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Associations of overweight and obesity with drug-resistant epilepsy

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ABSTRACT

Background: Obesity and overweight have been well established as comorbidities of epilepsy in adults. However, the effects of overweight and obesity on the risk of adult drug-resistant epilepsy (DRE) has not been fully assessed. Thus, the objective of this study was to investigate the relationships between categories of body mass index (BMI) and DRE.

Methods: This was a case-control study. Patients with epilepsy hospitalized for Video electroencephalogram were included in the study from 2015 to 2020. Low/normal weight, overweight, and obesity were defined as BMI<23 and 23-24.9 and ≥25 kg/m^2, respectively. The proportions of patients diagnosed with DRE in each category were calculated.

Results: A total of 1272 patients with drug-responsive epilepsy and 345 patients with DRE were included in this study. More men than women had DRE (P=0.012). Higher proportions of patients with DRE had a history of status epilepticus (P<0.001), CNS infection (P=0.027), developmental delay (P=0.001), and comorbidity (P<0.001). Obesity (BMI≥25 kg/m^2) was associated with an increased risk of DRE (adjusted OR, 2.339; 95% CI, 1.724-3.171). No significant increase in the risk of DRE was found to be associated with overweight. Further stratified analyses by valproic acid (VPA) treatment attenuated the obesity-DRE relationship, but the associations remained statistically significant (adjusted OR, 1.79; 95% CI, 1.15-2.80).

Conclusion: Obesity, but not overweight, potentially plays a role in DRE, although confounders, such as antiseizure medications (ASMs) use, need to be explored. In the future, well-designed trials are needed to elucidate this issue.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders, and it affects approximately 68 million people worldwide [1]. One-third of patients with epilepsy require more effective antiseizure medications (ASMs) because their epileptic seizures remain uncontrolled with the currently available medical treatment, which leads to significant morbidity and imposes a heavy healthcare-related economic burden [2]. Consequently, there is a need to identify the risk factors associated with drug-resistant epilepsy (DRE) and develop adjuvant therapies.

Overweight/obesity is considered a common comorbidity in both children and adults with epilepsy [3,4]. Overweight and obesity are also recognized as important modifiers of the severity, treatment response, and prognosis of several chronic diseases [5,6]. Several studies have documented associations between overweight and/or obesity and epilepsy. In a cross-sectional survey of patients with epilepsy, the proportion of patients with overweight/obesity was higher in the group with DRE than in the group with drug-responsive epilepsy (DSE) (36.9% versus 24.6%) [4]. In newly diagnosed childhood absence epilepsy patients, the body mass index (BMI) z score predicts differential drug response, which is independent of pharmacokinetic differences [7]. Preclinical data also provide indirect evidence [8-11].

Overweight and obesity are potentially preventable risk factors for DRE. Thus, further investigation into overweight and obesity in people with epilepsy is needed to inform the development of preventive strategies and reduce the incidence of DRE. To our knowledge, few studies have assessed how overweight and obesity influence the risk of DRE in people with epilepsy. Therefore, we sought to examine how overweight

Abbreviations: ASM, antiseizure medication; DRE, drug-resistant epilepsy; DSE, drug-responsive epilepsy; BMI, body mass index; VPA, valproic acid; CBZ, carbamazepine; PB, phenobarbitone; TPM, topiramate; LEV, levetiracetam; OXC, oxcarbazepine; PH, phenytoin; LTG, lamotrigine; VEM, video electroencephalogram.

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and obesity influence the risk of DRE.

2. Methods

2.1. Study design and patient selection

This was a retrospective population-based study. Patients with epilepsy hospitalized for Video electroencephalogram (VEM), which was used to assist diagnosis, monitor effect of ASMs and for preoperative localization of epileptic foci, in the Neurology Department of West China Hospital, Sichuan University from January 2015 to March 2020 were consecutively included. Outcomes of ASM treatment were categorized as drug resistance, seizure freedom, and undetermined. Participants were followed until October 2020, death, or the diagnosis of DRE, DSE, or undetermined. Patients were followed up by telephone interviews or face-to-face assessments in the outpatient department. Data analysis was performed from November to December 2020.

