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Review Article

A meta-analysis of Alzheimer's disease's relationship with human ApoE gene variants

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Abstract: Purpose: To explore the association between Alzheimer's disease and apolipoprotein E (ApoE). Studies on this relationship are plentiful, but they mostly suffer from the disadvantage of inadequate sample size, so we conducted this meta-analysis to assess the association between ApoE polymorphisms and AD in humans. Method: The research literature centered on the association between Alzheimer's disease and ApoE polymorphisms was searched using databases including EMBASE, CQVIP, Medline, Web of knowledge, PubMed, Cochrane Library, CNKI, and Wanfang Data up to July 2020. The quality of the included literature was assessed using the NOS scale. We used RevMan 5.3 statistical software for the data extraction and meta-analysis. Results: A total of 569 studies were retrieved according to the search strategy and the inclusion criteria. After removing the duplicate studies and studies that did not match the topic, 155 studies were obtained. 39 publications were finally included according to the inclusion and exclusion criteria. Five of them were selected for the meta-analysis after a careful evaluation. Conclusion: Patients with Alzheimer's disease have a high positive rate of the ε4 allele (OR = 2.19, 95% CI: 1.38-3.48) and a low positive rate of the ε3 allele, but there is no significant association between the ApoE ε2 allele and AD (OR = 0.71, 95% CI: 0.19-2.58). The positivity rates of the ε4/ε4 and ε3/ε4 genotypes were higher in the case group (OR = 3.82, 95% CI: 1.86-7.84; OR = 2.07, 95% CI: 1.40-3.06), but the positivity rates of the ε2/ε3 and ε3/ε3 genotypes were significantly lower in the case group than in the control group (OR = 0.62, 95% CI: 0.18-2.11; OR = 0.52, 95% CI: 0.36-0.75).

Keywords: Apolipoprotein E, polymorphisms, Alzheimer's disease, meta-analysis

Introduction

Alzheimer's disease (AD) is a degenerative disease of the central nervous system characterized by a gradual decline in memory, reasoning, and other abilities over time, a decline that significantly reduces patients' quality of life [1]. It is divided into two subtypes, early-onset (LOAD, age ≤ 65 years) and late-onset (EOAD, age > 65 years) [2]. Due to the increasing prevalence of AD, its treatment and mechanisms attract increasing interest [3]. However, there are only five approved therapies for AD, and they only control the progression of the disease, but they do not cure it, let alone prevent it. There is also no unanimous opinion on the specific pathogenesis of AD. A variety of hypotheses, including hormonal decline and neurotransmitter depletion, partially explain the onset and progression of the disease [4, 5].

In recent years, the genetic polymorphisms of this disease have become a hot topic in exploring the mystery of AD. AD is particularly closely linked to apolipoprotein E (ApoE) [6], the ApoE gene located on chromosome 19 with a molecular weight of about 34 kDa, and mainly sourced from the liver and brain [7]. In humans, ε2, ε3, and ε4 are the three most common alleles of ApoE, with ε4 having the closest relationship to AD [8]. These three alleles can be combined into six corresponding genotypes, ε2/ε2, ε2/ε3, ε2/ε3, ε2/ε3, ε3/ε4, and ε4/ε4 [9]. The link between the onset of AD and ApoE is particularly strong because it has been well documented that the risk of having AD with an ApoE

ε4 allele is three times higher than without [10], and the elimination of this gene can significantly improve the condition, which is very compelling [11]. There are now a large number of studies examining the association between AD and ApoE, but most of the studies were based on small sample sizes, so we conducted this meta-analysis to assess the association between ApoE polymorphisms and AD.

Materials and methods

Ethics

This study was approved by the Ethics Committee of Affiliated Hospital of Nanjing University of Chinese Medicine.

Inclusion and exclusion criteria

Inclusion criteria: (1) articles studying patients diagnosed with AD according to the diagnostic manual, (2) articles covering patients who signed an informed consent, (3) articles in Chinese or English, and (4) articles with full-text information available. Exclusion criteria: (1) reviews, case reports, (2) articles with incomplete data or inaccessible full text, (3) articles incompatible with the study topic, and (4) articles that did not clearly indicate the method of diagnosing AD.

