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Review

Association of apolipoprotein E genotypes with epilepsy risk: A systematic review and meta-analysis

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ABSTRACT

Objective: The objective of this study was to identify the association between certain genotypes or alleles of the *APOE* (*Apolipoprotein E*) gene and the epilepsy risk.

Methods: All studies on human *APOE* genotypes associated with epilepsy were included. Separate meta-analyses were conducted between the patients with epilepsy and the control group from the following three aspects: *ε4* carriers or *ε2* carriers vs *ε3/ε3* (the *ε2/ε4* genotype was excluded), *ε4* carriers vs *ε2* carriers, and five genotypes vs *ε3/ε3*. The subgroup analysis was conducted on the ethnicity, the control group was healthy or not, and type of epilepsy.

Results: Nine studies with 2210 individuals were included. Compared with *ε3/ε3* genotype, *ε4* carriers increased the epilepsy risk (odds ratios [ORs]: 1.27; 95% confidence intervals [CI]: 1.01 to 1.59; $P = 0.042$), while *ε2* carriers had no association with epilepsy risk (OR: 0.88; 95% CI: 0.66 to 1.18; $P = 0.184$). The risk of epilepsy was 1.45 times greater in *ε4* carriers compared with *ε2* carriers (OR: 1.45; 95% CI: 1.02 to 2.04; $P = 0.037$). When the number of *APOE ε4* allele increased, the ORs increased progressively (no *ε4* alleles, OR: 0.88, 95% CI: 0.66 to 1.18; one *ε4* allele, OR: 1.25, 95% CI: 0.99 to 1.57; two *ε4* alleles, OR: 1.84, 95% CI: 0.83 to 4.10). Apolipoprotein E *ε4* carriers had a higher epilepsy risk in the population without primary diseases (OR: 1.43; 95% CI: 1.09 to 1.88), and a higher risk in Asian populations (OR: 1.67; 95% CI: 1.12 to 2.49).

Conclusions: Apolipoprotein E *ε4* allele genotype was associated with an increased epilepsy risk, which was more prominent in the Asian and the population without primary diseases. These findings may be used to guide the directions of prevention and treatment on epilepsy. Larger clinical studies are needed.

1. Introduction

Epilepsy is a group of neurological disorders characterized by epileptic seizures, whose lifetime prevalence has been measured at 7.60 per 1000 persons [1]. Despite the arrival of almost 20 new antiepileptic drugs (AEDs), the rate of seizure-free has not been improved significantly [2]. About 20–30% of patients still suffer from uncontrolled seizures, even when the appropriate pharmacotherapy has been applied [3]. Therefore, more sophisticated ways are needed to abrogate epilepsy.

There is an increasing number of patients with known genetic abnormalities causing both severe and mild epilepsies [4]. Recent studies have indicated the major effect of variation within genes in the molecular basis for epilepsy [5]. For example, pathogenic variants in *SCN8A* are associated with a wide spectrum of epilepsy phenotypes, including a treatable epilepsy with mild cognitive impairment, rare benign familial infantile seizures (BFIS), as well as severe developmental and epileptic encephalopathies (DEE) [6]. The findings of these genetic studies might potentially guide treatment options of the individual patient. The best-known example is Dravet syndrome in which more than 80% of patients have a pathogenic variant of *SCN1A*; there is evidence for the efficacy of stiripentol [7], and there are medications to avoid, especially carbamazepine, lamotrigine, and valproate [8]. Patients with a missense *SCN8A* mutation and epilepsy have been shown to respond well to high-dose phenytoin [9].

Apolipoprotein E (APOE), as the main carrier of lipids in the brain, is thought to be especially important for repair mechanisms in the central nervous system (CNS). The *APOE* gene has been proven to be a major genetic risk factor in Alzheimer's disease (AD) [10], as well as other vascular and neurodegenerative diseases [11,12]. Considering an increasing risk of epilepsy in patients with these diseases (such as AD and stroke) [5,13], it is reasonable to explore the association between the *APOE* gene and epilepsy risk. Some studies have shown an increased incidence of *APOE* ε4 alleles in patients presenting with temporal lobe epilepsy (TLE) [14,15], refractory epilepsy [16], posttraumatic seizures [17], and seizures that occur secondary to AD or cardiovascular diseases [18,19],

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while other studies have failed to support this relationship [20,21]. The contradiction may be partly due to the absence of a distinction among *APOE* genotypes.

There are three common isoforms of human *APOE*: E2, E3, and E4, which arise from three different alleles (*ε2*, *ε3* and *ε4*, respectively) [22]. Apolipoprotein E *ε3*/*ε3* is the most common genotype. Apolipoprotein E *ε4* allele tends to be considered a harmful factor, whereas the *ε2* allele is considered to be a potential neuroprotective factor [23]. Studies focusing only on *ε4* carriers may include population with *APOE ε2*/*ε4* genotype, where the opposite effect of the *ε2* allele may interfere with the outcomes. Meanwhile, there is also a dose-dependent effect for the number of *APOE ε4* alleles [24]. That means that the six possible genotypes of *APOE* (*ε2*/*ε2*, *ε2*/*ε3*, *ε2*/*ε4*, *ε3*/*ε3*, *ε3*/*ε4*, and *ε4*/*ε4*) may have different effects. Although some studies have explored the effects of different *APOE* genotypes on epilepsy risk, small sample sizes have limited the statistic effect [25].

Consequently, a systematic review and meta-analysis were required urgently to identify and investigate the association between certain genotypes or alleles of the *APOE* gene and the epilepsy risk. Since *APOE* is a modifiable factor, related studies may provide a route to the development of novel therapeutic targets for epilepsy treatment.

2. Methods

2.1. Criteria for considering studies

This systematic review has been registered in the PROSPERO public database (CRD42019121541; http://www.crd.york.ac.uk/PROSPERO).

