	56.55 (1.3)	50.08 (1.0)*	49.42 (.8)*	9.79	<.001
TRF total	57.75 (2.1)	58.79 (1.4)	52.32 (1.2)*	50.70 (.9)*	9.44	<.001

Note: In children with epilepsy, Child Behavior Checklist and TRF scores differ among SD categories, such that those who fall into the SD-3 group show significantly poorer neurobehavior scores compared to those with less sociodemographic disadvantage. Values without an asterisk differ significantly from values with one asterisk, which differ significantly from values with two asterisks according to post hoc analysis using Tukey honest significant tests.

Abbreviations: SD, sociodemographic disadvantage; TRF, Teacher Report Form.

epilepsy syndromes) and focal/localization-related (focal unaware and focal aware seizures with or without secondary generalization). In this cohort, MRI abnormalities included multiple various abnormalities (e.g., bilateral or unilateral hippocampal atrophy/sclerosis, ventricular enlargement, volume loss, cortical dysplasias, heterotopias, angiomas, encephalomalacia, and old hemorrhages) as described in detail elsewhere.[69] 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.[51] With regard to family sociodemographic characteristics (specifically household income), our sample was nearly identical to national statistics for the United States at the time of recruitment.[52]

3.2 | SD score subgroup characteristics

The sample was divided into four subgroups based on their SD score. Subgroup characteristics are reported in Tables S2 and 3. The disadvantage assessment was conducted at the baseline visit only, with the intent to determine whether SD has a lasting impact over time. As would be expected, families who fell into the SD3 category were primarily of non-White race and showed the lowest levels of income, caregiver education, and married parental status, whereas families who fell into the SD0 category were all of White race and showed the highest levels of income, caregiver education, and married parental status (Table S2). Notably, univariate analysis of the children with seizures showed no significant differences in child's age, child's sex, child's education, or other clinical seizure characteristics or test evaluation results among the SD groups (Table 3).

3.3 | SD and neurobehavioral outcomes (parent and teacher report)

Based on parental and teacher reports, the children with seizures exhibited significant differences in neurobehavior (CBCL and TRF) depending on their SD score, such that those who fell into the SD3 category showed higher neurobehavioral problems compared to those who fell into the SD0 category (see Table 4). Furthermore, each category—SD3, SD2, SD1, and SD0—differed from the others in neurobehavior scores as assessed both by teachers and by parents. Similar findings were noted in the CBCL results among siblings (see Table 5). In addition,

these differences remained stable and significant over a 3-year period (at baseline, 18 months later, and 36 months later) in both children with seizures and their siblings (Figure 1).

3.4 | SD and neurobehavioral outcomes (child report)

Our data indicate that children with seizures have significant differences in depression (CDI-2), anxiety (MAACL), and hostility (MAACL) depending on their disadvantage index score, such that those who fall into the SD3 category show greater anxiety, depression, and hostility scores compared to those who fall into the SD0 category (see Table 6 and Figure 2). In addition, these differences remained stable and significant over a 3-year period (at baseline, 18 months later, and 36 months later). Table S3 provides background information regarding the intercorrelations among the neurobehavioral outcomes measures within and across the data collection points.

3.5 | Predictive characteristics of neurobehavioral outcomes in children with seizures

Using linear regression, we determined the relative explanatory power (percent variance or R^2) for the variables of interest across the dependent measures from the CBCL, TRF, CDI-2, and MAACL. Using both the corrected and uncorrected significance of standardized beta coefficients, SD consistently represented a significant predictor of the neurobehavioral outcomes, with a greater influence on those emotional–behavioral outcomes (CBCL, TRF), depression (CDI-2), and anxiety and hostility (MAACL) compared to the clinical seizure variables (see Table 7). Some of the clinical factors such as age at onset of seizures, seizure burden, and ASMs played a significant role in the regression analysis (uncorrected significance findings). However, none explained as much variance as disadvantage. Notably, only SD consistently survives false discovery rate significance corrections across the three time points (baseline, M18, and M36).

4 | DISCUSSION

The general risk of emotional–behavioral concerns is known to be elevated in youths with epilepsy, a risk that has been examined in light of the cause, course, characteristics, and treatment of the child's epilepsy, but rarely are sociodemographic factors considered. The goal of the

TABLE 5 Neurobehavior in siblings over 36 months.