Literature search method

The PubMed, CQVIP, EMBASE, China Knowledge, and Wanfang data databases were searched up to July 2020. The search filter was set as ("AD"[Mesh]) OR (AD)) OR (Dementia, Senile)) OR (Senile Dementia)) OR (Dementia, Alzheimer Type)) OR (Alzheimer Type Dementia)) OR (Alzheimer-Type Dementia (ATD))) OR (Alzheimer Type Dementia (ATD))) OR (Dementia, Alzheimer-Type (ATD))) OR (Alzheimer Type Senile Dementia)) OR (Primary Senile Degenerative Dementia)) OR (Dementia, Primary Senile Degenerative)) OR (Alzheimer Sclerosis)) OR (Sclerosis, Alzheimer)) OR (Alzheimer Syndrome)) OR (Alzheimer Dementia)) OR (Alzheimer Dementias)) OR (Dementia, Alzheimer)) OR (Dementias, Alzheimer)) OR (Senile Dementia, Alzheimer Type)) OR (Acute Confusional Senile Dementia)) OR (Senile Dementia, Acute Confusional)) OR (Dementia, Presenile)) OR (Presenile Dementia)) OR (AD, Late Onset)) OR (Late Onset AD)) OR (AD, Focal Onset)) OR (Focal Onset AD)) OR (Familial Alzheimer Disease (FAD))) OR (Alzheimer Disease, Familial (FAD))) OR (Alzheimer Diseases, Familial (FAD))) OR (Familial Alzheimer Diseases (FAD))) OR (Alzheimer Disease, Early Onset)) OR (Early Onset Alzheimer Disease)) OR (Presenile Alzheimer Dementia) AND (ApoE). When searching the Chinese database by title or keyword, the search filter is "Alzheimer" OR "AD" AND "ApoE".

Data extraction

The extracted data included the title, first author, publication date, number of cases in each group, country and ethnicity of the patients, type of study, criteria for AD diagnosis, and genotype distribution.

The literature search was conducted by two researchers based on the inclusion and exclusion criteria. When disagreements arose about the inclusion, a third researcher helped decide the final results. The quality of the included literature was assessed on a case-by-case basis using the NOS scale.

Statistical methods

The statistical analysis was performed using RevMan 5.3 statistical software. An I^2 test was used to determine the heterogeneity among the studies, and if $I^2 < 50\%$, then the studies were considered homogeneous, and the fixed effect model was used to analyze the included data. If $I^2 \geq 50\%$ the studies were considered heterogeneous, and then the random effect model was used to analyze the included data. In the meta-analysis, $P < 0.05$ indicates a difference is statistically significant. A bias analysis of the included studies was performed using a funnel plot, and the results of the analysis were represented by forest plots.

Results

Baseline data for including the literature

The detailed selection procedure is shown in **Figure 1**. The initial search using the search strategy produced a total of 569 articles. 155 studies were obtained after a careful examination. 39 publications were finally chosen with regard to the inclusion and exclusion criteria. Five of them were included in the meta-analysis after a careful evaluation. **Table 1** shows the basic information of the five included studies.