The inclusion criteria were as follows: 1) age ≥18 years and 2) epilepsy diagnosed according to the 2017 guidelines of the International League Against Epilepsy (ILAE) [12,13]. The exclusion criteria were the existence of any of the following: 1) psychogenic nonepileptic seizures; 2) acute symptom onset; 3) pregnancy or lactation; 4) chronic medical issues (cancer, hepatic or kidney failure); 5) ketogenic diet treatment, comorbidities (thyroid disease, Cushing syndrome) or existing treatment (steroids, glucocorticoids) known to affect weight; 6) persistent poor adherence to treatment (unrelated to tolerability); and 7) a lack of baseline height or weight data. The protocol was approved by the Ethics Committee of West China Hospital. Written informed consent was obtained from all patients.

Patients were considered to have DRE if adequate trials of two tolerated pharmacological interventions (whether as monotherapies or in combination) failed to achieve sustained seizure freedom; adequate trials were defined as ASM treatment having been dispensed for at least 3 months [14]. DSE was defined as seizure freedom for at least 12 months or three times the longest pretreatment inter-seizure interval [14].

2.2. Data collection and the definitions of overweight and obesity

Patient information was extracted from the database established at our hospital. For each patient, baseline characteristics and risk factors for DRE were recorded on admission. The following variables was collected: age, sex, race, current smoking status, age at seizure onset, epilepsy duration, seizure type, etiology, duration of epilepsy pretreatment, family history of epilepsy, febrile seizures, perinatal injury and craniocerebral injury, developmental delay, history of status epilepticus or CNS infection and metabolic variables. Comorbidities such as anxiety and depression were assessed with the Generalized Anxiety Disorder-7 and Neurological Disorders Depression Inventory for Epilepsy scales, respectively. Height and weight data were collected on admission. Standing height was measured without shoes using a stadiometer. Weight was measured without shoes but in light clothing.

According to the definitions of the World Health Organization, BMI was calculated as weight in kilograms divided by height in meters squared and was categorized for individuals in Asia as follows: underweight, BMI less than 18.5 kg/m^2; normal weight, BMI of 18.5-22.9 kg/m^2; overweight, BMI of 23 to 24.9 kg/m^2; obesity I, BMI of 25 to 29.9 kg/m^2; and obesity II of 30 kg/m^2 or greater [15].

2.3. Statistical analysis

We described the baseline demographic and clinical characteristics of the study population based on the presence or absence of DRE. Continuous variables are summarized as the median and interquartile range (IQR) (nonnormal distribution) and were compared using the Mann-Whitney U test. Categorical variables are described as numbers (n) with a percentage (%), and significant differences between 2 or 3 groups were analyzed by Pearson's χ^2 test.

We constructed multivariable logistic regression models to assess the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to evaluate the association between BMI and DRE before and after adjusting for the following potential confounders based on the covariates with $P<0.1$ in the univariate model: sex, age at onset, duration of epilepsy, developmental delay, history of status epilepticus, CNS infection, febrile seizures, and comorbidity. All data analysis was performed with SPSS software version 25.0 (IBM, Armonk, NY, USA). All P values were two-sided, and $P<0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline demographics and clinical characteristics

Fig. 1 showed the flowchart of included patient inclusion. A total of 8271 potential study participants from January 2015 to March 2020 were consecutively included. We included 2578 patients with epilepsy were included and followed up after a preliminary round of exclusion. We excluded 961 patients because they did not meet the diagnostic criteria for DRE and DSE. A total of 1617 patients were included in the final analysis. The detailed clinical and demographic characteristics are summarized in Table 1. Of these patients, 1272 (78.7%) had DSE. More men than women had DRE (52.0% versus 44.3%, P=0.012). The median age at onset was 15 (IQR: 9-22) years, and the duration of epilepsy was 11 (IQR: 7-17) years in patients with DRE.

Higher proportions of the group of patients with DRE than the group with DSE had a history of status epilepticus ($P<0.001$), a history of CNS infection (P=0.027), and developmental delay (P=0.001). A greater proportion of patients with DRE had anxiety and depression (8.7% versus 3.1%). The median BMI was higher in DRE patients than in DSE patients ($P<0.001$). There were no differences in terms of race, smoking, drinking, age, seizure type, etiology, duration of epilepsy pretreatment, family history of epilepsy, perinatal injury, history of febrile seizures, craniocerebral injury history, previous surgery for epilepsy, or metabolic variables between the DSE and DRE groups.