Neurobehavior	SD-3, $n = 21$	SD-2, $n = 40$	SD-1, $n = 59$	SD-0, $n = 103$	$F_{3, 219}$	p
Baseline						
Internalizing	50.81 (2.4)	50.85 (1.8)	51.41 (1.5)	48.68 (1.1)	.91	.435
Externalizing	53.43 (2.5)	54.73 (1.8)	52.10 (1.5)	48.04 (1.1)*	4.18	.007
Total	52.48 (2.6)	53.93 (1.9)	52.09 (1.5)	47.54 (1.2)*	3.88	.010
18 months later						
Internalizing	51.26 (2.4)	47.56 (1.8)	48.49 (1.4)	45.81 (1.1)	1.71	.167
Externalizing	57.58 (2.5)	51.38 (1.9)	49.15 (1.5)*	46.83 (1.2)*	5.54	.001
Total	55.16 (2.6)	49.50 (1.9)	47.71 (1.6)	45.04 (1.2)*	4.70	.003
36 months later						
Internalizing	49.81 (2.6)	49.68 (1.9)	46.43 (1.5)	46.43 (1.1)	1.14	.335
Externalizing	54.25 (2.6)	54.14 (2.0)	47.10 (1.5)*	46.79 (1.2)*	5.30	.002
Total	52.06 (2.8)	53.50 (2.1)	45.47 (1.6)*	45.10 (1.2)*	5.36	.002

Note: In siblings, Child Behavior Checklist scores differ among SD categories such that those who fall into the SD-3 group show significantly poorer neurobehavior scores compared to those with less sociodemographic disadvantage. These patterns remain persistent over the 36-month period. Data are presented as mean (SE). *F* represents analysis of variance statistic with degrees of freedom. Values without an asterisk differ significantly from values with an asterisk according to post hoc analysis using Tukey honest significant tests.

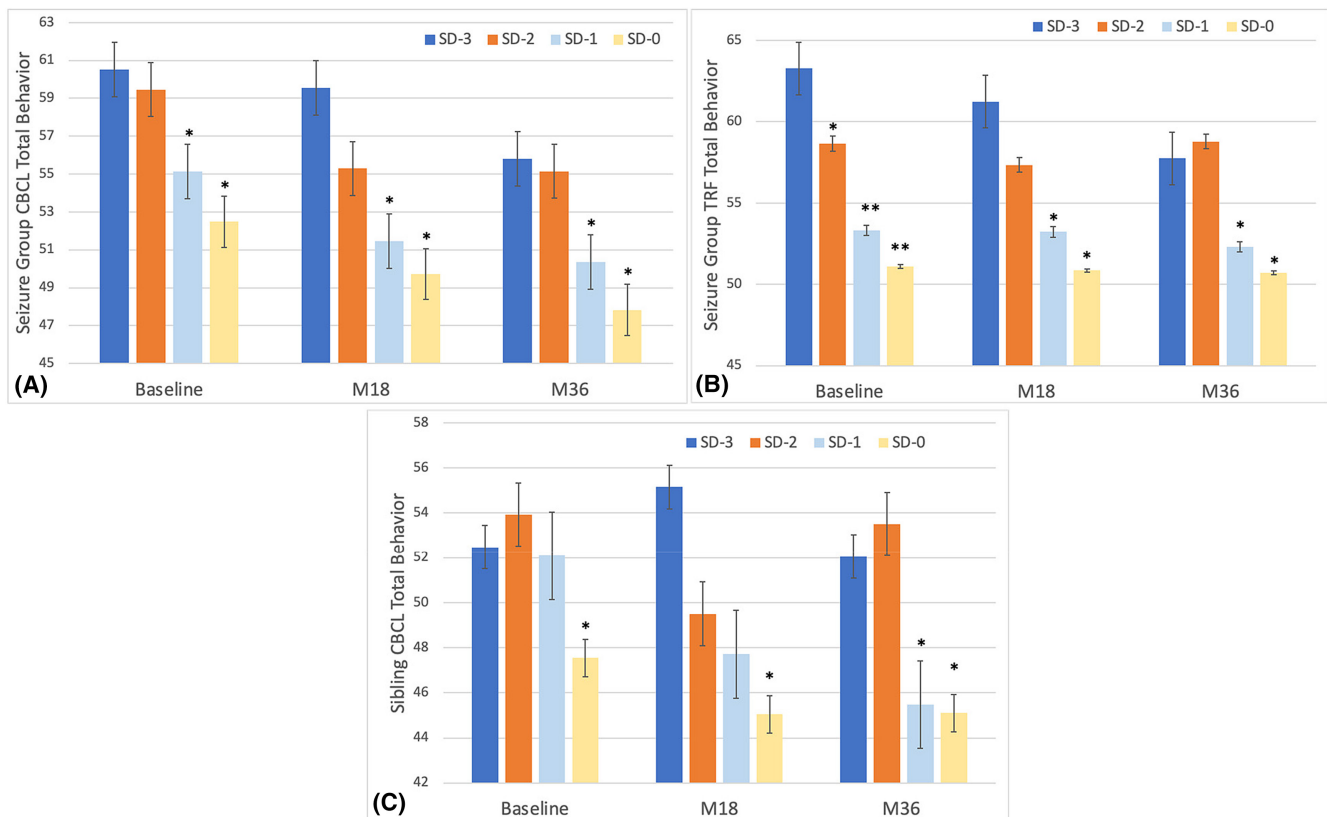Abbreviation: SD, sociodemographic disadvantage.