We included all studies on human *APOE* genotypes associated with epilepsy. Eligible studies had to meet all of the following criteria: (1) inclusion of patients with a diagnosis of epilepsy or seizure disorder, (2) inclusion of a control population without epilepsy or prior seizure onset, and (3) numbers of individuals where data on *ε2*/*ε2*, *ε2*/*ε3*, *ε2*/*ε4*, *ε3*/*ε3*, *ε3*/*ε4*, and *ε4*/*ε4* genotypes were available. Exclusion criteria were as follows: (1) duplicated publications or studies with overlapping data; (2) case reports, or family studies; and (3) abstracts, letters, reviews, or other meta-analysis. There were no inclusion restrictions on the basis of patient and study characteristics, such as age, sex, and types of epilepsy. The population with a primary disease that may lead to a secondary epilepsy or seizure onset was also included.

2.2. Search methods and study selection

We searched MEDLINE, EMBASE, and Web of Science (science and social science citation index) without language restriction up to December 1st, 2018. Further relevant studies were obtained by a manual search of reference lists of all available records identified in the initial search. The authors were contacted for further information regarding unpublished trials and reports found in published databases. Keywords used in the searches were the name of *APOE* and all of its known aliases ("*APOE* OR (apolipoprotein E) OR AD2 OR LPG; APO-E; ApoE4; LDLCQ5"), and "epilepsy OR seizure*" (see online Supplementary File 1). Two reviewing authors independently decided on the selection, based on title and abstract. Any disagreement between reviewing authors was resolved by discussion. If there was still disagreement, a further reviewer and expert (Dr. Zhao) was consulted.

2.3. Data extraction and quality assessment

In the included studies, the data were extracted by two reviewers (Liang, Zhou) independently. A prepiloted data extraction form was used: study name, study characteristics, patient characteristics (ethnicity, sex, primary diseases, type of epilepsy, the age at time of first seizure), genotyping method, and genotype frequencies by categorical disease outcome. Corresponding authors would be contacted for any missing information. Discrepancies were resolved by discussion and by adjudication of a third reviewer (Zhao). If multiple publications from the same study group were found, we selected the one with the most complete and recent results.

All included studies are observational studies. Methodology quality was assessed for each predefined outcome in each study using the Newcastle-Ottawa Scale (NOS). Disagreements were settled by consensus. Scores ranged from 0 (lowest) to 9 (highest). Studies above 5 points would be included in the meta-analysis.

2.4. Statistical analysis

A Hardy–Weinberg Equilibrium (HWE) analysis for the control population was performed, first using the chi-square test. If the rare *APOE ε2* and *ε4* alleles resulted in cell frequencies less than 5, exact tests would be used, as appropriate. Studies that meet the HWE were included in the meta-analysis.

Separate meta-analyses were conducted between the patients with epilepsy and the control group from the following three aspects: *ε4* carriers or *ε2* carriers vs *ε3*/*ε3* (the *ε2*/*ε4* genotype was excluded), *ε4* carriers vs *ε2* carriers (the *ε2*/*ε4* genotype was excluded), and five genotypes vs *ε3*/*ε3* (in the following prespecified order: *ε2*/*ε2*, *ε2*/*ε3*, *ε3*/*ε3*, *ε3*/*ε4*, and *ε4*/*ε4*, with the position of *ε2*/*ε4* genotype inserted after data exploration). The odds ratios (ORs), with 95% confidence intervals (CI), were calculated by a fixed effects' model or a random effects' model. The pooled effect size was assessed by utilizing the Z test [26]. I^2 and Q tests were used to reflect the between-study heterogeneity [27,28]. A fixed effects' model was adopted in case of insignificant heterogeneity among studies (I^2 test exhibited ≤50%; and $P > 0.1$); otherwise, the random effects' model was applied [28,29].

The subgroup analysis was conducted on the ethnicity (divided into Caucasian, Asian, or African based on the study country of origin), the control group was healthy or not, type of epilepsy, the age at time of first seizure, and types of study. Publication bias was assessed using funnel plots and a Harbord test [30,31]. Sensitivity analysis was carried out by omitting each study to assess its impact on the pooled risk estimates. The level of significance was set at 5%. The data were analyzed using Stata software (version 14.1, StataCorp, College Station, TX).

3. Results

3.1. Study identification and characteristics

The PRISMA flow diagram of studies selection is depicted in Fig. 1. A total of 355 references in the primary search were identified. After removal of the duplicates as well as exclusions based on screening of the titles and the abstracts, 42 were included in the narrative review. One study was excluded because the patients had febrile convulsion rather than epilepsy. Twenty studies were excluded because the specific *APOE* genotypes were not available. Eight studies without a control group were also excluded. Out of two studies from Salzmann et al., we selected the one with the largest and most recent sample size [32]. Data from 12 of these studies were available. Three of them were removed because they did not meet HWE [23,33,34]. Eventually, nine studies [32,35–42] with 2210 individuals met our criteria and were included in the meta-analysis (see Table 1). Of the nine studies, six [32,35,36,39–41] involved Caucasians, and three [37,38,42] were based on Asian populations. One [35] of these studies was based in a cohort study; one [40] was a cross-sectional survey; and the others were case–control studies. Except for one study [39] that did not report the genotyping method, all of the other used polymerase chain reaction (PCR)-based methods to establish *APOE* genotypes. The overall allele frequencies among people without epilepsy were 0.07 for *ε2*, 0.82 for *ε3*, and 0.11 for *ε4*; the overall genotype frequencies were 0.002 for *ε2*/*ε2*, 0.114 for *ε2*/*ε3*, 0.018 for *ε2*/*ε4*, 0.677 for *ε3*/*ε3*, 0.181 for *ε3*/*ε4*, and 0.008 for *ε4*/*ε4*. The distribution of *APOE* genotypes was consistent with what is typically observed in the general population and did not deviate from the HWE. The methodological quality of the

