Obesity is a common comorbidity for pediatric patients with untreated, newly diagnosed epilepsy

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ABSTRACT

Objective: This study aimed to determine the frequency and factors associated with obesity in a cohort of children and adolescents with newly diagnosed untreated epilepsy.

Methods: Body mass index (BMI) Z-scores and percentiles, both adjusted for age, were used as measures for obesity. Potential covariates associated with these BMI measures included age, etiology (cryptogenic, idiopathic, symptomatic), seizure type (generalized, partial, unclear), concomitant medications (stimulants, nonstimulants, none), and insurance status (privately insured, Medicaid). The primary analysis compared the epilepsy patients' BMI Z-scores to Centers for Disease Control and Prevention data for healthy children. The secondary analysis compared the epilepsy patients' BMI Z-scores to those of a regional healthy control group. Additional analyses incorporated the secondary outcome measure BMI percentiles indexed for age.

Results: Children with newly diagnosed untreated epilepsy had higher BMI Z-scores compared to standard CDC growth charts ($p < 0.0001$) and the healthy control cohort ($p = 0.0002$) specifically at both of the 2 tail ends of the distribution. Overall, 38.6% of the epilepsy cohort were overweight or obese (BMI $\geq$ 85th percentile for age). Differences in age, etiology, and concomitant nonepilepsy medications were significantly associated with variability in age-adjusted BMI Z-score. Patients in adolescence had higher adjusted BMI Z-scores than younger patients. Patients with symptomatic epilepsy had lower adjusted BMI Z-scores than patients with idiopathic epilepsy. Patients on stimulant psychotropics exhibited lower adjusted BMI Z-scores than patients on no medication.

Conclusion: Obesity is a common comorbidity in children with newly diagnosed untreated epilepsy and correlates with increasing age, idiopathic etiology, and absence of concomitant medication.

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GLOSSARY

BMI = body mass index; **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **IRB** = institutional review board; **WMW** = Wilcoxon-Mann-Whitney.

In 2007, the National Institute of Neurological Disorders and Stroke published updated epilepsy benchmarks aimed at guiding research directions toward, among multiple goals, improving safe and effective therapy for people with epilepsy. A new area of research was identified that focused on comorbidities. Several comorbidities in epilepsy have been previously addressed in some depth.¹ However, obesity is a potential comorbidity which has been poorly examined.

Obesity in childhood ($\geq$ 95th percentile of body mass index [BMI] for age) is increasingly identified as one of the premier public health concerns facing the pediatric population.² National surveys show that 17.1% of children are obese with an increasing trend toward obesity for all children and adolescents.³ With no sign that this trend is being reversed, weight-related

Editorial, page 654

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diseases, once thought to be specific to adults, are now recognized with increasing prevalence in the pediatric population. Heart disease, type II diabetes, and other obesity-related sequelae are not only immediate health concerns but chronic conditions which, if left untreated, can carry into adulthood.⁴⁻⁷

Obesity in epilepsy is particularly concerning given the adverse weight effects and endocrine changes associated with many commonly used antiepileptic medications.^{8,9} However, it is not known if children with newly diagnosed untreated epilepsy exhibit the same prevalence of obesity as the general pediatric population. Knowing this information would be useful in selecting initial medication for therapy and establishing early intervention strategies to prevent obesity while treating epilepsy. The purpose of this study was to determine if obesity is a common comorbidity for children with epilepsy. We hypothesized that children and adolescent patients with newly diagnosed untreated epilepsy would have a high rate of obesity compared to published national standards (Centers for Disease Control and Prevention [CDC] growth curves) but exhibit no difference in comparison to a regional healthy control group.

METHODS Population. Patients treated through the new onset seizure clinic at Cincinnati Children's Hospital Medical Center between July 7, 2003, and October 30, 2006, were identified for the study. This clinic evaluates children with a suspected first time seizure or suspected new onset epilepsy within 10 days of referral from an 8-county region of southwestern Ohio. Eligible patients were between 2 and 18 years old (inclusive), newly diagnosed with epilepsy, and not previously treated with antiepileptic medication. Patients were excluded if they had serious chronic medical issues (e.g., cancer, hepatic failure). Informed consent was obtained as part of an institutional review board (IRB)-approved pharmacogenomics study. Information abstracted from the charts included demographic information, seizure/epilepsy type, epilepsy etiology, concomitant medications (at the visit when antiepileptic medication was first prescribed for the patient), and insurance status. The patient's seizure type, epilepsy type, and epilepsy syndrome were classified according to the International League Against Epilepsy's Classification for Seizure, Epilepsies, and Epilepsy Syndromes.¹⁰⁻¹² Concomitant medications were categorized as stimulants, nonstimulants, or none. Stimulants included all methylphenidate and amphetamine formulations. Insurance status (dichotomized as privately insured or Medicaid) was collected at the time of the first visit.

