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Causal Relationships among Sedentary Behavior, Physical Activity, and Epilepsy: A Mendelian Randomization Analysis

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Abstract: *This study aimed to investigate the causal relationship between sedentary behavior, physical activity, and epilepsy using two-sample Mendelian randomization. Genome-wide data were utilized for an association analysis, with sedentary behavior and physical activity as exposure factors and epilepsy as the outcome variable. MR-Egger, weighted median, and random-effects IVW methods were employed for the two-sample Mendelian randomization analyses, accompanied by heterogeneity tests, horizontal multivariate analyses, and sensitivity analyses. The results of MR-Egger regression, weighted median method, and random effect IVW method were 1.006 (0.994 - 1.018), 1.000 (0.996 - 1.004), and 1.001 (0.999 - 1.004), respectively, indicating that sedentary behavior and physical activity are risk factors for epilepsy development, and there is a positive association between them. In conclusion, there is a causal relationship between sedentary behavior, physical activity, and the risk of epilepsy.*

Keywords: *Sedentary Behavior; Physical Activity; Epilepsy; Mendelian Randomization*

1. Introduction

Sedentary behavior is defined as any waking behavior characterized by an energy expenditure of ≤1.5 METs (metabolic equivalent, a unit indicating the intensity of physical activity) while in a sitting or reclining position, specifically including activities such as watching television, using a computer, and driving [1]. Physical activity refers to any physical movement produced by skeletal muscles that requires energy expenditure [2]. Technological advancements have led to significant lifestyle changes, resulting in an increase in sedentary behavior and a decrease in physical activity. Ekelund et al [3] demonstrated that sedentary behavior is associated with higher all-cause mortality, while physical activity reduces this risk.

Epilepsy is a chronic brain disorder characterized by recurrent seizures, defined as at least two unprovoked seizures separated by more than 24 hours or one with a high risk of recurrence, or a diagnosis of epileptic syndromes. A patient is considered cured when seizure-free for 10 years and off medication for 5 years [4]. As the most prevalent serious chronic neurological disorder, epilepsy affects 70 million people worldwide, with significant cognitive, social, psychological, and economic impacts [5,6]. Existing studies have shown that extracerebral secretions can be reduced or disappear during exercise, leading to a reduction in seizure recurrence. Thus, physical activity is encouraged in people with epilepsy [7,8]. However, patients with epilepsy face many barriers to reducing sedentary behavior and engaging in physical activity, such as comorbid anxiety and depression, fear of exercise-induced epilepsy, and the side effects of antiepileptic medications, which may prevent them from being physically active. In this context, considering physical activity as a therapeutic intervention for epilepsy patients may be biased[9]. Overall, the causal relationship between sedentary behavior, physical activity, and epilepsy remains somewhat controversial.

Mendelian randomization (MR) utilizes genetic variation as a tool based on single nucleotide polymorphisms (SNPs) from large sample genome-wide association studies (GWAS) and is widely used in epidemiology to assess potential causal relationships between exposure factors and clinical diseases[10]. Since the random assignment of alleles in individuals in MR analysis precedes the onset of disease and minimizes the effect of confounding factor bias [11], it improves the accuracy of the study [12]. Therefore, this study employed Mendelian randomization to explore the causal relationship between sedentary behavior, physical activity, and epilepsy, aiming to provide new insights for epilepsy prevention and treatment.

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2. Information and Methods

2.1 Study Design

In this study, SNPs from GWAS were used as the basis for two-sample Mendelian randomization analysis. Sedentary behavior and physical activity were the exposure factors, and epilepsy was the outcome variable to assess the correlation and causation among them. The validity of the results was tested by sensitivity analysis. To obtain reliable results, three key assumptions of MR needed to be satisfied: (1) the correlation assumption: the SNPs must have a close correlation with sedentary behavior and physical activity; (2) the independence assumption: the SNPs should not be correlated with known confounders; and (3) the exclusivity assumption: the SNPs affect epilepsy only through sedentary behavior and physical activity and are not directly related to epilepsy. The specific process is illustrated in Figure 1.