The differences in the proportions of overweight and obesity between patients with epilepsy and the general population were also calculated. We used the freely available data published in the China Health and Nutrition Survey (CHNS) database for 2015 [16]. We matched the general population and patients with epilepsy for age and redefined the overweight and obesity to ensure comparability with the results. We found that the group with epilepsy included in this study had a lower proportion of individuals with overweight and obesity than the general population (23.1% versus 42%) in 2015 (Supplementary Table 1). However, the proportion of patients with obesity in the groups with DRE was significantly higher than that in the general population (17.9% versus 7.1%).

3.2. Relationships between ASM use and BMI in patients of this study

ASMs are known to influence weight. To clarity the influence of ASM on the relationship between BMI and DRE in the present study. We further analyzed the association between baseline ASM use and BMI in patients (Table 2). Those ASMs associated with weight gain include valproic acid (VPA), gabapentin, carbamazepine (CBZ), phenobarbitone (PB), and possibly pregabalin. The ASMs associated with weight loss include topiramate (TPM) and zonisamide. Levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PH), and lamotrigine (LTG) are not thought to affect weight [4,7,17]. Because very few patients were treated with gabapentin, pregabalin and zonisamide, we mainly focused on the differences in BMI distributions among patients treated with VPA, CBZ, TPM, and PB. Of the included patients, 336 were newly diagnosed untreated patients with epilepsy, 582 were monotherapy-treated

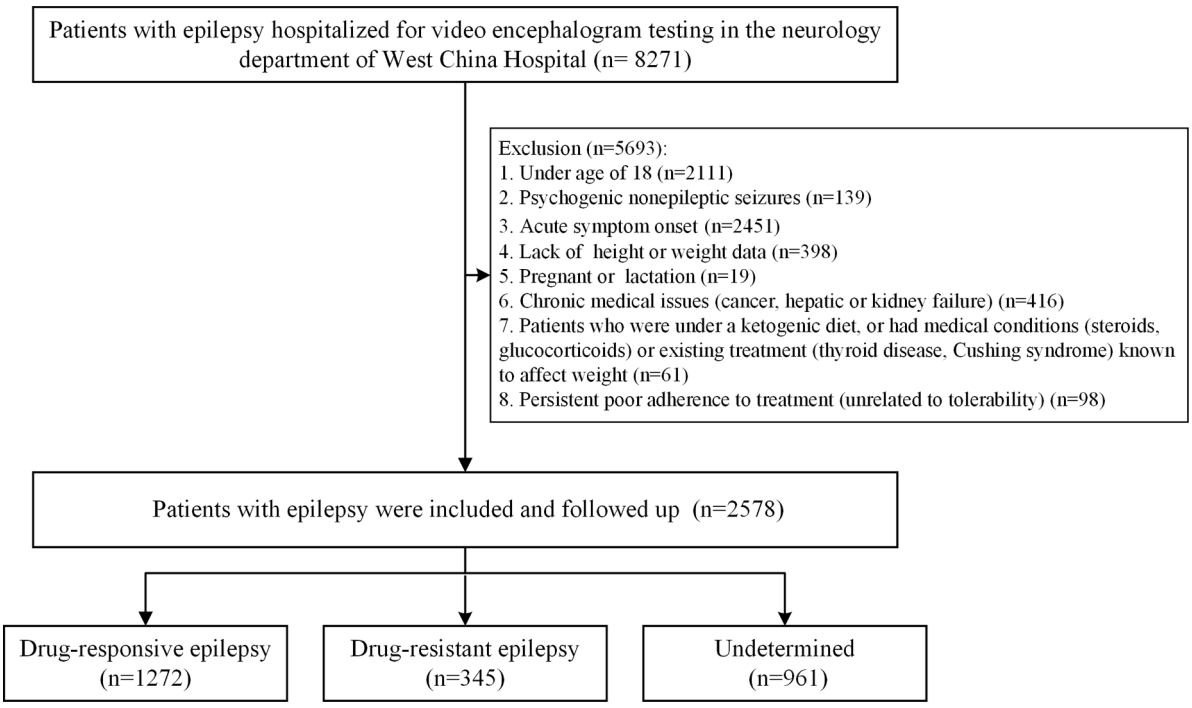

Fig. 1. Flow chart of patient selection.

patients, and 699 were polytherapy-treated patients. Overweight/-obesity was more prevalent in patients treated with VPA ($P<0.001$). There were no differences in BMI distribution among patients treated with CBZ, TPM, and PB.