Data for the regional healthy control group came from the Cincinnati Children's Genomic Control Cohort initiative. This IRB-approved study aimed to enroll normally developing children from the regional community to serve as controls in studies

of rare diseases. Multiple strategies, including media campaigns and targeted community recruitments through schools and day care centers, were employed to ensure that this cohort of children was representative of the population of the region with respect to race and ethnicity, gender, and socioeconomic status. All children were evaluated by a single board-certified pediatrician using a standardized assessment approach to ensure study subjects were growing and developing normally at time of enrollment. The geographic region that was defined for this study was 7 contiguous counties in southwestern Ohio and northern Kentucky that comprise the greater Cincinnati region.

BMI determination. The weights of the patients with epilepsy were measured on 1 of 2 stand-up electronic Scale-Tronix scales calibrated annually. The heights of patients with epilepsy were measured using a Holtain Limited height bar. The height and weight used in this analysis were obtained at the visit when antiepileptic medication was first prescribed for the patient. BMI percentiles and Z-scores adjusted for age were generated using a SAS program for Centers for Disease Control and Prevention growth charts (<http://www.cdc.gov/nccdphp/dnpa/growthcharts/resources/sas.htm>).¹³ As a secondary response, BMI percentiles were classified into the following categories: 1) obese: BMI $\geq$ 95th percentile for age, 2) overweight: 85th percentile $\leq$ BMI <95th percentile for age, 3) healthy weight: 10th percentile $\leq$ BMI <85th percentile for age, and 4) underweight: BMI <10th percentile for age.

Statistical analysis. Descriptive statistics were used to characterize the patient population. χ^2 (for categorical variables) or Wilcoxon-Mann-Whitney (WMW) (for continuous type variables) tests were used to compare demographic variables between the study populations. Epilepsy patients' BMI Z-scores and healthy control patients' BMI Z-scores were compared to the standard CDC growth chart (assumed to have a standard normal distribution) using a 1-sample *t* test. A second analysis compared the BMI Z-distribution of the epilepsy group to the healthy control group. Here, a generalized rank sum test¹⁴ was used to detect heterogeneity in the data which cannot be captured using the standard WMW test. The generalized test is appropriate when group differences are most apparent at the tail ends of the distribution as was the case upon examination of the data. For this test, the role of the response variable and the grouping variable is switched so that the rank of BMI Z-score and the square of the rank of BMI Z-score were modeled as predictor variables and group status was used as the dependent variable. Demographic variables including sex, age, race, and insurance were added using a logistic regression model when unadjusted effects had a *p* value of <0.20. Here, age was kept as a continuous variable and race was dichotomized as African American and non-African American.

To determine the relationship between BMI Z-scores and potential covariates in the epilepsy group, a series of univariable and multivariable analyses were conducted using analysis of variance and analysis of covariance. All variables that reached a *p* value <0.20 in univariable analyses entered the subsequent multivariable analysis. Potential covariates analyzed were age, sex, race, etiology (cryptogenic, idiopathic, symptomatic), seizure type (general, partial, unclassified), concomitant medications (stimulants, nonstimulants, none), and insurance status (privately insured, Medicaid). For the above models, age was treated as a continuous measure.

Separate Pearson χ^2 tests were used to test associations between the categorized BMI status (obese, overweight, healthy weight, and underweight) and the significant covariates of age, concomitant medications, and etiologies; in these analyses age

Table 1 Demographic characteristics of the study populations			
Characteristics	Regional healthy controls (n = 597)	Epilepsy (n = 251)	p Value*
Sex			0.42
Male	296 (49.6)	132 (52.6)	
Female	301 (50.4)	119 (47.4)	
Race			0.009*
Black	149 (25.0)	42 (16.7)	
White	424 (71.0)	199 (79.3)	
Other	24 (4.0)	10 (4.0)	
Age, quartiles	8.5/12.1/14.7	5.4/8.7/12.0	<0.0001
Insurance			0.22
Insured	450 (75.4)	179 (71.3)	
Medicaid	147 (24.6)	72 (28.7)	

* χ^2 tests were used to determine regional control and epilepsy group differences for the categorical variables sex, race, and insurance; Wilcoxon-Mann-Whitney tests were used to determine group differences for age.