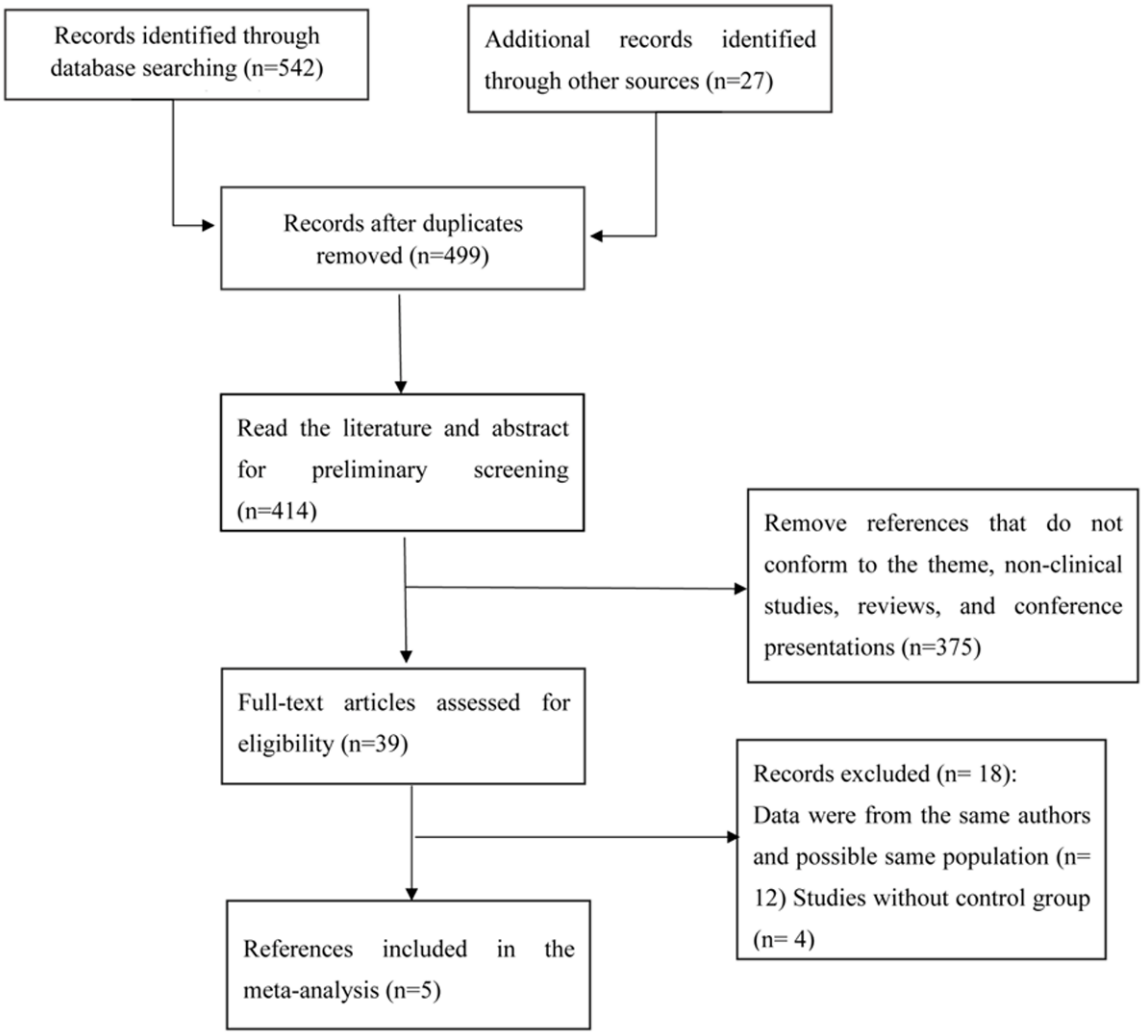

Figure 1. Detailed flowchart for selecting the studies.

Table 1. Basic information on the included studies

First author	Year	Country	Research type	Controls/Cases	NOS score	Diagnostic method
Mary Ganguli [27]	2000	America	retrospective	4450/886	9	DSM
Arjen JC Slooter [30]	1998	Netherland	retrospective	997/97	8	DRS
Scott C. Neu [31]	2017	Canada	prospective	9279/10485	8	DSM
Xiao Y. Dai [32]	1994	Japan	retrospective	186/176	7	DRM
R Katzman [33]	1997	China	retrospective	363/103	7	MMSE

*The number of alleles and genotype-positive cases corresponding to the case and control groups in each study (**Table 2**)*

Figure 2 is a forest plot of the association between the ApoE ε3 allele and AD, and **Figure 3** is a forest plot of the association between the ApoE ε4 allele and AD. It was clear that the ε3 allele positivity rate was lower in patients with AD than in the normal controls (OR = 0.55, 95% CI: 0.35-0.86). The AD patients had a higher rate of positivity for the ε4 allele (OR = 2.19, 95% CI: 1.38-3.48), suggesting that the ε4 allele is a risk factor for AD. **Figure 4** is a forest plot of the association between the ApoE ε2 allele and AD, which shows that there is no

Table 2. The OR values of the 6 genotypes and three alleles within the case and control groups in each study