FIGURE 1 Neurobehavior scores (Child Behavior Checklist [CBCL] and Teacher Report Form [TRF]) for children with epilepsy and their siblings, by sociodemographic disadvantage (SD) score and time point. In both seizure and sibling groups, CBCL and TRF scores differ between at least SD-3 and SD-0 at all time points, such that families who fall into the SD-3 group show significantly poorer neurobehavioral scores compared to the SD-0 group. Poor neurobehavior decreases significantly and consistently as SD decreases. In addition, this pattern remains persistent over the 36-month period. For each visit (baseline, 18 months later [M18], 36 months later [M36]), bars without an asterisk differ significantly from those with one asterisk, which differ significantly from those with two asterisks according to post hoc analysis using Tukey honest significant tests.

TABLE 6 Neurobehavior in children with seizures over 36 months.

Neurobehavior	SD-3	SD-2	SD-1	SD-0	$F_{3, 307}$	p
Baseline						
Depression	11.32 (1.5)	10.29 (1.0)	8.98 (.9)	6.26 (.7)*	5.56	.001
Anxiety	3.19 (.5)	3.56 (.4)	3.13 (.3)	2.5 (.3)	2.03	.109
Hostility	2.03 (.3)	1.79 (.2)	1.45 (.2)	1.17 (.2)**	2.75	.043
18 months later						
Depression	11.46 (1.3)	9.36 (.9)	7.08 (.78)*	6.05 (.63)*	6.48	<.001
Anxiety	3.89 (.5)	2.46 (.3)~	2.40 (.29)*	2.26 (.23)*	3.31	.02
Hostility	2.46 (.3)	1.54 (.2)	1.75 (.2)	1.60 (.2)	2.06	.107
36 months later						
Depression	9.76 (1.1)	7.06 (.8)	6.77 (.7)	5.30 (.5)*	4.78	.003
Anxiety	3.12 (.5)	2.86 (.4)	2.57 (.3)	2.22 (.3)	1.13	.339
Hostility	2.76 (.4)	1.75 (.3)	1.62 (.2)*	1.42 (.2)*	3.67	.013

Note: In children with epilepsy, Children's Depression Inventory and Multiple Affect Adjective Check List scores differ among SD categories such that those who fall into the SD-3 group show significantly poorer neurobehavior scores compared to those with less sociodemographic disadvantage. This pattern persists over the 36-month period. Data are presented as mean (SE). *F* represents analysis of variance statistic with degrees of freedom. Values without an asterisk differ significantly from values with an asterisk according to post hoc analysis using Tukey honest significant tests.

Abbreviation: SD, sociodemographic disadvantage.

~ $p < .1$ (trend toward significance).

current study was to determine the contributions of the social determinants of health, specifically SD, to the neurobehavioral status of children with newly diagnosed seizures and their unaffected siblings, assessing this relationship via a cross-sectional approach at three time periods.