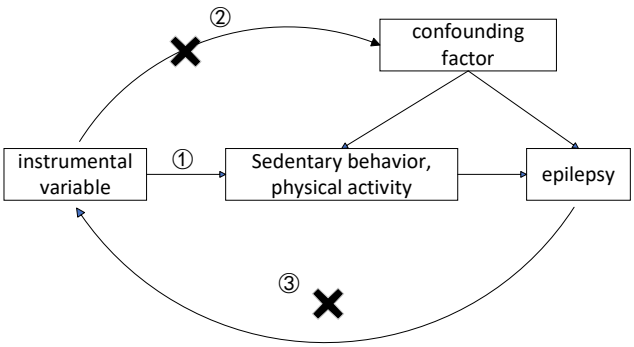

Figure 1: Schematic of the two-sample Mendelian randomization analysis

2.2 Source of Data

The data of epilepsy (ID: ebi-a-GCST90038645) was obtained from the IEU OpenGWAS project database, which consisted of 3,900 European population cases and 480,698 controls, with 9,587,836 SNPs. The data of exposure and outcome factors were acquired from public databases. The exposure factors, sedentary behavior and physical activity, were sourced from the UK BioBank (UKBB) with a sample size of over 500,000 people. In this study, the MR-Base platform was used to obtain the UK BioBank database data on sedentary behavior and physical activity (ID: ukb-b-5192, ukb-b-4522, ukb-b-3793). The sample sizes of the study were 437,887, 360,895, and 310,555 cases, respectively, and the number of SNPs was 9,853,867, 9,851,867, and 9,851,867. Since the data were obtained from public databases, no ethical review was involved.

2.3 Instrumental Variables

Firstly, based on the important assumption in Mendelian randomization that SNPs must have a strong correlation with sedentary behavior and physical activity, SNPs significantly correlated with epilepsy at the genome-wide level were screened ($P < 5\times10^{-8}$, $r^2 < 0.001$, genetic distance = 10000kb). Next, confounders associated with epilepsy were excluded using the Phenoscanner database. Finally, the statistical strength of the correlation between SNPs and exposure was assessed by calculating the F statistic. SNPs significantly associated with epilepsy were obtained and used as instrumental variables in this study. To determine whether the selected SNPs would cause weak instrumental variable bias in the results, the F statistic was calculated and evaluated. The F statistic was calculated as $F = R^2(N - K - 1)/(1 - R^2)$, where R^2 represents the variance of the exposure explained by the SNPs, N is the sample size of the GWAS for the exposure factor, and K is the number of SNPs. The specific formula for R^2 [13] is as follows: $R^2 = [2 \times MAF \times (1 - MAF) \times \beta^2]/[2 \times MAF \times (1 - MAF) \times \beta^2 + 2 \times MAF \times (1 - MAF) \times N \times sx(\beta)^2]$, where MAF is the frequency of the effect allele, β is the value of the allele effect, and sx(β) is the standard deviation of the genetic effect. If $F > 10$, it indicates that the possibility of weak instrumental variable bias is low, and thus instrumental variables with $F < 10$ can be excluded.

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2.4 Two-Sample MR Analysis

This study utilized three Mendelian randomization research methods, namely MR-Egger regression, weighted median, and inverse variance weighted (IVW), for analysis. Odds ratio (OR) and 95% confidence interval were used as evaluation indexes, and the test level $\alpha = 0.05$. The MR-Egger method is a powerful evaluation tool when the hypothesis that the direct effects of instrumental and outcome variables are independent from the correlated effects of instrumental variables and exposure factors holds, and it can provide an accurate estimation of causal effects [14]. The weighted median method indicates the validity of the results when the contribution of the instrumental variable in the genetic variance is greater than 50% [15]. The inverse variance weighting (IVW) method assumes that all IVWs are valid and combines the effects to produce a weighted total [16]. The IVW method allows for combining multiple MR results, thereby reducing the bias in the results due to the estimation of genetic variance [17]. Among the three two-sample MR statistics, the IVW method was used as the main analysis result in this study.