Study	Year	Groups	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	ε2	ε3	ε4
Mary Ganguli	2000	Controls	13	290	33	3515	577	22	178	3961	312
		Cases	2	103	16	595	159	11	62	726	97
Arjen JC Slooter	1998	Controls	10	148	19	563	241	16	157	558	256
		Cases	0	6	2	55	31	3	6	51	31
Scott C. Neu	2017	Controls	46	1061	203	5468	2257	244	-	-	-
		Cases	15	421	288	3578	4641	1542	-	-	-
Xiao Y. Dai	1994	Controls	0	5	2	71	14	1	7	161	18
		Cases	0	3	0	35	45	5	3	118	55
OR			0.33	0.62	1.47	0.52	2.07	3.82	0.71	0.55	2.19
95% CI			0.19-0.57	0.18-2.11	0.87-2.48	0.36-0.75	1.40-3.06	1.86-7.84	0.19-2.58	0.35-0.86	1.38-3.48

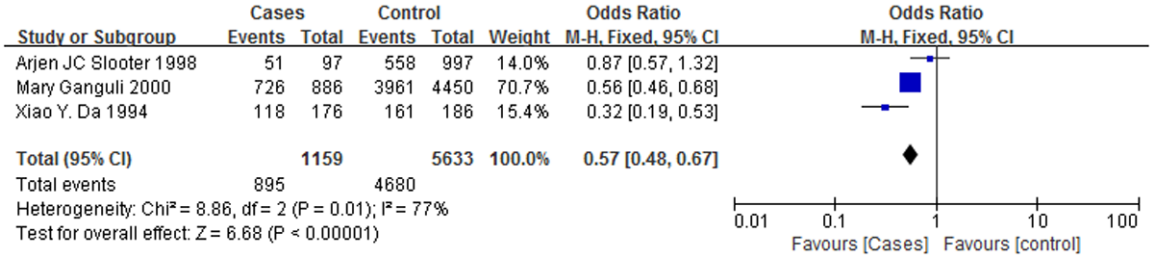

Figure 2. A forest plot of the association between the ApoE ε3 allele and AD.

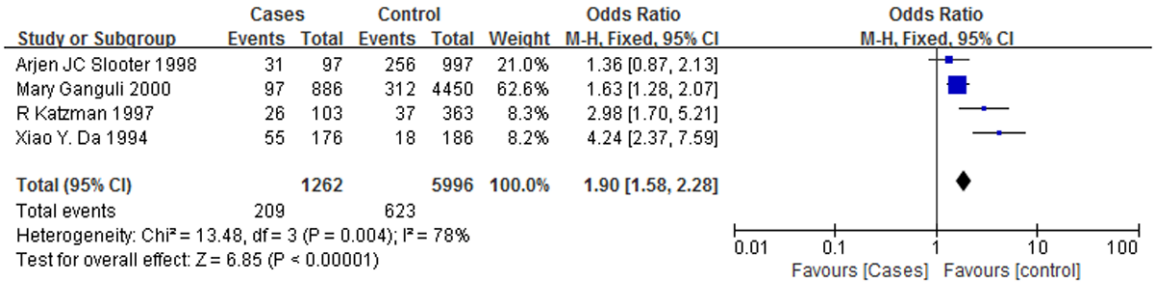

Figure 3. A forest plot of the association between the ApoE ε4 allele and AD.

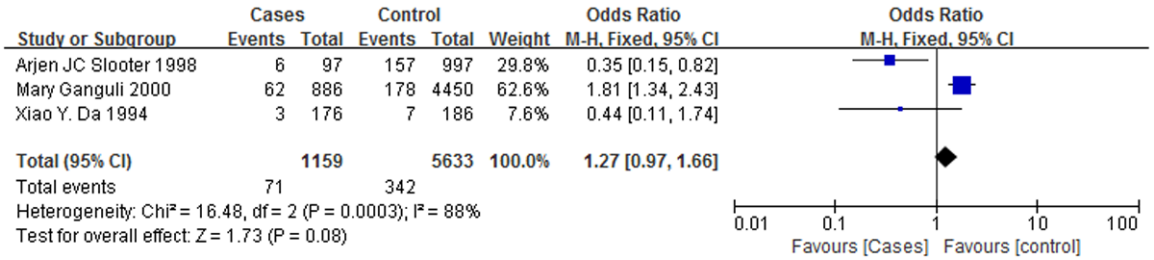

Figure 4. A forest plot of the association between the ApoE ε2 allele and AD.

significant association between the ApoE ε2 allele and AD (OR = 0.71, 95% CI: 0.19-2.58), but **Figure 5** is a funnel plot of the association between the ApoE ε4 allele and AD.

