Associations between Apolipoprotein E (APOE) Polymorphisms and Cerebral Palsy: A Meta-Analysis

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Abstract

Apolipoprotein E (APOE) is one of the main apolipoproteins that plays an important role in the central neuronal system. The relationship between its polymorphisms and cerebral palsy (CP) is ambiguous. We conducted eligible studies identified from Elsevier Science Direct, PubMed, Springer Link, WEB OF SCIENCE, Chinese National Knowledge Infrastructure and WanFang Data up to February 2019 to conduct a systematic review. In total, 10 eligible studies were included in this meta-analysis (1570 CP patients and 1982 healthy subjects). Significant associations with CP were observed for APOE polymorphisms in allele (ε4: \( P < 0.001, \text{OR} \ 2.05, \ 95\% \ CI \ 1.40 \text{ to } 2.99; \varepsilon2: \ P = 0.04, \text{OR} \ 1.41, \ 95\% \ CI \ 1.01 \text{ to } 1.96) and dominant (E4 carriers: \( P = 0.004, \text{OR} \ 1.90, \ 95\% \ CI \ 1.23 \text{ to } 2.92) models in overall analyses. Interestingly, subgroup analysis indicated a significantly increased risk for CP in Chinese individuals with APOE ε4 (\( P<0.00001, \text{OR} \ 3.71, \ 95\% \ CI \ 2.37 \text{ to } 5.78) and in E4 carriers (\( P<0.00001, \text{OR} \ 3.95, \ 95\% \ CI \ 2.38 \text{ to } 6.53) but not with in those with APOE ε2 (\( P=0.69, \text{OR} \ 1.09, \ 95\% \ CI \ 0.72 \text{ to } 1.65). Combined with the results of our analysis, we concluded that the risk of CP was significantly increased in individuals with the ε4 allele. However, meta-analysis yielded an incongruent result for the APOE ε2 allele between multi-ethnic samples and the Chinese subgroup. These conclusions should be confirmed through further studies.

Keywords: Apolipoprotein E; Cerebral palsy; Meta-analysis; Gene polymorphisms.

Introduction

Cerebral palsy (CP) is a group of motor and posture developmental disorders caused by non-progressive injuries in developing foetuses or infants, resulting in disordered movement and coordination. CP is a severe disability in children, with 40% of affected children being unable to walk independently, 1/3 having epilepsy, up to 1/3 being non-verbal and approximately 1/2 having some degree of cognitive impairment [1-6]. In recent years, evidence from several high-income countries (United States, Australia, Europe, Canada, Sweden, and Japan) has shown that the prevalence of CP has decreased (mainly in low birth weight and premature infants) but still remains at 2% ~ 3% [6]. Epidemiological survey results of more than 320,000 children aged 1-6 years old in 12 provinces and autonomous regions of China in 2013 showed that the
prevalence of CP was 2.46‰, which was consistent with
the international average [7]. In the United States, children
with CP are estimated to cost at least $1 million per person
for health care, educational needs, social services, and
lost economic opportunities [8]. The prevalence, severity,
and burden of CP is becoming an important public health
problem threatening children’s health.

The pathogenesis of CP is multifactorial and varied and
the causes are premature birth and inflammatory, anoxic
environmental, traumatic, metabolic and genetic factors.
Previous studies on the pathogenesis of CP have focused
on the clinical aetiology. In recent years, both domestic
and foreign studies have found that genetic factors are also
involved in the aetiology of CP, while the apolipoprotein
E (APOE) genotype is one of the most studied genetic risk
factors. Apolipoprotein E plays an important role in the
distribution of lipids in peripheral tissues such as the
peripheral nerve, arterial wall, and brain. The role of APOE
with relevance to therapeutic development and treatment
of Alzheimer’s disease has accelerated in recent years and
may now be relevant to CP treatment. The authors findings
are now important and combine environmental, metabolic
and genetic factors to be closely linked to the induction of
CP. In recent research the anti-aging gene Sirtuin 1 has been
shown to be linked to various metabolic diseases (obesity,
diabetes, NAFLD) and neurodegenerative diseases. The role
of therapeutics with relevance to CP treatment may require
Sirtuin 1 activators that may improve developmental
disorders by the increase in the neuroprotective protein
Sirtuin 1. APOE has now been shown to be linked to Sirtuin
1 levels and APOE therapeutics (compound identification)
have been shown to increase brain Sirtuin 1 levels [9-11].
The human APOE gene produces three protein subtypes:
APOE ε2 (112Cys/158Cys), APOE ε4 (112Arg/158Arg) and
wild-type APOE ε3 (112Cys/158Arg), and the six genotypes
(E2/2, E2/3, E2/4, E3/3, E3/4, and E4/4) are located on
chromosome 19q13.2 [12,13]. The APOE ε4 allele has been
reported to be related to Alzheimer’s disease, age-related
cognitive decline [14,15].