2.5 Sensitivity Analysis

In this study, the sensitivity of the study results was assessed by the MR-Egger method, Cochran Q test, and leave-one-out method to test for heterogeneity among instrumental variables. The results of the MR-Egger method can be affected by pleiotropy or heterogeneity and can be used as a basis for assessing the presence of horizontal pleiotropy. The intercept is used as a reference term. When the intercept is close to zero, the results are similar to those of the IVW method; if the intercept is far from zero, it indicates a higher possibility of horizontal pleiotropy among SNPs [18]. The Cochran Q test was used to assess the existence of heterogeneity among selected SNPs. Heterogeneity was considered to exist if $P < 0.05$. The leave-one-out method involves excluding individual SNPs one by one and calculating the combined effect of the remaining SNPs to determine whether a single SNP has a disproportionate effect on the outcome [19].

3. Results

3.1 Screening of Instrumental Variables and Determination of Weak Instrumental Variable Bias

In this study, 200 epilepsy-related SNPs from GWAS were finally screened as instrumental variables. The selected SNPs were significantly correlated and independent from each other ($P < 5\times10^{-8}$, $r^2 < 0.001$). Moreover, all the selected instrumental variables had a strong correlation with epilepsy with $F > 10$, indicating that the possibility of bias in the results due to weak instrumental variables was small and the results were reliable.

3.2 Results of Two-Sample MR Analysis

The results of the random effects IVW method in this study ($\beta = 0.001$, $sx = 0.001$, $P = 0.375$) are shown in Figure 2. It indicates that sedentary behavior and physical activity are risk factors for the development of epilepsy, with an OR value of 1.001 (95% CI: 0.999 - 1.004), suggesting that the occurrence and development of sedentary behavior and physical interactions can increase the epilepsy risk. The results of the three Mendelian randomizations are presented in Table 1, showing that the results obtained by the three analysis methods were similar. The direction of causal effects obtained by the various Mendelian randomization analysis methods is illustrated in Figure 3.

Table 1 Results of three Mendelian randomization analysis methods.

Method	nSNP	β	$s_{\bar{x}}$	P	OR(95%CI)
MR Egger	200	0.006	0.006	0.348	1.006(0.994-1.018)
Weighted median	200	<0.001	0.002	0.968	1.000(0.996-1.004)
Inverse variance weighted(multiplicative random effects)	200	0.001	0.001	0.375	1.001(0.999-1.004)