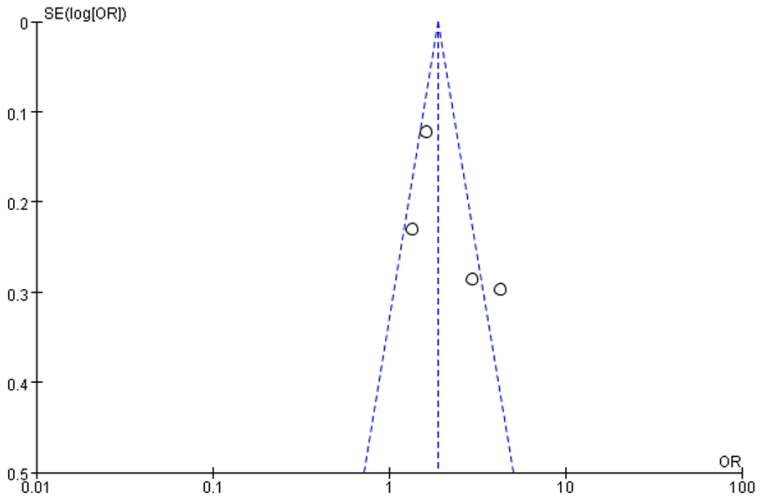

Figure 5. A funnel plot of the association between the ApoE ε4 allele and AD.

Table 3. The ApoE ε4 allele positive rates in the control and case groups among the studies

Study	Groups	ApoE ε4+	ApoE ε4-	Total	positive rate	P
Mary Ganguli	Controls	312	4138	4450	7.011%	< 0.05
	Cases	97	789	886	10.948%	
Arjen JC Slooter	Controls	256	741	997	25.67%	< 0.05
	Cases	31	66	97	31.96%	
R Katzman	Controls	37	326	363	10.2%	< 0.05
	Cases	26	77	103	25.4%	
Xiao Y. Dai	Controls	18	168	186	9.677%	< 0.05
	Cases	55	121	176	31.25%	

The positive rate for the ApoE ε4 allele is higher in individuals with AD than in normal individuals

Table 3 shows the number of positive cases and the corresponding positivity rates of the ApoE ε4 allele in the control and case groups in each study. The number of cases in each study that were positive for the ApoE ε4 allele was higher than it was the corresponding control group ($P < 0.05$). This is consistent with previous findings that people with AD have a higher positive rate for the ApoE ε4 allele than normal controls, and that the ApoE ε4 allele is a risk factor for AD.

Link between 6 genotypes and AD

Figure 6 is a forest plot of the association between the ε4/ε4 genotype and AD, and **Figure 7** is a forest plot of the association between the ε3/ε4 genotype and AD. The case groups showed a higher ε4/ε4 genotype positive rate (OR = 3.82, 95% CI: 1.86-7.84) and a higher ε3/ε4 genotype positive rate (OR = 2.07, 95% CI: 1.40-3.06), and the correlations with AD were similar for both genotypes. However, **Figures 8** and **9** are forest plots between the ε2/ε3 genotype (OR = 0.62, 95% CI: 0.18-2.11), the ε3/ε3 genotype (OR = 0.52, 95% CI: 0.36-0.75) and AD, respectively. The two genotypes, ε2/ε3 and ε3/ε3, have significantly lower positive rates among the case group than the control group, and it can also be said that patients who are positive for these two genotypes are less likely to suffer from AD.

Sensitivity analysis

After excluding the articles one by one, a meta-analysis was carried out on the remaining articles, and the combined OR values showed no significant changes, all of which were statistically significant.