Currently, whether there is a link between the APOE
genotype and the risk of CP has been investigated [16-27].
However, the existing results are conflicting. Some studies
have shown that there was a highly significant association
between the ε2 [20,22] or ε4 [22,23] alleles and the risk of
CP, whereas others have shown no association [18,19,21].
Due to the small number of samples, the complex genetic
relationship may not be detected in individual studies. The
purpose of this research is to comprehensively evaluate the
possible relationship between APOE polymorphisms and CP
risk.

Methods

Search strategy

We conducted a systematic study of the research articles
published up to February 2019 through Elsevier Science
Direct, PubMed, Springer Link, WEB OF SCIENCE, Chinese
National Knowledge Infrastructure (CNKI, in Chinese) and
WanFang Data (in Chinese). Two authors independently
searched the literature using the following keywords: (Apolipoprotein E OR APOE) AND (cerebral palsy OR CP)
AND (gene OR polymorphism OR genotype OR variation OR allele). Some of the relevant literature in the review articles
was reviewed to identify additional publications. Studies
that met our eligibility criteria were included in the meta-
analysis.

Inclusion criteria

To be included, studies needed to (a) explain the
association between the APOE gene polymorphism and CP
and (b) offer enough original data of the allele frequency
or genotype distribution; in addition, (c) when the same
case and control subjects appeared in multiple articles, the
study with the largest number of participants was included.
Conference reports or summaries were not included.

Data extraction and quality assessment

Two authors (C-HY, Y-H) identified eligible articles
independently in accordance with the inclusion criteria. The
authors also looked up the following data independently:
year of publication, first author’s family name, population,
study type, types of CP, gene genotyping methods, source
of controls (hospital-based vs. population-based), APOE
genotype and allele distribution. The Newcastle Ottawa Scale
(NOS) was used to assess the quality of the studies included
in the meta-analysis. The genotype distribution reported in
percentages was calculated for figures. The Hardy–Weinberg
equilibrium (HWE) was evaluated in the control groups
by the chi-square test (p<0.05 was considered significant).
Extracted data were contrasted; if there were discrepancies,
they would be resolved through discussion with the third
author (Z-XW).

Meta-analysis methods and bias testing

Based on the allele and genotype frequency between the
case and the control, the odds ratio (OR) was adopted to
evaluate the intensity of the correlation between the APOE
polymorphism and CP susceptibility. We calculated ORs
and 95% CIs to assess potential associations between APOE
polymorphisms and CP in allele, dominant and recessive
models based on genotypic distributions of investigated
polymorphisms. The Chinese subgroup was then divided
deciding according to ethnicity. On the basis of the Q-test, we used the
χ² test to analyse the heterogeneity, which was thought to be
statistically significant at a P value <0.05 [28]. To quantify
heterogeneity, the F value was calculated and clarified as
follows: no heterogeneity, F=0%; low heterogeneity, F=25%;
moderate heterogeneity, F=50% and high heterogeneity,
F=75% [29,30].The summary OR was derived by using the
Mantel-Haenszel (MH) method with the assumptions of
an fixed effects model, as well as by using the DerSimonian
and Laird method with the assumptions of a random-effects
model [31,32]. The value of the OR was also evaluated using
the Z test, and a P value <0.05 was considered statistically
significant.

Publication bias was evaluated by visual examination
of Begg’s funnel plots. An asymmetric funnel indicated a
publication bias, and after that, Egger’s test was performed.
We have also implemented the Duval and Tweedie nonparametric “trim and fill” process to evaluate the possible impact of publication bias in our meta-analysis. The whole statistical analysis was conducted in Stata 12.0 (Stata Corp, College Station, TX, USA) and RevMan V.5.3 (Cochrane, Oxford, UK).

Results

Description of studies

Our literature search generated 351 studies, 274 of which remained when 77 duplications were removed. This number was reduced to 38 after screening the title and abstract (Figure 1). After reading the full text of these papers, 18 studies were excluded, as they were review articles, and another 8 studies were excluded because an overlapping population was analysed or the data were not related to the APOE polymorphism. Then, 12 studies were included in the meta-analysis, but two studies were removed because the data were incomplete. Finally, 10 eligible studies were identified, published from 1995 to 2019, that reported on genotypes of APOE and risk of CP, of which four were published in Chinese [24-27] and the other six were published in English [16-23].

Some studies have been put forward in this field in Brazil, China, the United States, Norway, Australia and Turkey. The combined participants included 1570 CP patients and 1982 healthy subjects. The main features of the studies involved in the meta-analysis are provided in Table 1. We used the NOS rating scale to assess the quality score of each study, as shown in Table 1. The data for the frequencies of APOE alleles and genotypes in the individual studies are shown in Table 1S. The deviation from HWE in the control population was found in three studies [17,21,22].