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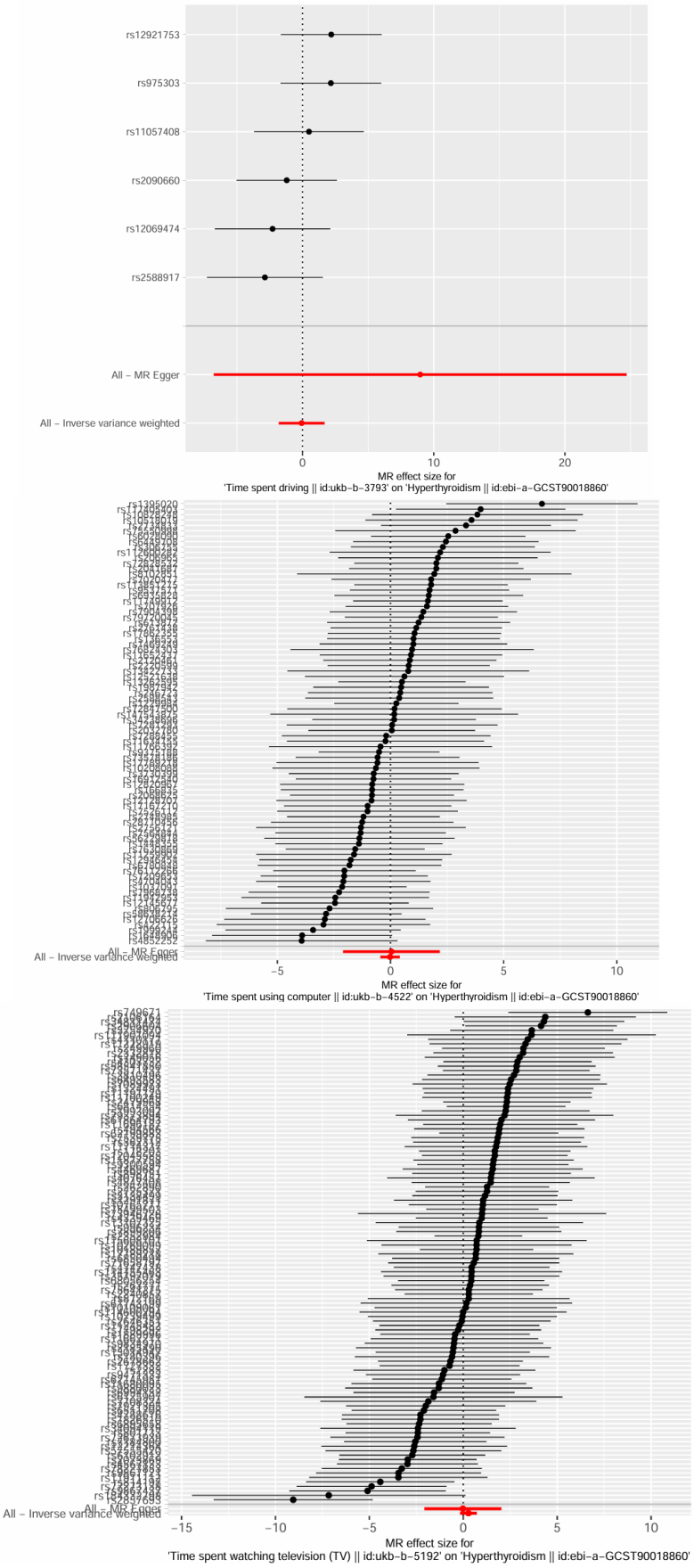

Figure 2 Forset plot of two-sample Mendelian randomization analysis

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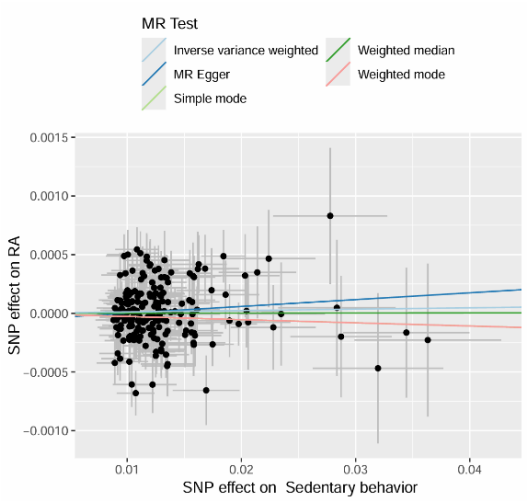

Figure 3 Scatter plot of two-sample Mendelian randomized analysis

3.3 Sensitivity Analysis

3.3.1 Horizontal Pleiotropy Test

The intercept term of the MR-Egger's method was used to assess horizontal pleiotropy. The results showed P = 0.442 (> 0.05), indicating that there was no evidence of horizontal pleiotropy among the selected SNPs and that the selected instrumental variables were reliable.