Specificity analysis

The included literature in this study had the same design type, experimental purpose, and intervention measures, ensuring clinical homogeneity. If $I^2 \geq 50\%$ was calculated using the RevMan 5.3 software, it was considered that there was statistical heterogeneity among the various articles. Therefore, the random effects model was used to analyze the included data.

Discussion

The onset of AD is insidious, slow, and irreversible [12], so patients with the AD can only be treated with drugs, and there is no effective way to prevent it [13]. Once diagnosed, it can seriously affect one's ability to learn and understand, resulting in a dramatic decline in quality of life. The morbidity and mortality rates of AD

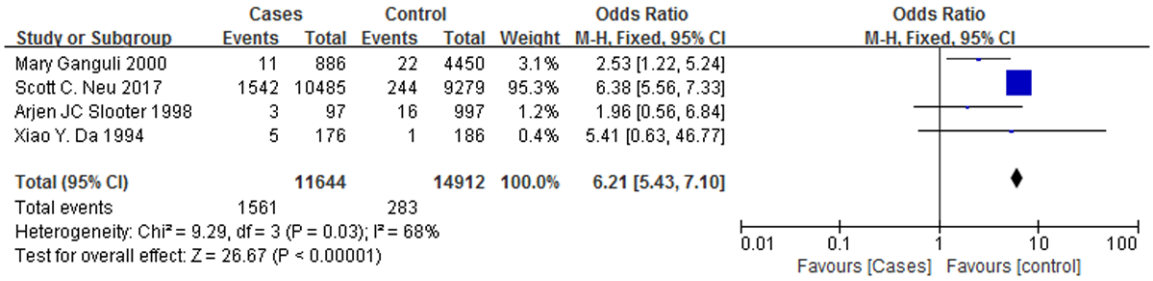

Figure 6. A forest plot of the ApoE ε4/ε4 genotypes associated with AD.

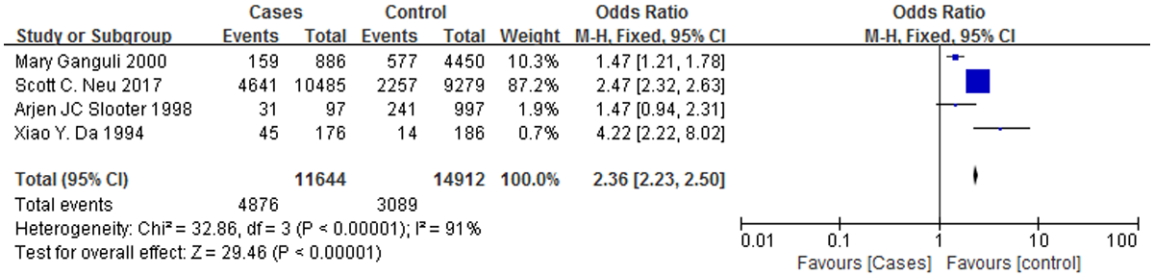

Figure 7. A forest plot of the ApoE ε3/ε4 genotypes associated with AD.

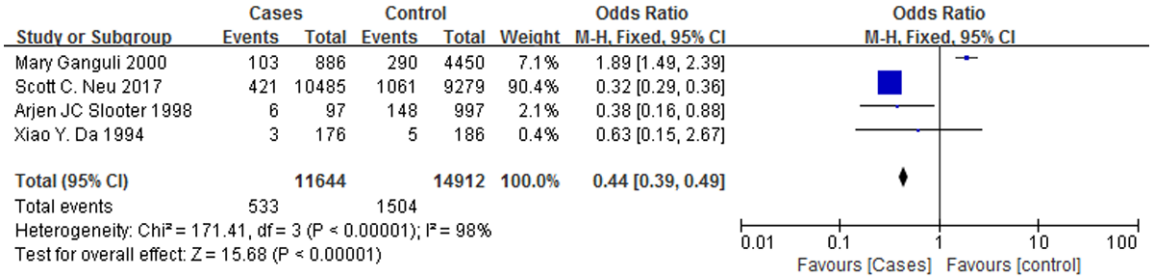

Figure 8. A forest plot of the ApoE ε2/ε3 genotypes associated with AD.