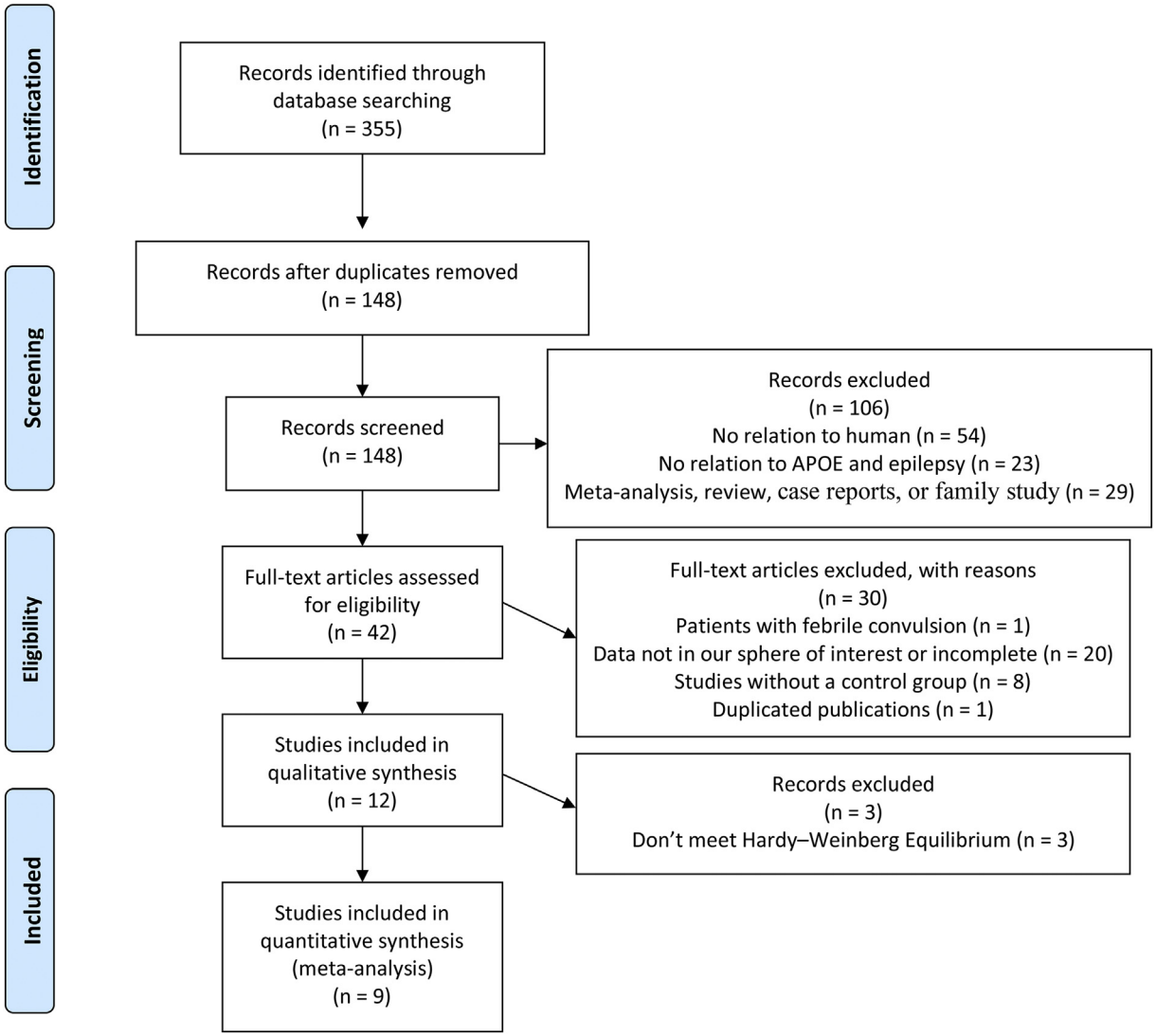


Fig. 1. PRISMA flow diagram.

included studies is shown in online Supplementary File 2. All of the studies were above five points.

3.2. Pooled effect estimates for outcome measures

In comparison with the most common *ε3/ε3* genotype, *ε4* carriers were associated with an increased epilepsy risk (OR: 1.27; 95% CI: 1.01 to 1.59; $P = 0.042$), while there is no strong evidence that *ε2* carriers have a reduced epilepsy risk (OR: 0.88; 95% CI: 0.66 to 1.18; $P = 0.184$) (Fig. 2). When comparing *ε2* carriers, the risk of epilepsy was 1.45 times greater in *ε4* carriers (OR: 1.45; 95% CI: 1.02 to 2.04; $P = 0.037$) (Fig. 2).

There is no strong evidence that different *APOE* genotypes have different epilepsy risks. Compared with the *ε3/ε3* genotype, the epilepsy risk ORs for *ε2/ε2*, *ε2/ε4*, *ε2/ε3*, *ε3/ε4*, *ε4/ε4* genotypes were 2.85 (95% CI: 0.72 to 11.27), 0.78 (95% CI: 0.37 to 1.63), 0.83 (95% CI: 0.62 to 1.12), 1.25 (95% CI: 0.99 to 1.57), and 1.84 (95% CI: 0.83 to 4.10), respectively (Fig. 3A). Although the linear relationships of *APOE* genotypes (when ordered *ε2/ε2*, *ε2/ε4*, *ε2/ε3*, *ε3/ε3*, *ε3/ε4*, *ε4/ε4*) with epilepsy risk could not be observed, the positive dose-dependent association of *APOE ε4* allele genotype and epilepsy risk could be identified (Fig. 3B). When the number of *APOE ε4* allele increased, the ORs increased progressively (no *ε4* alleles, OR: 0.88, 95% CI: 0.66 to 1.18; one *ε4* allele, OR: 1.25, 95% CI: 0.99 to 1.57; two *ε4* alleles, OR: 1.84, 95% CI: 0.83 to 4.10). In contrast, the negative dose-dependent association of *APOE ε2* allele genotype and epilepsy risk could not be observed (Fig. 3C).

3.3. Subgroup analysis, publication biases, and sensitivity analysis

In the subgroup analysis, compared with the *ε3/ε3* genotype, *APOE ε4* carriers had a higher epilepsy risk in the population without primary diseases rather than in those underlying diseases (OR: 1.43; 95% CI 1.09 to 1.88), and a higher epilepsy risk in Asian populations (OR: 1.67; 95% CI: 1.12 to 2.49) (Fig. 4). These results were not observed between *ε2* carriers and a *ε3/ε3* genotype (Fig. 4). Considering subtypes of epilepsy, no difference was found between groups with refractory and without refractory epilepsy in neither *ε4* nor *ε2* carriers (Fig. 4). The subgroups' analysis based on the age at time of first seizure and types of study was not conducted because of the limited amounts of data available.