The core findings of this investigation include the following (1): SD is closely associated with the neurobehavioral status of children with seizures at the onset of the disorder as assessed by three different sources (parent, teacher, and child) using multiple measures of neurobehavioral status; (2) SD similarly impacts the behavioral status of unaffected siblings of children with seizures; (3) SD at baseline is predictive of the behavioral status of youths with seizures and their siblings up to 3 years after their initial evaluation; and (4) SD accounts for more variance in the behavioral outcomes of children with seizures compared to traditional clinical epilepsy factors, suggesting the clinical significance of disadvantage in this population. These findings significantly extend the current literature by revealing the role of disadvantage on important health-related outcomes, such as neurobehavioral functioning.[48] To our knowledge, this is the first investigation examining the role of SD on the neurobehavioral status of children with newly diagnosed seizures and their siblings over an extended time period. Our findings presented here extend our understanding of the impact and role of disadvantage in the epilepsy literature, which is consistent with health care outcome findings in multiple other disorders including asthma, autism, COVID-19, diabetes, and sleep health.[29–48]

Examining the influence of disadvantage at the time of diagnosis as well as at 18 and 36 months later, we find that behavior problems, as rated by parents, the child's teacher, and the child with seizures him-/herself, all indicate that behavioral risk increases with greater social disadvantage. This unanimity of effect, across all informants, with the consistency of relationship over time, points to the robustness and reliability of the effect of disadvantage. This disadvantage–behavioral problem relationship is furthermore evident across multiple metrics that include summary measures of total behavior problems (parental and teacher reports), total internalizing problems, and especially total externalizing problems, as well as child-completed metrics of depression and multiple measures behavioral distress. Also of note is that the teacher completing the TRF for the children varied over time, yet the disadvantage–behavioral problem relationship persisted. Finally, it should be remembered that disadvantage was determined at baseline and the persistence of the effect over 3 years speaks to the enduring influence of disadvantage in the absence of systematic intervention.

The presence of neurobehavioral comorbidities among unaffected siblings of youths with epilepsy has generated considerable interest regarding potential genetic contributions to the cognitive and behavioral complications of epilepsy.[19,21,22,25] Here, we demonstrate that social disadvantage impacts the emotional–behavioral status not only of youths with seizures but of their unaffected siblings as well, pointing to the complexity of forces that may underlie family aggregation effects. The behavioral measures
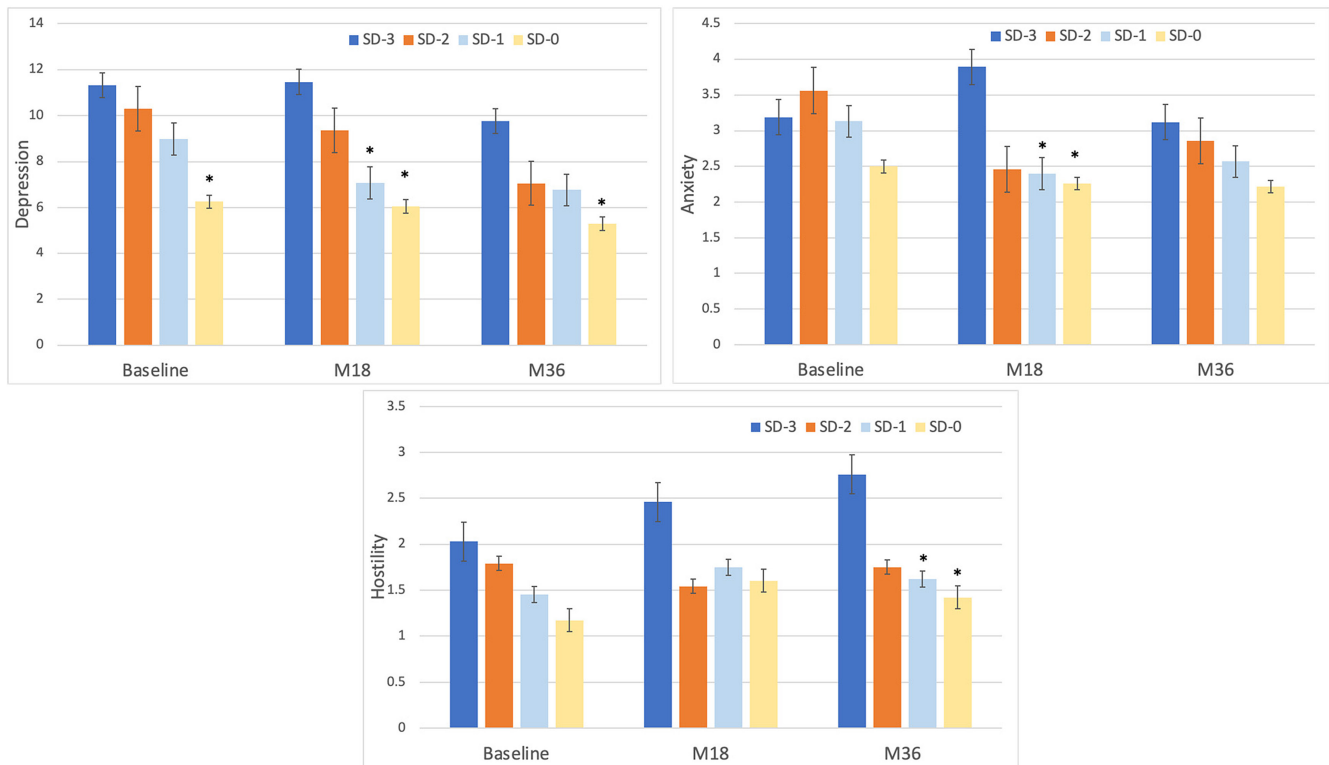
FIGURE 2 Neurobehavior scores (Children's Depression Inventory [CDI-2] and Multiple Affect Adjective Check List [MAACL]) for children with epilepsy, by sociodemographic disadvantage (SD) score and time point. In both seizure and sibling groups, CDI-2 and MAACL scores differ between at least SD-3 and SD-0 at all time points, such that families that fall into the SD-3 group show significantly poorer neurobehavior scores compared to the SD-0 group. Poor neurobehavioral status decreases significantly and consistently as SD decreases. In addition, this pattern remains persistent over the 36-month period. For each visit (baseline, 18 months later [M18], 36 months later [M36]), bars without an asterisk differ significantly from those with an asterisk according to post hoc analysis using Tukey honest significant tests.