3.3. Univariate and multivariable analyses of the association between BMI and DRE

Univariate binary regression (Table 1) showed that sex ($P=0.012$), age at onset ($P<0.001$), duration of epilepsy ($P<0.001$), BMI ($P<0.001$), developmental delay ($P=0.001$), history of status epilepticus ($P<0.001$), history of CNS infection ($P=0.027$) and comorbidity ($P<0.001$) were associated with DRE.

Multivariate regression analysis revealed that after adjustment for confounding variables, BMI≥25 kg/m^2 ($P<0.001$), age at onset ($P<0.001$), duration of epilepsy ($P<0.001$), developmental delay ($P=0.035$), history of status epilepticus ($P=0.004$) and comorbidity ($P<0.001$) were independently and simultaneously associated with DRE (Table 3).

3.4. Subgroup analysis

The above results suggested that only baseline VPA use had an impact on BMI in this study (Table 2). Thus, we stratified patients by VPA use to explore the association between BMI and DRE (Table 4). Among the patients who used VPA at baseline, obesity was associated with the risk of DRE (adjusted OR, 2.61; 95% CI, 1.66-4.10). Furthermore, in patients who were not treated with VPA at baseline, we also found an association between obesity and DRE (adjusted OR, 1.79; 95% CI, 1.15-2.80).

Fig. 2 showed the probability of DRE stratified by BMI category in patients treated and not treated with VPA. The J-shaped relationship between BMI and DRE seems to be monotonic with increased BMI in multivariable analyses, which used BMI as a continuous variable and adjusted for confounding variables.

4. Discussion

4.1. Main results

This study included 1617 patients with DRE or DSE investigated the association between obesity and DRE. Patients showed that obesity, but not overweight, was associated with DRE. The risk of DRE was higher among patients with epilepsy and obesity than among adults without obesity. The associations were independent of sex, age at onset, epilepsy duration, developmental delay, history of status epilepticus, CNS infection, febrile seizures, and comorbidity.

4.2. Overweight and obesity in adults with epilepsy

Overweight/obesity affects multiple organ systems and is an independent risk factor for the development of cardiovascular disease, hypertension, diabetes and cancer. Overweight/obesity is also a common comorbidity in patients with epilepsy. A survey of the health status and behavior patterns of adult epilepsy patients showed that 34.0% of them exercised less and 23.7% were more obese than the healthy population, even if their seizures were under control [17].

ASMs influence body weight, and some cause obesity [7]. In our study, the proportions of patients with overweight and obesity were higher in the group with polytherapy. The group treated with VPA at baseline had higher proportions of patients with overweight and obesity, which is consistent with previous studies [4,18]. VPA treatment changes sex hormone levels and thyroid function, which in turn may affect weight gain [19]. Other ASMs may also affect leptin and related hormones [20]. There are also indications that epilepsy itself affects hormone levels [20]. Adipose tissue is also an active endocrine organ and can enhance the effect of ASMs on hormone balance. TPM has traditionally been associated with weight loss. However, in this sample, there was no difference in BMI distribution between patients treated and not treated with TPM. This finding may be due to polytherapy treatment and selective bias regarding the use of TPM among patients with comorbid obesity in clinical practice.

Table 1
Demographic and clinical characteristics in patients with epilepsy.