*This p value was derived from a χ^2 test with race dichotomized as African American and non-African American.

was categorized into preadolescents (2–12 years) and adolescents (13–18 years) for comparison purposes. S-Plus 8.0 (TIBCO Software Inc., Palo Alto, CA) was used for statistical modeling. The Hmisc and Design packages (<http://biostat.mc.vanderbilt.edu/wiki/bin/view/Main/RS>, last visited in January 2009) were used for statistical modeling within the S-Plus statistical package. All tests were 2-sided and used a 0.05 significance level except the tests for the inclusion of predictors, which were set at significance level of 0.20.

RESULTS Patient population. There were 251 eligible patients with newly diagnosed untreated epilepsy with complete data available for analysis while there were 597 subjects in the regional healthy control group. Table 1 shows the common characteristics of the study populations (sex, race, age, and insurance status). Differences in race and age ($p < 0.2$) were controlled for in the subsequent generalized rank sum tests.

The majority of epilepsy patients had partial onset seizures (59.8%), had idiopathic epilepsy (74.5%), and were not on any medication (72.5%). Stimulants were used by 8.4% of patients and nonstimulants were used by 19.1% of the patients. The bulk of nonstimulant medications were antihistamines or other antiallergens. Two patients were taking risperi-

done. There were no patients in the epilepsy or the regional healthy control group with cerebral palsy or other causes of severe motor impairment.

BMI distribution. A total of 19.9% of epilepsy patients were obese (BMI $\geq$ 95th percentile for age) while 18.7% were overweight (85th percentile $\leq$ BMI <95th percentile for age). Overall, 38.6% of the epilepsy groups were considered overweight or obese (BMI $\geq$ 85th percentile for age). There was a difference in mean BMI Z-scores between the epilepsy cohort and the standard CDC growth curve ($p < 0.0001$).

A total of 13.7% of regional healthy control patients were obese (BMI $\geq$ 95th percentile for age) while 14.7% were overweight (85th percentile $\leq$ BMI <95th percentile for age). For the regional healthy control group, 28.4% were considered overweight or obese (BMI $\geq$ 85th percentile for age). There was a difference in mean BMI Z-scores between the regional healthy control group and the standard CDC growth curve ($p < 0.0001$). The distribution of BMI Z-scores between the epilepsy group and the regional healthy control group was different ($p = 0.0009$) using the adjusted generalized rank sum test (table 2); this difference was not detected by the WMW test ($p = 0.14$). There was also a difference in BMI between the 2 groups ($p = 0.0004$) (table 2).

The cumulative probability plot and the density plot showed both the epilepsy group and the regional healthy control cohorts were to the right of the normal curve indicating a high rate of obesity in these 2 groups (figure). At the tail ends of the distribution, the epilepsy group exhibited more underweight and overweight patients in comparison to the regional healthy control group (figure).

Predictors of BMI. A series of univariable analyses were conducted on each covariate as a function of BMI in the epilepsy group to determine potential predictors to include in multivariable analyses. Sex, race, and insurance did not meet the p value < 0.20 , the preestablished threshold. The covariates included in the final model were age, etiology, seizure type, and concomitant medications.

A multivariable linear regression model showed age, etiology, and concomitant medications were significant predictors on the response (BMI Z-score) in the epilepsy group (table 3). Patients with age at the mean years of the adolescent group (15 years) had almost a half-unit higher BMI Z-score than patients with age at the mean years of the preadolescent group (7 years) (95% confidence interval [CI] 0.14 to 0.70; $p = 0.004$). Patients with symptomatic epilepsy had a lower mean BMI Z-score by 0.62 units than pa-

Table 2 Description of body mass index measures between the 2 study populations			
Response	Regional healthy control	Epilepsy	p Value*
BMI	17.0/19.1/22.3	15.9/17.9/21.4	0.0004
BMI-Z	-0.069/0.50/1.10	-0.157/0.63/1.44	0.0009

Values are 25th/50th/75th percentiles.

*Generalized Wilcoxon-Mann-Whitney tests were used to assess heterogeneity in BMI and BMI Z-scores between control and epilepsy groups adjusting for race and age.

BMI = body mass index; BMI-Z = body mass index Z-score indexed for age.

Figure Cumulative probability plot (A) and density plot (B) of body mass index Z-scores from the regional control population, epilepsy samples, and published national standards (Centers for Disease Control and Prevention growth curves), where the latter was represented by a standard normal curve

tients with idiopathic epilepsy (95% CI 0.15 to 1.10; $p = 0.02$ for any seizure type differences). Patients on stimulants had almost a 1-unit lower (0.91 mean difference) mean BMI Z-score than patients not on any medication (none) (95% CI 0.39 to 1.44; $p = 0.003$ for any concomitant medications differences). Seizure type did not contribute to the prediction of BMI Z-score ($p = 0.38$).