administered to the siblings were more limited in scope, but the relationships remained similar.

Furthermore, another noteworthy finding is the relative explanatory power of social disadvantage compared to the diverse array of clinical seizure characteristics. The results of the regression analyses demonstrate that disadvantage remains a significant predictor of parent-, teacher-, and child-reported behavioral problems, across all administered behavioral measures, across all the assessment epochs, even when a wide diversity of clinical seizure variables were also considered. Overall, it appears that social disadvantage is a factor deserving of greater empirical and theoretical consideration. It has been shown that disadvantage is a substantial factor of relevance in child and adult epilepsy and is linked to the incidence and prevalence of epilepsy.[42–48] We show evidence here that it also plays a role in neurobehavioral status. It is important to note, however, that these findings do not negate the finding that brain structural and connectivity factors as well as the underlying epilepsy disorder play a significant role in neurobehavioral status. Despite this, our findings indicate that sociodemographic factors need to be considered as a significantly impactful factor

as well. Beneficial future research would directly determine whether the impact of disadvantage as defined here is modifiable. It is likely that the markers of social determinants of health utilized here are reflective of broader issues linked to disadvantage, issues that might include but not be limited to 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, decreased socialization, overall medical comorbidity burden, and other factors. These considerations, alone or in contribution, deserve greater investigation to clarify their relative impact, modifiability, and ensuing impact on children with epilepsy and their family members.

This study has limitations that should be mentioned. 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 seizures were not assessed here and may have played a role in the neurobehavioral findings we presented. In addition, course and treatment details can

TABLE 7 Linear regression models over 36 months.