Comparison-adjusted funnel plots (Fig. 5) were used to reveal any reporting bias in the 9 studies used. The plot was basically symmetrical (Harbord test for *ε4* carriers, $P = 0.303$; Harbord test for *ε2* carriers, $P = 0.205$). Sensitivity analysis found no single study exerted substantial influence on the pooled effect sizes after removing any one of the studies each time (Fig. 6).

Table 1
Demographic and clinical characteristics of included studies.

Study	Country	Study design	Genotyping method	Case group								Control group							
				Female/n (%)	Type of epilepsy	The age at time of first seizure (x ± SD years)	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	Female/n (%)	Primary diseases	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4
Rauramaa 2018	Finland	Cohort	PCR-RFLP	11/11 (100)	Epilepsy	72.6 ± 6.8	0	0	0	3	5	3	47/53 (88.7)	AD	0	2	2	17	29	3
Leal 2017	Portugal	Case–control	PCR-RFLP	101/188 (53.7)	MTLE-HS (hippocampal sclerosis)	13.6 ± 10.7	0	15	3	133	37	0	212/342 (62.0)	Health	0	40	3	248	50	1
Li 2016	China	Case–control	PCR-RFLP	124/308 (40.3)	Nonlesional MTLE	19.9 ± 11.8	3	39	2	209	55	0	137/302 (45.4)	Health	1	33	2	230	36	0
Huang 2015	China	Case–control	PCR-RFLP	21/46 (45.7)	Refractory MTLE	NR	3	2	0	27	13	1	7/19 (36.8)	12 trauma and 7 cerebral hemorrhage	0	3	0	13	3	0
Lott 2012	USA	Case–control	NR	11/24 (45.8)	Seizure	NR	1	2	0	15	5	1	17/29 (58.6)	DS with AD	0	5	2	12	9	1
Braga 2010	Brazil	Cross-sectional	PCR-RFLP	NR/78	Epilepsy	NR	0	11	3	44	16	4	NR/165	CP	0	16	5	104	40	0
Salzmann 2008	France	Case–control	PCR	NR/109	Refractory nonlesional TLE	ε4+: 10.54 ± 6.36; ε4−: 16.51 ± 9.90	0	9	1	72	27	0	NR/227	Health	0	25	5	151	43	3
Wilhelm 2007	Germany	Case–control	RT-PCR (reverse transcription PCR)	NR/52	Alcohol withdrawal seizure	NR	1	2	0	42	7	0	NR/142	Alcohol dependence	1	25	5	84	25	2
Kumar 2006	India	Case–control	PCR-RFLP	15/58 (25.9)	TLE	11.7	0	1	0	46	9	2	17/57 (29.8)	Health	0	3	0	46	7	1

NR = not reported, PCR = polymerase chain reaction, PCR-RFLP = PCR-restriction fragment length polymorphism, SD = standard deviation, MTLE = mesial temporal lobe epilepsy, TLE = temporal lobe epilepsy, AD = Alzheimer's disease, DS = Down syndrome, CP = cerebral palsy.

4. Discussion

The International League Against Epilepsy (ILAE) has emphasized the importance of choosing the appropriate treatments based on the etiology of the patient's epilepsy [5]. Genetic etiology is key for appropriate specialist counseling and the consideration of novel therapies [5]. The results of our meta-analysis show that *APOE ε4* allele genotype was associated with an increased epilepsy risk, which implies that *APOE* may be a potential contributing factor in this affliction.

Apolipoprotein E *ε4* carriers had a higher epilepsy risk. These findings can be partially explained biologically. In the CNS, *APOE* modulates multiple mechanistic pathways that collectively affect cognition including cholesterol/lipid homeostasis, synaptic function, glucose metabolism, neurogenesis, mitochondrial function, tau phosphorylation, neuronal atrophy, neuroinflammation, and the metabolism and aggregation of amyloid-β (Aβ) [43]. Although researches on the role of *APOE* in epilepsy are limited, we try to explain the potential mechanisms from four aspects. The first one might be Aβ accumulation. In patients with TLE, the association between *APOE ε4* carriers and amyloid deposition has been observed, which is independent in the elderly or those already with dementia [44]. Adults with childhood onset epilepsy, particularly *APOE ε4* carriers, have an increased brain amyloid load by late middle age [45]. Contrary to the mature dense core neuritic plaques, observed in patients with epilepsy with *APOE ε4/ε4* genotype, the Aβ in *APOE ε3/ε3* baring subjects appeared as diffuse neuritic plaques [13,33]. These studies indicate that amyloid may play a role in epileptogenesis, which is partially mediated by the specific *APOE* gene alleles. The specific pathogenic mechanisms have been explored in animal models and in humans [46,47]. Another mechanism is glia-related neuroinflammatory events. Amyloid-β precursor protein (β-APP) and its secreted derivative Aα precursor protein (sAPP-α) are a powerful inducer of glial activation [48], and can increase the release of many proinflammatory cytokines [49], which may be early contributors to epilepsy pathogenesis. This process is modulated in the different *APOE* genotypes [48]. In the tissue samples resected from patients with TLE, higher interleukin-1α (IL-1α) levels, more activated microglia, lesser neuronal DNA damage, and larger, more robust neurons were observed in *ε3/ε3* genotype compared to *ε4/ε4* genotype [13,33]. This indicates that the *ε3/ε3* genotype better protects neurons. Microvascular disease, which contributes to gliosis and blood–brain barrier breakdown, may be the third mechanism. In animal studies, *APOE ε4* increases microvascular injury [50] and exacerbates diabetes-related microvascular disease [51]. Microvascular-related damage is involved in epileptogenesis [52–54]. A study of patients with intracerebral hemorrhage (ICH) found that possession of *APOE ε4* copies was associated with delayed seizures [18]. The loss of synaptic contacts and neuronal connectivity may also promote the epileptogenesis. After brain injury, APOE is produced by astrocytes to transport cholesterol to the damaged neuronal and synaptic membranes. However, the repair and remodeling of damaged synapses appear to be less effective by APOE4 than other isoforms [55]. Similarly, elderly *APOE ε4* carriers also have reduced functional connectivity (FC) observed by resting-state functional Magnetic Resonance Imaging (MRI) (rsfMRI) compared with *ε4-* carriers, even in absence of Aβ plaques [56], which is more likely attributable to the neural component on the blood oxygen level-dependent (BOLD) signal, rather than to the possible interference of the vascular contribution [57]. Of course, considering the multiple effects of *APOE*, the potential mechanism would involve more. In addition to the diversity of the causes of epilepsy, the mechanism should be analyzed on a case-by-case basis.