3.3.2 Heterogeneity Test

After the Cochran Q test, P = 0.028 (< 0.05), indicating that there was some heterogeneity among the selected instrumental variables. Therefore, the random effects IVW method was selected as the main outcome of this study. Additionally, the results of the funnel plot showed that the distribution of the causal effects of the selected instrumental variables was basically symmetrical, and no bias was found to exist (Figure 4).

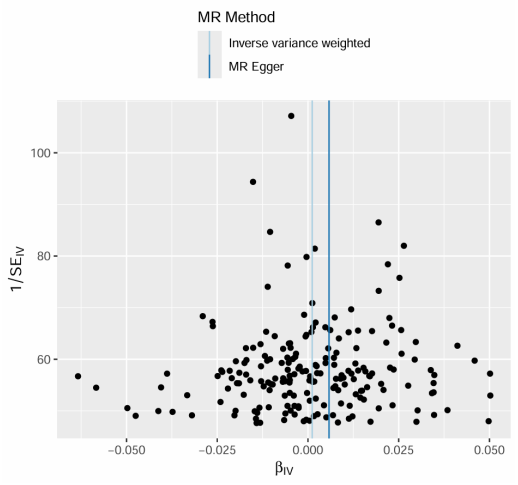

Figure 4: Funnel plot of two-sample Mendelian randomized analysis

3.3.3 Leave-One-Out Sensitivity Analysis

The leave-one-out method analysis evaluated the results by leave-one-out sensitivity analysis. Individual SNPs were excluded one by one, and the impact on the overall causality was analyzed. The results showed that no SNP sites had a significant impact on the overall causality (Figure 5).

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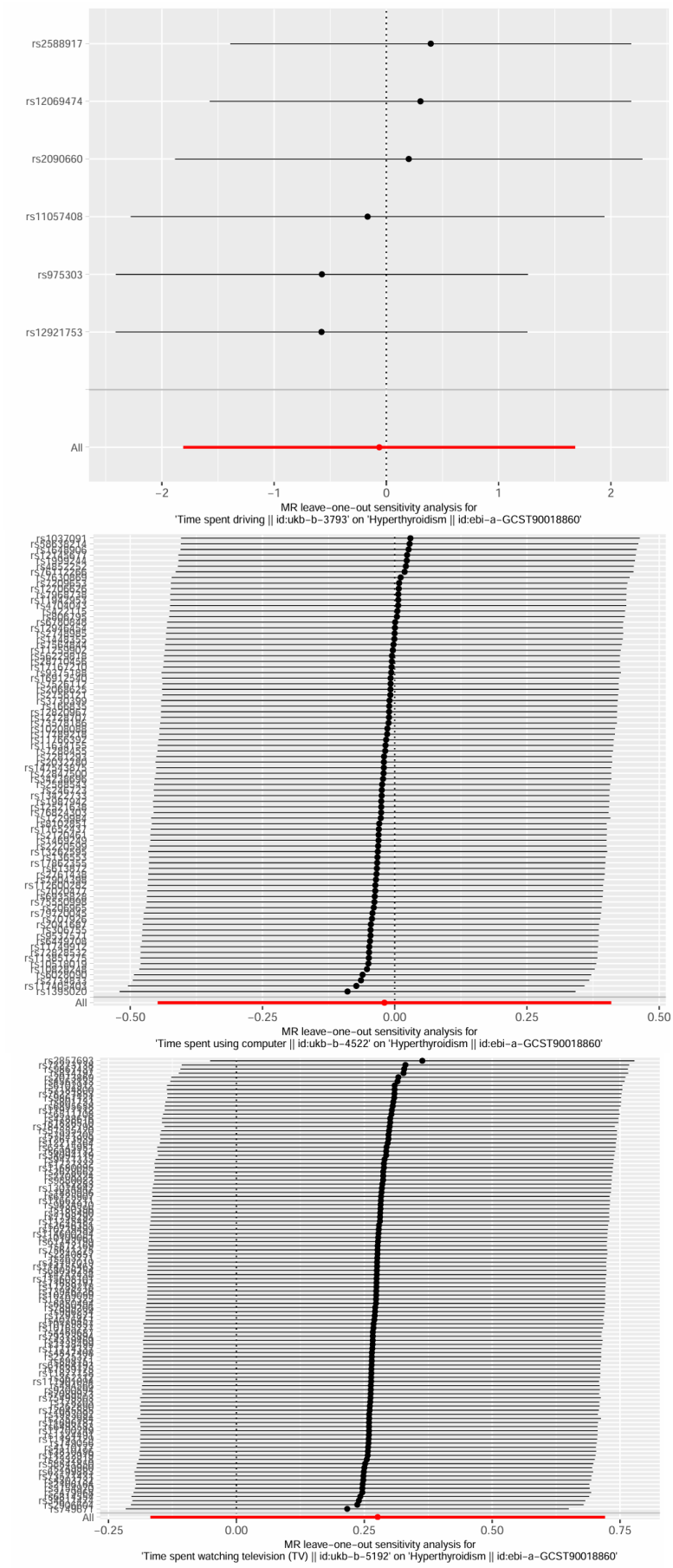