	Explained variance, R^2 (%)	Model p	SD, β	Seizure syndrome, β	EEG, β	MRI, β	Age at onset, β	Seizure burden, β	ASMs, β
Baseline									
CBCL Int	7.5	.022	**−.234****	−.053	−.062	.026	.032	−.020	.033
CBCL Ext	10.5	<.001	**−.266****	−.122	−.111	−.020	−.007	−.090	−.015
CBCL total	11.3	<.001	**−.277****	−.108	−.096	−.033	.040	−.068	.007
TRF Int	13.1	<.001	**−.314****	−.048	−.007	−.017	.068	−.032	−.098
TRF Ext	14.0	<.001	**−.322****	−.058	.065	.006	.017	.028	−.011
TRF total	17.4	<.001	**−.359****	−.116	−.004	−.038	.010	.013	−.084
Depression	7.1	.031	−.186*	−.104	−.016	.001	.075	−.075	.040
Anxiety	4.5	.264	−.142*	−.116	−.024	.016	−.036	−.045	−.032
Hostility	5.8	.102	−.210*	−.041	−.029	−.001	.021	−.055	.084
18 months later									
CBCL Int	8.7	.012	**−.215****	−.038	−.075	−.036	−.094	−.096	.026
CBCL Ext	10.2	.003	**−.232****	−.124	−.027	−.028	−.100	−.145*	.048
CBCL total	13.1	<.001	**−.245****	−.135*	−.086	−.052	−.122	−.149*	−.003
TRF Int	8.0	.030	**−.218****	.018	−.013	−.026	−.032	−.095	−.076
TRF Ext	14.7	<.001	**−.334****	−.054	−.016	.036	−.064	.016	−.105
TRF total	13.1	<.001	**−.330****	−.056	−.052	−.047	−.083	−.026	−.062
Depression	3.7	.512	−.156	.026	−.032	.035	−.017	−.045	−.043
Anxiety	6.1	.116	−.166*	−.020	−.012	−.012	−.033	−.112	−.045
Hostility	5.7	.148	−.110	.043	−.015	−.076	−.068	−.099	.045
36 months later									
CBCL Int	9.2	.012	−.158	−.029	−.113	−.017	−.166*	−.138*	−.066
CBCL Ext	12.5	<.001	**−.254****	−.106	−.059	−.047	−.167*	−.126	−.006
CBCL total	13.7	<.001	**−.251****	−.111	−.100	−.058	−.147*	−.159*	−.052
TRF Int	6.7	.148	−.223*	.006	−.055	−.045	.086	−.001	−.047
TRF Ext	13.9	<.001	**−.312****	−.026	.016	−.020	.041	.056	.055
TRF total	12.8	<.001	**.306****	−.009	−.064	−.054	.030	.078	−.013
Depression	4.1	.453	−.120	−.026	−.036	−.012	−.030	−.073	−.005
Anxiety	4.2	.440	−.102	−.028	−.052	.018	−.102	−.015	−.130*
Hostility	6.2	.133	−.176*	.017	.055	−.053	−.069	−.070	.025

Note: This table indicates the amount of variability explained by the model (R^2), significance of the model (model p-value), and best predictors of neurobehavioral problems in children with epilepsy (standardized β coefficients). Throughout the 36-month period, disadvantage score (SD) remains significant and impactful, whereas age at onset of epilepsy, MRI/EEG findings, seizure burden, number of ASMs, and seizure syndrome remain mostly nonsignificant in the models. Bold (corrected) values are the significant findings that survived false discovery rate adjustment (k significant findings).

Abbreviations: ASM, antiseizure medication; CBCL, Child Behavior Checklist; EEG, electroencephalography; Ext, externalizing; Int, internalizing; MRI, magnetic resonance imaging; SD, sociodemographic disadvantage; TRF, Teacher Report Form. *$p < .05$, **$p < .001$.

vary between individuals and also over time, and can play a significant role in neurobehavioral outcomes. We do not have these data and could not include this information in our analyses. Finally, there were evident correlations among the diverse measures of emotional and behavioral outcomes within and across time points and sources of information (Table S3). Our presentation was at a measure-level orientation, typical for research in pediatric epilepsy–behavioral research. However,

interesting for research of this type, as well as for the field more broadly, would be a construct-level approach. For example, identifying an underlying general psychopathology factor ("p") similar to metrics of global cognitive ability ("g") may have utility. This approach has been undertaken rarely in epilepsy research but appears to have promise.[70]

Future studies investigating these details in relation to disadvantage and behavior would be key to gaining a

full understanding of neurobehavioral abnormalities in epilepsy. One further limitation of the measure of social disadvantage is that family income data were based on family report.

In summary, SD exerts a powerful impact on psychological and behavioral performance in children with newly diagnosed seizures and their unaffected siblings. This strong and robust association is enduring over time and has a familial aggregation pattern. The behavioral and neurobiological impact of SD on youths with epilepsy (and their siblings) deserves further examination and inclusion in our clinical epilepsy studies.

AUTHOR CONTRIBUTIONS

Temitayo Oyegbile-Chidi, Bruce Hermann, and Jana Jones conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Joan Austin, David Dunn, and Anna Byars designed and conceptualized the larger original study cohort, designed the data collection instruments, collected data within each of their study sites, carried out the initial analyses of the larger cohort, and reviewed and revised the manuscript. Danielle Harvey coordinated and supervised the data analysis, conceptualized statistical methods, and critically reviewed the manuscript for important statistical content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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[Correction added on 17 July 2023, after first online publication: The references are set in the correct order].

SUPPORTING INFORMATION

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