Despite the evidence of the association between *ε2* carriers and epilepsy risk that is not enough in our analysis, it is too early to deny the protective effect of the *ε2* allele because of the small sample size of *ε2* carriers. A recent meta-analysis has indicated that *APOE ε2* carriers have less amyloid load than the *ε3/ε3* genotype [58]. It has been observed that the *APOE ε2* allele is associated with an absence of Aβ plaques in epilepsy; their neuronal sizes were larger than those with an *ε4* allele [33]. The onset age of nonlesional TLE in *ε2/ε3* allele carriers was later than that in those *ε3/ε4* genotype. It is necessary to further explore the differences between patients that possess *ε2* and *ε4* alleles. Since, in our analysis, it was observed that when an *ε2* allele was combined with an *ε4* allele (possessing an ε2/ε4 genotype), it may reduce more epilepsy risk than in *ε2* allele carriers. If this trend occurred, the risk associated with the *ε4* allele may be underestimated in the studies that just compared the presence and absence of ε4. This may cause the failure to replicate the results conducted by the same research team [21,59].

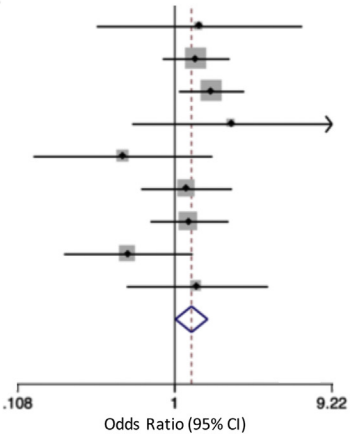
Although the linear relationships of *APOE* genotypes with epilepsy risk could not be observed, the positive dose-dependent association of an *APOE ε4* allele genotype and epilepsy risk could be identified here, which was consistent with a previous large cohort study [24]. Generally, the shape of the association of *APOE* genotype with the disease endpoint should be consistent in the direction of the association with an intermediate phenotype on the causal pathway. It has been confirmed that the level of Aβ in dual-allele *APOE ε4* carriers was higher than that in singleallele carriers [58]. However, it would require large-scale cohorts to confirm that the positive dose–response is mainly due to its effect on Aβ or other intermediate phenotypes. In addition, an apparent increase on epilepsy risk, indexed by the genotypes *ε2/ε2*, was observed. This phenomenon has also been observed in other analysis between *APOE* and other diseases, such as stroke and coronary disease [12,60]. One analysis indicated that a potential explanation could be due to genotyping errors [12]. However, in our examination, all the studies used improved or newer genotyping methods, which could overcome this limitation. One cause may be the less frequent *ε2/ε2* genotype (only contributed 0.45% of the total cases). The small sample size of *ε2/ε2* genotype may also lead to the failure to identify the dose-dependent effect of an *APOE ε2* allele.

Apolipoprotein E *ε4* carriers had a higher epilepsy risk in the population without basic diseases rather than in those underlying diseases. This suggests that the *APOE* gene may directly participate in the pathogenesis of epilepsy, rather than by being a secondary effect of other diseases. This hypothesis can be supported by some biological evidence. The investigation within the brains of rats shows that the *APOE ε3* allele gene was significantly underexpressed in the brains of the seizure-prone embryos compared to the seizure-resistant embryos [61]. In the population with different epilepsy syndromes, the increased brain amyloid deposition may be linked to the pathophysiology of epilepsy rather than to seizure control and the duration of active epilepsy [45]. In addition, Aβ plaques in epilepsy are evident at young ages [13]. In our study, the onset age of epilepsy was also under 20 for most patients. Subgroup analysis also found that among Asians, *APOE ε4* carriers were at greater risk of epilepsy. This is similar with the point that the three *APOE* polymorphisms demonstrate remarkable, ethnicity-specific differences in the risk for AD and other late onset diseases [62]. The *APOE*-by-ancestral background interaction is likely hiding critical gene–gene interactions that will reveal novel protein interactions and potential drug targets, and is also a factor that clinicians need to consider when assessing the risk of developing epilepsy [62]. Although previous studies have suggested that selective *APOE* genotype inheritance was associated with refractory epilepsy, our analysis did not find this association. However, it may be due to the misdiagnosis of patients with refractory epilepsy in the subgroup without refractory epilepsy. A large-scale study about AD has found that the penetrance of *APOE* is influenced by the age of onset of AD and sex [63]. A meta-analysis about epilepsy also showed that *APOE ε4* carriers had epilepsy onset almost 4 years earlier than noncarriers [64]. Unfortunately, because of the inability unavailability of the individual data, we were unable to analyze the association between different *APOE* genotypes and the age of seizure onset or gender.