Characteristic	DSE (n=1272)	DRE (n=345)	*P*-value
Sex, female, n (%)	661(52.0)	153(44.3)	0.012
Race, Han, n (%)	1217(95.7)	328(95.1)	0.630
Smoking, n (%)	164(12.9)	52(15.1)	0.291
Drinking, n (%)	98(7.7)	30(8.7)	0.545
Age, y, median (IQR)	26(21-35)	27(22-33)	0.580
Age at onset, y, median (IQR)	18(14-27)	15(9-22)	<0.001
Duration of epilepsy, y, median (IQR)	6(3-10)	11(7-17)	<0.001
Body mass index, kg/m^2	21.76(19.47-23.99)	22.83(20.20-26.04)	<0.001
Seizure type, n (%)			0.820
Focal	991(77.9)	274(79.4)	
Generalized	239(18.8)	61(17.7)	
Unknown	42(3.3)	10(2.9)	
Etiology [a,b] n (%)			0.290
Structural	575(45.2)	167(48.4)	
Nonstructural	697(54.8)	178(51.6)	
Duration of epilepsy pretreatment, n (%)			0.158
≤12 months	822(64.6)	237(68.7)	
>12 months	450(35.4)	108(31.3)	
Family history of epilepsy, n (%)	6(0.5)	2(0.6)	0.800
Perinatal injury, n (%)	54(4.2)	18(5.2)	0.438
History of febrile seizure, n (%)	84(6.6)	33(9.6)	0.060
Craniocerebral injury history, n (%)	158(12.4)	41(11.9)	0.788
Developmental delay, n (%)	20(1.6)	16(4.6)	0.001
History of status epilepticus, n (%)	15(1.2)	15(4.3)	<0.001
History of CNS infection, n (%)	58(4.6)	26(7.5)	0.027
Previous surgery for epilepsy, n (%)	97(7.6)	20(5.8)	0.245
Comorbidity, n (%)			<0.001
Anxiety and depression	39(3.1)	30(8.7)	
Sleep disorders	82(6.4)	18(5.2)	
Headache	4(0.3)	3(0.9)	
Sleep apnea	5(0.4)	2(0.6)	
Others	85(6.5)	35(10.7)	
Metabolic variables, median (IQR)			
SBP, mmHg	116(108-124)	117(107-125)	0.376
DBP, mmHg	75(70-82)	76(70-82)	0.157
Glucose, mmol/L	4.70(4.45-4.98)	4.73(4.45-5.07)	0.193
HDL-C, mmol/L	1.35(1.14-1.62)	1.39(1.12-5.07)	0.146
LDL-C, mmol/L	2.24(1.88-2.74)	2.30(1.84-2.75)	0.758
Triglyceride, mmol/L	0.82(0.60-1.23)	0.88(0.62-1.29)	0.106

Abbreviations: DSE, drug-responsive epilepsy; DRE, drug-resistant epilepsy; IQR, interquartile range; CNS, central nervous system; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

[a] No patients had a metabolic or immune etiology in this study.

[b] Others included patients with hearing loss, chronic gastritis, hypertensive disease, and patent foramen ovale et al.

4.3. Relationships between obesity and DRE

This study indicated that obesity, but not overweight, was associated with DRE. This effect was not completely mediated by ASM use, as we investigated the epilepsy group by stratifying patients into groups with or without VPA use.

There have been few investigations into the association between obesity and DRE. Several animal studies have provided evidence of a possible association between obesity and seizures. Adiponectin-deficient mice fed a high-fat diet had increased seizure severity, and in another study, the administration of adiponectin reduced kainic-induced excitotoxicity [8]. Kang et al. found that kainic acid-treated mice fed a high-fat diet showed a greater number of seizure spike-trains and exacerbated neuronal death of the hippocampus [9]. Moreover, *ob/ob* mice were vulnerable to seizure-induced hippocampal neuronal

Table 2
Association of baseline ASM use and BMI.

Characteristic	N	BMI< 23	BMI (23-24.9)	BMI≥25	*P*-value
All	1617	998 (61.7)	288(17.8)	331 (20.5)	
VPA use, n (%)					<0.001
With VPA	503(31.1)	254 (25.5)	99(34.4)	150 (45.3)	
Without VPA	1114 (68.9)	744 (74.5)	189(65.6)	181 (54.7)	
CBZ use, n (%)					0.342
With CBZ	125(7.7)	76(7.6)	18(6.3)	31(9.4)	
Without CBZ	1492 (92.3)	922 (92.4)	270(93.8)	300 (90.6)	
TPM use, n (%)					0.778
With TPM	144(8.9)	85(8.5)	27(9.4)	32(9.7)	
Without TPM	1473 (91.1)	913 (91.5)	261(90.6)	299 (90.3)	
PB use, n (%)					0.170
With PB	15(0.9)	7(0.7)	2(0.7)	6(1.8)	
Without PB	1602 (99.1)	991 (99.3)	286(99.3)	325 (98.2)	
Others [a], n (%)	6(0.3)	5(0.5)	1(0.3)	0	-[b]

Abbreviations: ASM, antiseizure medication; N, number; BMI, body mass index; VPA, Valproic acid; CBZ, carbamazepine; TPM, topiramate; LEV, levetiracetam; OXC, oxcarbazepine; LTG, lamotrigine.