Figure 5: Result of"leave-one-out"sensitivity analysis

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4. Discussion

This study employed two-sample Mendelian randomization to assess the causal relationship between sedentary behavior, physical activity, and the risk of epilepsy. The results demonstrated a positive association between sedentary behavior, physical activity, and the risk of epilepsy in the European population, indicating that longer periods of sedentary behavior and reduced physical activity are risk factors for epilepsy.

This study is consistent with the findings of previous observational studies, which suggested that sedentary behavior promotes epileptogenesis and increased physical activity reduces the risk of epileptogenesis. For example, Irene Dustin et al [20] included 30 outpatients with an average of six seizures per month to explore the relationship between activity and the development of epilepsy and found a positive correlation between the two. Nathalia Volpato et al [21] conducted a cross-sectional study with 58 subjects and showed that physical activity significantly improved the quality of life of epilepsy patients. All these studies imply a causal relationship between sedentary behavior, physical activity, and epilepsy, and this study further confirms that reducing sedentary behavior and increasing physical activity can decrease the risk of epilepsy through the two-sample Mendelian randomization method.

Previous studies have also shown age-dependent differences in seizure types, as well as in physical activity and sedentary levels. There are variations in sedentary behavior and physical activity among children and adolescents, adults, and middle-aged and elderly populations [9]. Hence, age affects the frequency of sedentary behavior and physical activity in epilepsy patients.

Due to the characteristics of Mendelian randomization, such as causal significant correlation, small potential effect of confounders, and being unaffected by reverse causality and having a study design similar to random assignment [22], the results of this study can avoid being influenced by confounders or other biases, demonstrating a clear correlation between sedentary behaviors, physical activity, and epilepsy. The consistency of the results obtained from the three statistical methods of Mendelian randomization analysis in this study further supports the reliability of the findings.

However, this study has several limitations. Firstly, the “exposure - outcome” data in this study were only related to the European population, which may be affected by certain geographical and cultural factors, limiting the generalization of the results to other ethnic groups and countries. Moreover, the prevalence of the disease in East Asian populations differs from that in European populations. Secondly, this study only focused on the causal relationship between sedentary behavior, physical activity, and epilepsy, without considering the association between patients' age and epilepsy, which is a shortcoming of the research.

In conclusion, this study utilized Mendelian randomization to explore the causal association between sedentary behavior, physical activity, and epilepsy. The results showed a positive association between sedentary behavior, reduced physical activity, and epilepsy onset[23]. Considering the age-related differences in epilepsy incidence and the variations in sedentary behavior and physical activity among different age groups of epilepsy patients can contribute to a better understanding and prevention of epilepsy, reducing its incidence and improving the prognosis of patients. Non-pharmacological treatment approaches targeting sedentary behavior and physical activity may offer new perspectives for future epilepsy prevention and treatment.

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