These results have a number of important implications. On one hand, compared with rare gene mutations, *APOE*, as one of the common variations in genes, probably will turn out to generate an important

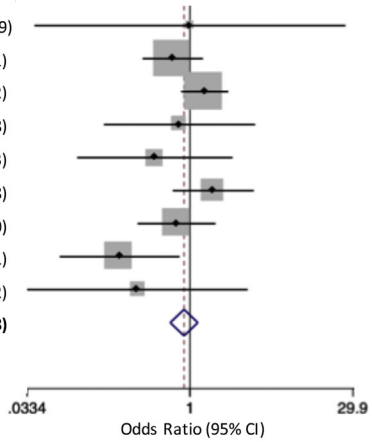
ε4 Carriers vs an ε3/ε3 Genotype

Source	Cases: Total No.	Cases: ε4 Carriers, No. (%)	Cases: ε3/ε3 Genotype, No. (%)	Controls: Total No.	Controls: ε4 Carriers, No. (%)	Controls: ε3/ε3 Genotype, No. (%)	Odds Ratio (95% CI)
Rauramaa 2018	11	8 (72.7)	3 (0.3)	53	32 (60.4)	17 (0.3)	1.42 (0.33-6.05)
Leal 2017	188	37 (19.7)	133 (0.7)	342	51 (14.9)	248 (0.7)	1.35 (0.84-2.17)
Li 2016	308	55 (17.9)	209 (0.7)	302	36 (11.9)	230 (0.8)	1.68 (1.06-2.66)
Huang 2015	46	14 (30.4)	27 (0.6)	19	3 (15.8)	13 (0.7)	2.25 (0.55-9.22)
Lott 2012	24	6 (25)	15 (0.6)	29	10 (34.5)	12 (0.4)	0.48 (0.14-1.70)
Braga 2010	78	20 (25.6)	44 (0.6)	165	40 (24.2)	104 (0.6)	1.18 (0.62-2.25)
Salzmann 2008	109	27 (24.8)	72 (0.7)	227	46 (20.3)	151 (0.7)	1.23 (0.71-2.14)
Wilhelm 2007	52	7 (13.5)	42 (0.8)	142	27 (19)	84 (0.6)	0.52 (0.21-1.29)
Kumar 2006	58	11 (19)	46 (0.8)	57	8 (14)	46 (0.8)	1.38 (0.51-3.73)
Total	**874**			**1336**			**1.27 (1.01-1.59)**



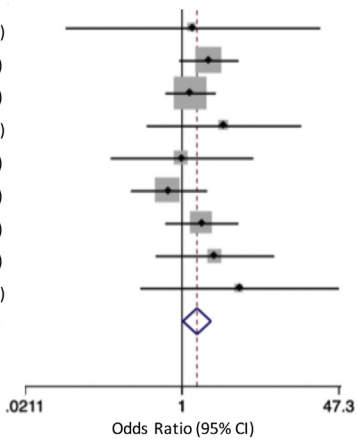
ε2 Carriers vs an ε3/ε3 Genotype

Source	Cases: Total No.	Cases: ε2 Carriers, No. (%)	Cases: ε3/ε3 Genotype, No. (%)	Controls: Total No.	Controls: ε2 Carriers, No. (%)	Controls: ε3/ε3 Genotype, No. (%)	Odds Ratio (95% CI)
Rauramaa 2018	11	0 (0)	3 (0.3)	53	2 (3.8)	17 (0.3)	1.00 (0.04-25.69)
Leal 2017	188	15 (8)	133 (0.7)	342	40 (11.7)	248 (0.7)	0.70 (0.37-1.31)
Li 2016	308	42 (13.6)	209 (0.7)	302	34 (11.3)	230 (0.8)	1.36 (0.83-2.22)
Huang 2015	46	5 (10.9)	27 (0.6)	19	3 (15.8)	13 (0.7)	0.80 (0.17-3.88)
Lott 2012	24	3 (12.5)	15 (0.6)	29	5 (17.2)	12 (0.4)	0.48 (0.09-2.43)
Braga 2010	78	11 (14.1)	44 (0.6)	165	16 (9.7)	104 (0.6)	1.63 (0.70-3.78)
Salzmann 2008	109	9 (8.3)	72 (0.7)	227	25 (11)	151 (0.7)	0.75 (0.34-1.70)
Wilhelm 2007	52	3 (5.8)	42 (0.8)	142	26 (18.3)	84 (0.6)	0.23 (0.07-0.81)
Kumar 2006	58	1 (1.7)	46 (0.8)	57	3 (5.3)	46 (0.8)	0.33 (0.03-3.32)
Total	**874**			**1336**			**0.88 (0.66-1.18)**



ε4 Carriers vs ε2 Carriers

Source	Cases: Total No.	Cases: ε4 Carriers, No. (%)	Cases: ε2 Carriers, No. (%)	Controls: Total No.	Controls: ε4 Carriers, No. (%)	Controls: ε2 Carriers, No. (%)	Odds Ratio (95% CI)
Rauramaa 2018	11	8 (72.7)	0 (0)	53	32 (60.4)	2 (3.8)	1.31 (0.06-29.88)
Leal 2017	188	37 (19.7)	15 (8)	342	51 (14.9)	40 (11.7)	1.94 (0.93- 4.01)
Li 2016	308	55 (17.9)	42 (13.6)	302	36 (11.9)	34 (11.3)	1.24 (0.67- 2.29)
Huang 2015	46	14 (30.4)	5 (10.9)	19	3 (15.8)	3 (15.8)	2.80 (0.42-18.69)
Lott 2012	24	6 (25)	3 (12.5)	29	10 (34.5)	5 (17.2)	1.00 (0.17- 5.77)
Braga 2010	78	20 (25.6)	11 (14.1)	165	40 (24.2)	16 (9.7)	0.73 (0.29- 1.86)
Salzmann 2008	109	27 (24.8)	9 (8.3)	227	46 (20.3)	25 (11)	1.63 (0.66- 4.00)
Wilhelm 2007	52	7 (13.5)	3 (5.8)	142	27 (19)	26 (18.3)	2.25 (0.52- 9.63)
Kumar 2006	58	11 (19)	1 (1.7)	57	8 (14)	3 (5.3)	4.13 (0.36-47.30)
Total	**874**			**1336**			**1.45 (1.02-2.04)**