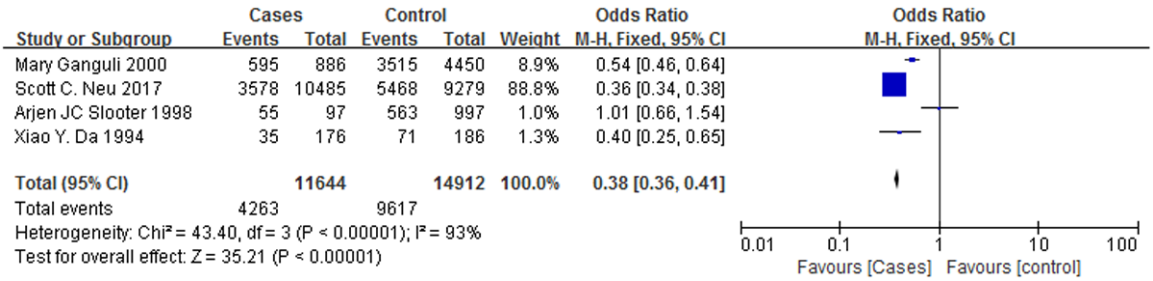

Figure 9. A forest plot of the ApoE ε3/ε3 genotypes associated with AD.

have been rising yearly in both developed and developing countries, so it has become a common public concern [14-16].

AD is characterized by deposits of amyloid plaques, so the detection of these plaques can be used to confirm the diagnosis [17]. There have been several studies that have found ApoE [18] present in the amyloid plaques in the brains of patients with AD. There have also been many studies demonstrating a link between Apo and AD, such as a significant

increase in Apo levels, the release of large amounts of inflammatory factors, and a high susceptibility to atherosclerosis [19-21]. The systemic hardening of the blood vessels increases the likelihood of having AD or worsens the condition in patients already diagnosed with AD [22]. This meta-analysis therefore focused on studies exploring the connection between ApoE and AD, with the aim of expanding the sample size and increasing the credibility.

Of all the apolipoprotein alleles, ε4 is the most studied and is considered the strongest risk factor for AD [23], as confirmed by the results of the present meta-analysis, namely a high positivity rate of the ε4 allele was observed in patients with AD (OR = 2.19, 95% CI: 1.38-3.48). We also found that the patients with AD had a lower positive rate for the ε3 allele (OR = 0.55, 95% CI: 0.35-0.86), but there was no significant association between the ApoE ε2 allele and AD (OR = 0.71, 95% CI: 0.19-2.58). The positivity rates of the ε4/ε4 and ε3/ε4 genotypes were significantly higher in the case group (OR = 3.82, 95% CI: 1.86-7.84; OR = 2.07, 95% CI: 1.40-3.06), but the positivity rates of the ε2/ε3 and ε3/ε3 genotypes were significantly lower than they were in the control group (OR = 0.62, 95% CI: 0.18-2.11; OR = 0.52, 95% CI: 0.36-0.75). The studies found that the ApoE ε4 allele significantly increases the risk of AD, and the higher the number of this gene, the higher the prevalence of AD [24, 25]. It has also been shown that the ApoE ε3 allele decreases the risk of AD [26]. The present meta-analysis is consistent with the results of the previous studies, and the possible mechanism is that different phenotypes of the ApoE gene can participate in the immune regulation of the nervous system, among which the immune response of the central nervous system induced by ε4+ is stronger than the immune response induced by ε3+, and the excessive immune response further leads to brain damage, thus causing AD [27].

In conclusion, the various alleles and six genotypes of ApoE have positive and negative differences among Alzheimer's patients and normal individuals [28], and these differences undoubtedly provide direction for AD treatment, providing a possibility of genetically curing this disease, or even preventing it [29].

The present meta-analysis also has some shortcomings, such as not exploring the association between the ApoE alleles, genotypes, and AD separately by country and gender, and not categorizing AD as LOAD and EOAD. In addition, the diagnosis of AD is inconsistent, leading to possible errors. Research on the relationship between ApoE and AD is continuing, and it is expected to become a breakthrough point in the prevention and treatment of AD.

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Disclosure of conflict of interest

None.

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