[a] The Other category included lacosamide (n=4) and pregabalin (n=2).

[b] Because of the small size of the subgroup, no statistical analysis was performed.

Table 3
Multiple logistic regression analysis of variables associated with DRE in epilepsy patients.

Variable	B	S.E.	Sig	Exp (B)	95%CI for EXP (B)[a]	
					Lower	Upper
BMI≥25	0.850	0.155	<0.001	2.339	1.724	3.171
Age at onset	-0.032	0.007	<0.001	0.969	0.956	0.982
Duration of epilepsy	0.350	0.009	<0.001	1.036	1.018	1.054
History of status epilepticus	1.222	0.419	0.004	3.395	1.494	7.716
Developmental delay	0.778	0.369	0.035	2.176	1.057	4.482
Comorbidity	0.561	0.160	<0.001	1.753	1.282	2.397

Abbreviations: BMI, body mass index; Exp(B), the exponent of B; DRE, drug-resistant epilepsy.

[a] Model was adjusted for sex, age at onset, BMI, duration of epilepsy, developmental delay, history of status epilepticus, CNS infection, febrile seizures, and comorbidity.

Table 4
The correlation between DRE and BMI was stratified by VPA use in patients.

BMI	No. (%) Study Participants		OR (95%CI) [a]	
	DSE (n=1272)	DRE (n=345)	Adjusted	*P*-value
With VPA use				
<23	184(56.3)	70(39.8)	1.0	
23-24.9	68(20.8)	31(17.6)	1.19(0.69-2.03)	0.536
≥25	75(22.9)	75(17.6)	2.61(1.66-4.10)	<0.001
Without VPA use				
<23	638(67.5)	106(62.7)	1.0	
23-24.9	164(17.4)	25(14.8)	0.98(0.59-1.62)	0.924
≥25	143(15.1)	38(22.5)	1.79(1.15-2.80)	0.011

Abbreviations: BMI, body mass index; OR, odds ratio; DSE, drug-responsive epilepsy; DRE, drug-resistant epilepsy; VPA, valproic acid.

[a] Model was adjusted for sex, age at onset, duration of epilepsy, developmental delay, history of status epilepticus, CNS infection, febrile seizures, and comorbidity.