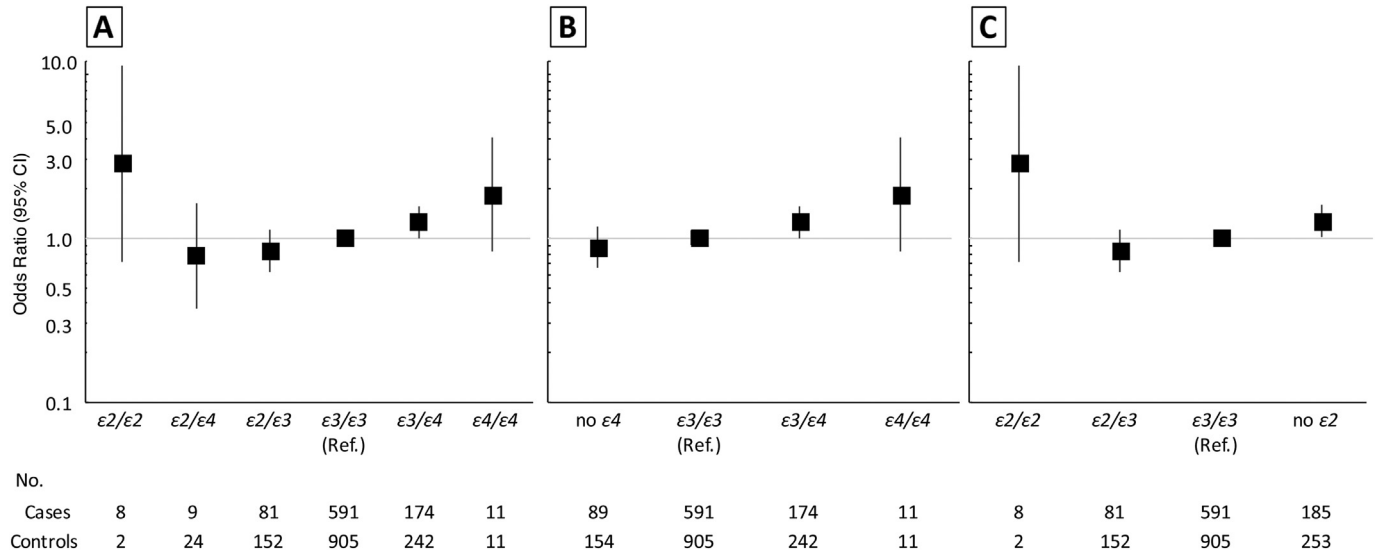


Fig. 3. Odds ratios for epilepsy with different apolipoprotein E genotypes. The ε3/ε3 genotype as the reference group. A. The epilepsy risk odds ratios for ε2/ε2, ε2/ε4, ε2/ε3, ε3/ε4, and ε4/ε4 genotypes. B. The epilepsy risk odds ratios for no ε4 alleles, one ε4 allele, and two ε4 alleles. C. The epilepsy risk odds ratios for no ε2 alleles, one ε2 allele, and two ε2 alleles.

The status of controls	No. of Cases[a]	No. of Controls	Odds Ratio (95% CI) *ε4* Carriers vs an *ε3/ε3* Genotype	Odds Ratio (95% CI) *ε2* Carriers vs an *ε3/ε3* Genotype
with primary disease	241	361	0.94 (0.62-1.44)	0.71 (0.41-1.25)
healthy	440	1135	1.43 (1.09-1.88)	0.96 (0.68-1.35)
Ethnicity				
Caucasian	466	925	1.1 (0.83-1.46)	0.71 (0.49-1.04)
Asian	215	571	1.67 (1.12-2.49)	1.22 (0.77-1.92)
Type of epilepsy				
non-refractory	549	1233	1.25 (0.97-1.61)	0.91 (0.66-1.25)
refractory	132	263	1.27 (1.01-1.59)	0.88 (0.37-1.57)
Total	**681**	**1496**	**1.27 (1.01-1.59)**	**0.88 (0.66-1.18)**

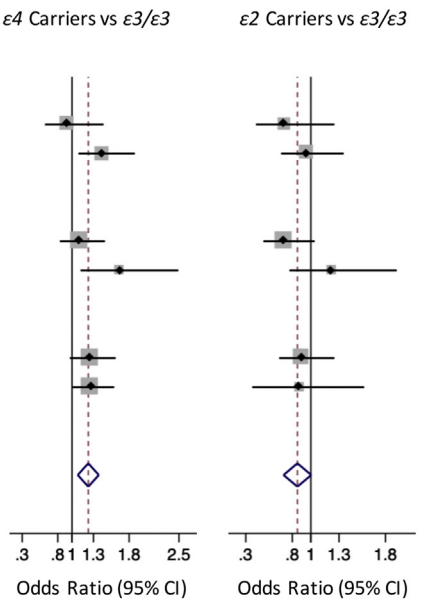


Fig. 4. Subgroup analysis for epilepsy with different apolipoprotein E alleles carriers. The ε3/ε3 genotype as the reference group. Size of the data markers is proportional to the inverse of the variance of the odds ratios. CI = confidence intervals. [a]Total number for exposed and reference groups.

contribution towards epilepsy and drug resistance phenomena. On the other hand, because *APOE* is involved in many physiological and metabolic processes, it is expected to become a new therapeutic target. The penetrance of *APOE* is considered to be variable and potentially modifiable [65]. Dietary intervention may be an example on how to target this gene and its protein products. Apolipoprotein E *ε2* may lead to decreased catabolism, while *APOE ε4* has an increased catabolism [66]. A recent study showed that greater polyunsaturated fat (PUFA) intake was associated with better memory performance in healthy middle-aged adults who were *APOE ε4* noncarriers, but not for *ε4* allele carriers [67]. Considering the effect of a ketogenic diet (KD) on refractory epilepsy, the *APOE* gene and its protein products may be involved in the mechanism of KD in the treatment of epilepsy [68], which suggests that we may need to select treatment options according to the individual patient's *APOE* genotype. Drugs that interfere with the APOE pathway may become another potential target for an antiepileptic regimen. Animal study suggests that E-64d is potentially useful in the treatment of developmental seizure-induced brain damage partly through the modulation of altered lipid metabolism, via the APOE/clusterin pathway, in hippocampus [69].

However, there are also some limitations in our study. The small sample size, especially for *APOE ε2* carriers, can be a major limitation. The effects of different *APOE* genotypes on epilepsy risk still need further investigation with larger samples. Considering the incomplete penetrance of *APOE* and the strong interaction of some variables, such as ancestral background and sex, with *APOE* [62], individual participant data would be needed to assess any interactions with other potentially relevant characteristics not recorded in the present study.