BMI status. There was no association between age and categorized BMI status ($p = 0.32$) or concomi-

tant medications and categorized BMI status ($p = 0.21$) (table 4). Etiology was associated with categorized BMI status ($p = 0.049$) (table 4). More patients with symptomatic epilepsy (22.2%) had BMI below the 10th percentile for age compared to those with cryptogenic (2.7%) or idiopathic epilepsy (5.4%).

DISCUSSION Obesity is a common comorbidity in children with newly diagnosed untreated epilepsy. Specifically, 19.9% of patients were obese (BMI ≥ 95 th percentile for age) while 18.7% were overweight (85th percentile $\leq$ BMI < 95 th percentile for age). Overall, 38.6% were overweight or obese (BMI ≥ 85 th percentile for age), more than double the rate of overweight patients expected in a normally distributed population. Both the epilepsy group and the regional healthy control cohort demonstrated a high rate of obesity. However, the epilepsy group exhibited more underweight and overweight patients compared to the regional healthy control group.

These findings are important for the treatment of epilepsy in several respects. On a basic level, obesity is difficult to treat and can be associated with a variety of long-term multisystem sequelae.^{15,16} Increased blood pressure, heart disease, and type II diabetes in children have increased in prevalence as the frequency and severity of obesity has risen.¹⁷⁻¹⁹ Compounding this issue in epilepsy is the potential for several antiepileptic drugs (i.e., valproic acid, carbamazepine, gabapentin, and vigabatrin) to cause weight gain.²⁰

It is unclear if the elevated rate of obesity in the epilepsy population is coincidental or a result of a common mechanism. Future studies of potential common seizure and obesity pathways (e.g., Mtor pathway^{21,22}) are needed to clarify this potential link. In the meantime, there is a clear need for early treatment and prevention to assure success in long-term weight management.²³

When examining BMI Z-scores on a continuous scale, adolescent patients had higher BMI Z-scores than nonadolescent patients. Overall, 27.0% of adolescents were obese (≥ 95 th percentile) while 17.6% of preadolescents were obese. Body image awareness is high in adolescence²⁴ and alterations in appearance may lead to treatment nonadherence, which increases the likelihood of breakthrough seizures. Adherence problems in pediatric epilepsy treatment occur in anywhere from 14% to 44% of patients.²⁵⁻²⁷ Monitoring BMI closely and addressing weight gain could improve adherence and diminish the disease burden obesity can pose.

Patients with symptomatic epilepsy had a lower frequency of obesity (14.8%) compared to patients

Table 3 Adjusted means (95% confidence intervals) for BMI Z-scores from each comparison within each covariate

Predictor	Comparison	Adjusted difference	p Values*
Age	7 years*	Reference	0.004
	15 years	0.42 (0.14, 0.70)	
Etiology	Idiopathic	Reference	0.02
	Cryptogenic	0.17 (-0.24, 0.58)	
	Symptomatic	-0.62 (-1.10, -0.15)	
Seizure type	Partial	Reference	0.38
	Generalized	0.21 (-0.12, 0.54)	
	Unclassified	-0.08 (-0.59, 0.43)	
Concomitant medications	None	Reference	0.003
	Nonstimulant	-0.15 (-0.52, 0.22)	
	Stimulant	-0.91 (-1.44, -0.39)	

*p Values are from multivariable analysis.

*Age treated as continuous and comparison made between mean age of preadolescents (7 years) and mean age of adolescents (15 years).

BMI = body mass index.

Table 4 Cross-tabulation of significant covariates (etiology, age, and medications) and BMI percentile-for-age groups in epilepsy samples

Predictor	BMI groups				p Value
	<10%	10% to 85%	85% to <95%	<95%	
Epilepsy group	17 (7)	137 (55)	47 (19)	50 (20)	—
Age*					0.32
Preadolescent	14 (8)	107 (57)	34 (18)	33 (18)	
Adolescent	3 (5)	30 (48)	13 (21)	17 (27)	
Etiology					0.049
Cryptogenic	1 (3)	22 (60)	7 (19)	7 (19)	
Idiopathic	10 (5)	101 (54)	37 (20)	39 (21)	
Symptomatic	6 (22)	14 (52)	3 (11)	4 (15)	
Medications					0.21
Stimulant	2 (10)	15 (71)	2 (10)	2 (10)	
Nonstimulant	6 (13)	22 (46)	8 (17)	12 (25)	
None	9 (5)	100 (55)	37 (20)	36 (20)	

Values are n (%).