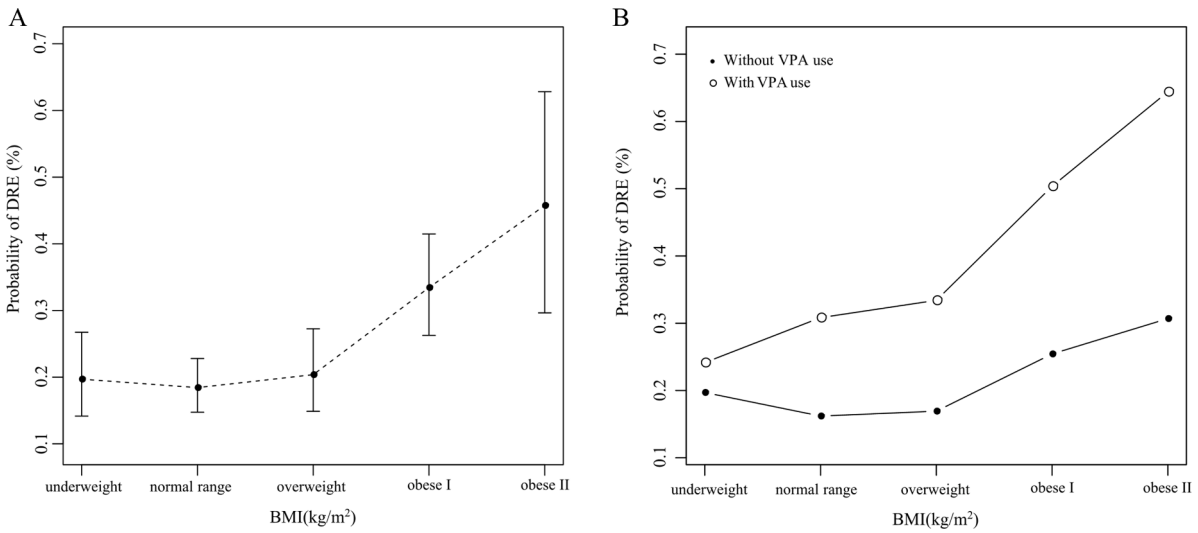

Fig. 2. Adjusted data for the rate of DRE plotted against BMI and fitted with a curve indicating the J-shaped relationship between BMI and DRE. (A) Adjusted OR and 95% CI for DRE according to BMI. (B) Adjusted OR for DRE according to BMI was stratified by VPA use in patients. Models were adjusted for sex, age at onset, BMI, duration of epilepsy, developmental delay, history of status epilepticus, CNS infection, febrile seizures, and comorbidity. Abbreviations: DRE, drug-resistant epilepsy; VPA, valproic acid; BMI, body mass index.

damage, and the intracerebral injection of leptin had a neuroprotective effect on the hippocampal neurons [10]. In two rodent animal models, both the direct injection of leptin into the cortex and the intranasal administration of leptin exerted anticonvulsant effects [11].

4.4. Mechanism underlying the associations of obesity with DRE

The proportion of obesity was lower in patients with epilepsy and in the mean Chinese population than in patients with DRE. What is the mechanism underlying these observations? Obesity causes an inflammatory response and elevates the levels of neuroinflammatory mediators, including interleukin-6, interleukin-8, tumor necrosis factor, and C-reactive protein [21-23]. Adipocytes are altered as weight increases, eventually releasing proinflammatory adipokines. Seizures also lead to inflammation. Therefore, obesity and epilepsy combine to result in chronic inflammatory state, which may create abnormal microenvironment that results in a reduced drug response.

Obesity is also related to the neuroendocrine control of energy intake and expenditure, which is affected by the activation of leptin and insulin signals and acts on the hypothalamus [24]. The association between obesity and neurological dysfunction is influenced by a multitude of neurotransmitters. The mTOR signaling pathway, which plays an important role in adipocyte metabolism and drug resistance in epilepsy, may also be a potential mechanism that links obesity and drug resistance [22,25]. The interaction between a baseline BMI indicating overweight/obesity and DRE remains to be fully characterized. Moreover, regardless of the exact mechanisms underlying the association between obesity and DRE, there are means for neurologists to prevent and treat DRE, including through a more individualized approach.

4.5. Limitations

Our study has several limitations. The first limitation is mainly related to its retrospective nature, potential recall bias existed due to its retrospective design cannot be avoided. Second, not all of the enrolled patients were newly diagnosed. Thus, the baseline BMI in this study could have been affected by drugs, and causal relationships cannot be inferred, although we performed analyses stratified by ASM use to clarify the effects of baseline ASMs on BMI. Future studies should focus on the dynamic monitoring of BMI in patients to explore the relationships between obesity and DRE. In addition, because of interactions between genetic and environmental factors, the cause of DRE may be multidimensional. Although we controlled for a broad range of factors potentially associated with the risk of DRE, the existence of other possible confounding factors, such as exercise, nutrition, and socioeconomic factors, may have biased the results. Additionally, BMI was used as the indicator of adiposity, although it is practical, BMI does not take into account muscle mass or fat distribution. Considering these limitations, further well-designed prospective investigations are needed to confirm these results.

5. Conclusion

In conclusion, we found in the present study that obesity, but not overweight, was associated with DRE. The risk of DRE was higher among patients with epilepsy with obesity than among adults without obesity. With regard to the clinical treatment of patients with epilepsy, obesity should be taken into account. Physical activity, diet, lifestyle counseling, and the selective use of ASMs to maintain normal weight and avoid further weight gain can provide potential protection against DRE. Further high-quality prospective studies with unselected populations that taken into account sociodemographic and family factors are needed to confirm these findings and the causal relationship between obesity and DRE.

Declaration of Competing Interests

The authors report no conflicts of interest in relation to this work.

Acknowledgment

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.07.019.

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