Fig. 2. Odds ratios for epilepsy with different apolipoprotein E alleles carriers. Assessment of heterogeneity: *ε4* carriers vs an *ε3/ε3*: $I^2 = 2.8\%$, $P = 0.412$. *ε2* carriers vs an *ε3/ε3*: $I^2 = 29.4\%$, $P = 0.184$. *ε4* carriers vs *ε2* carriers: $I^2 = 0.0\%$, $P = 0.790$. Size of data markers indicates the weight of each study in the analysis. CI = confidence intervals.

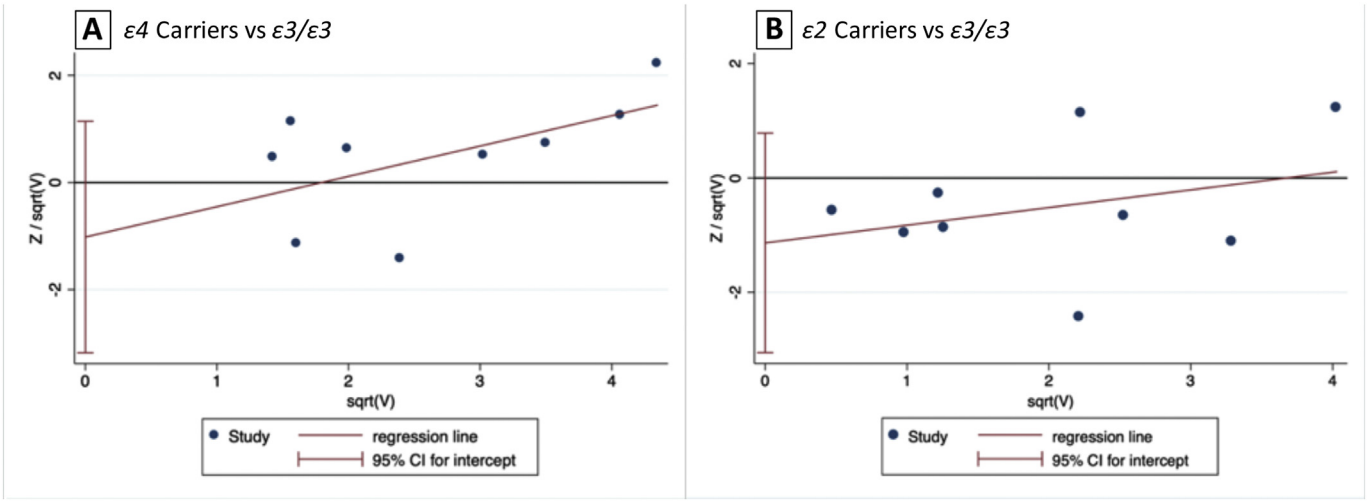


Fig. 5. Comparison-adjusted funnel plots. CI = confidence intervals. A. Funnel plot for *ε4* carriers compared with the *ε3/ε3* genotype (Harbord test, $P = 0.303$). B. Funnel plot for *ε2* carriers compared with the *ε3/ε3* genotype (Harbord test, $P = 0.205$).

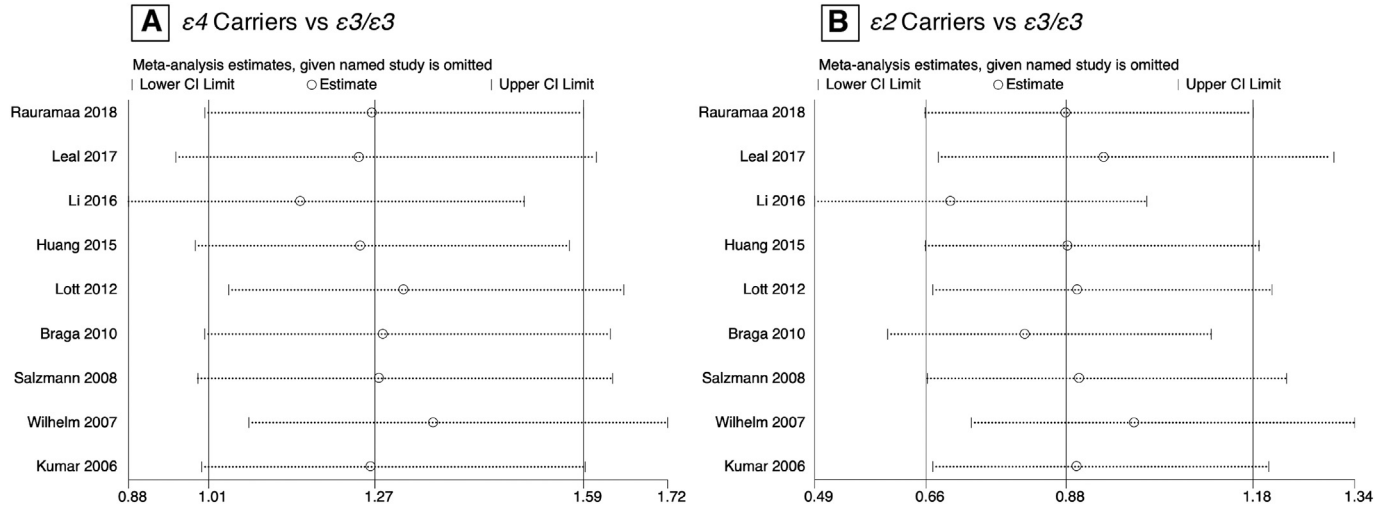


Fig. 6. The plot in the sensitivity. Given named study was omitted. CI = confidence intervals. A. The plot for *ε4* carriers compared with the *ε3/ε3* genotype. B. The plot for *ε2* carriers compared with the *ε3/ε3* genotype.

5. Conclusion

Among the *APOE* genotypes, *ε4* allele was a risk factor for epilepsy, while *ε2* allele was not associated with epilepsy risk. The results were more prominent in the Asian and the population without primary diseases. These findings may be used to guide the directions of prevention and treatment in patients with epilepsy. Of course, the appropriateness of this conclusion needs to be further explored by large clinical studies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.06.015.

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Declaration of Competing Interest

None of the authors have any conflicts 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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