*Preadolescent 2 to 12 years old; adolescent 13 years and above.

BMI = body mass index.

with cryptogenic (18.9%) or idiopathic (20.9%) epilepsy. Symptomatic patients also exhibited a higher frequency of underweight patients (22.2%) compared to the cryptogenic (2.7%) and idiopathic (5.4%) patients. This finding explains the left tail end of the epilepsy cohort BMI Z-distribution. However, the exact origin of this etiologic based difference is not entirely clear. Several studies have evaluated nutritional status among children with neurologic impairments. One study found that children with refractory epilepsy were malnourished and this trend increased in severity for more disabled children.²⁸ Another study reported nutritional deficits in a subject population with mental retardation.²⁹ Whether these differences result from environmental causes, poor appetite, or an interaction of physiologic factors is not understood. However, children with severe impairments often have physical limitations as well as oral motor problems that affect feeding.^{30,31}

Stimulant drugs can also affect feeding by decreasing appetite, which may in turn decrease weight.³² In this study, patients on stimulant psychotropics exhibited a lower mean BMI Z-score close to 1 full unit on average (adjusted) compared to patients on no medication. Approximately 10% of patients on stimulant psychotropics were obese while close to 20% of patients taking no medications were obese. Furthermore, a sizeable proportion of patients were on stimulant psychotropics (8.4%). This percentage is greater than the general pediatric population (~3%),³³ but is likely explained by the higher prevalence of attention deficit hyperactivity disorder in patients with epilepsy.³⁴ Likewise, comorbid anxi-

ety and depression symptoms are also more common in epilepsy.³⁵ Atypical antipsychotics, well known for their positive weight effects, are widely prescribed for the treatment of many mental health disorders.³⁶ However, there were only 2 patients taking concomitant medications (risperidone) known to cause weight gain in our cohort.

Several socioeconomic factors hypothesized to affect BMI were not significant. Insurance status, race, and gender were not statistically associated with BMI Z-score. Obesity rates tend to go up in impoverished, female, and African American dominated populations³⁷; our study cohort tended to be white (79.3%), male (52.6%), and insured (71.3%). We acknowledge that insurance status has limited utility as a global marker for economic standing.³⁸

This study had several limitations. The greater proportion of African Americans in the regional healthy controls was addressed by considering race as a potential covariate in all of our comparisons. Multiple height and weight measurements (typical of research) were not taken as part of routine clinical care. Tanner staging was not conducted to categorize pubertal status. Nutritional status and activity measures were not collected to assess the differences in weight between the epilepsy group and the control group. This information would be useful in determining the etiology behind our findings and to develop future treatment interventions. Furthermore, longitudinal studies are needed to address if any of the significant independent factors continue to affect BMI after AED therapy has begun. Identifying factors that affect BMI over the long term may provide an avenue for a more individualized approach to treatment.

Overall, this study had several notable strengths. Seizure type, epilepsy type, and epilepsy syndrome were classified by the same epileptologist (T.A.G.) for consistency. The study was composed of a well-defined prospectively identified and consecutively enrolled cohort. It used standardized methods of anthropometric assessment. Importantly, it included a regional healthy control cohort for comparison. Most studies are confounded in their ability to examine the etiology of obesity in epilepsy patients due to the positive and negative weight affects of many AEDs. However, this study was able to examine the frequency of obesity in a newly diagnosed untreated epilepsy population and compare it to a healthy control population. We demonstrated that obesity is more common in epilepsy patients and certain factors (i.e., age, etiology, and concomitant medications) modulate the BMI Z-score distribution to some extent.

Given the frequency of pretreatment obesity, attention should also be given to complications due to medi-

cation or a sedentary lifestyle that can occur in some patients with epilepsy.³¹⁻³⁹ Examining a patient's BMI at the time of diagnosis is an important step in recognizing obesity and avoiding complications associated with weight gain. Nationally published guidelines base initial AED selection on considerations of efficacy/effectiveness, safety, tolerability, pharmacokinetic properties, formulation, and expense.⁴⁰ Our results indicate obesity status should be considered as another important factor in AED selection for initial monotherapy. In short, obesity is a common comorbidity; the problem segregates according to etiology and concomitant medication, and becomes more frequent in adolescents. Future studies are needed to determine the etiology of obesity in patients with new onset epilepsy but identifying these at-risk groups should help physicians recognize this comorbidity and address obesity to improve adherence and the overall health of their patients.

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Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.¹⁻³

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.