Overall analyses of the association between APOE polymorphisms and CP susceptibility

First, the meta-analysis of the APOE alleles and the CP risk was conducted. Overall, 10 studies were used to evaluate the effect of APOE alleles on CP risk [16,17,20-27]. Comparing the presence of ε2 vs. ε3 alleles within CP patients, as well as the control group, indicated heterogeneity between studies ($p=0.01, \chi^2=21.37, I^2=58\%$, Figure 2A). The random effects model was adopted. The findings showed that the existence of the ε2 allele conferred a risk of CP ($p=0.04, OR=1.41, 95\% CI 1.01$ to $1.96$, Figure 2A). Moreover, the presence of ε4 vs. ε3 alleles between CP patients and control groups was estimated. Because of the heterogeneity among

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**Figure 1:** Flow diagram of the study selection process. CNKI, Chinese National Knowledge Infrastructure.
Figure 2: Forest plots describing the association of APOE polymorphism with cerebral palsy (CP) (ε2 allele versus ε3 allele). A: Overall analyses; B: Overall analyses (P<0.05); C: Chinese subgroups analyses.

Table 1: Characteristics of studies investigating the association of APOE polymorphisms with cerebral palsy.

<table>
<thead>
<tr>
<th>ID</th>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>Study type</th>
<th>Types of CP</th>
<th>Source of controls</th>
<th>genotyping methods</th>
<th>Sample size</th>
<th>CP</th>
<th>Control</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gumus et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2018</td>
<td>Anatolian</td>
<td>case–control</td>
<td>spastic (unilateral, bilateral)</td>
<td>population-based</td>
<td>Real-time PCR</td>
<td>78</td>
<td>60</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Stoknes et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>2015</td>
<td>Norse</td>
<td>case-parent triads</td>
<td>spastic (unilateral, bilateral)</td>
<td>siblings</td>
<td></td>
<td>295</td>
<td>256</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Xu et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>2014</td>
<td>Chinese</td>
<td>case–control</td>
<td>spastic/ataxic/dyskinetic</td>
<td>population-based</td>
<td>MassARRAY</td>
<td>350</td>
<td>242</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>O’Callaghan et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>2012</td>
<td>Caucasian</td>
<td>case–control</td>
<td>hemiplegia/diplegia</td>
<td>population-based</td>
<td>MassARRAY</td>
<td>587</td>
<td>1154</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Braga et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>2009</td>
<td>Brazilian</td>
<td>cross-sectional</td>
<td>Spastic CP</td>
<td>hospital-based</td>
<td>Real-time PCR</td>
<td>243</td>
<td>243</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>McMichael et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2008</td>
<td>Caucasian</td>
<td>case–control</td>
<td>diplegia/hemiplegia</td>
<td>hospital-based</td>
<td>PCR—RFLP</td>
<td>342</td>
<td>773</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Kuroda et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2007</td>
<td>American</td>
<td>Cross-sectional</td>
<td>spastic CP</td>
<td>population-based</td>
<td>PCR—RFLP</td>
<td>209</td>
<td>209</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Barros et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2000</td>
<td>Brazilian</td>
<td>case–control</td>
<td>mild or moderate CP</td>
<td>population-based</td>
<td>PCR—RFLP</td>
<td>40</td>
<td>40</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Zhang et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>2016</td>
<td>Chinese</td>
<td>case–control</td>
<td>unclassified CP</td>
<td>population-based</td>
<td>PCR—RFLP</td>
<td>50</td>
<td>51</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Hua et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2011</td>
<td>Chinese</td>
<td>case–control</td>
<td>unclassified CP</td>
<td>population-based</td>
<td>PCR—RFLP</td>
<td>83</td>
<td>120</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Wang et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>2010</td>
<td>Chinese</td>
<td>case–control</td>
<td>spastic CP</td>
<td>population-based</td>
<td>PCR—RFLP</td>
<td>110</td>
<td>110</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Wang et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>2010</td>
<td>Chinese</td>
<td>case–control</td>
<td>unclassified CP</td>
<td>population-based</td>
<td>PCR—RFLP</td>
<td>120</td>
<td>120</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*Not including overlapping data; NA, not available; CP, cerebral palsy; HWE, Hardy-Weinberg Equilibrium; RFLP, Restriction Fragment Length Polymorphism;</sup>
the studies ($P<0.00001$, $\chi^2=41.01$, $F=78\%$, Figure 3A), the random effects model was used. The meta-analysis showed that there was a significant positive correlation between the $\varepsilon 4$ allele and CP risk ($P<0.001$, OR 2.05, 95% CI 1.40 to 2.99, Figure 3A). Moreover, the pooled data supported the result that E4 carriers showed significantly increased CP risk, contrasted with those with the E3/3 genotype ($P=0.004$, OR 1.90, 95% CI 1.23 to 2.92, Figure 4A). The random effects model was adopted due to heterogeneity across the 10 studies ($P<0.0001$, $\chi^2=34.68$, $F=74\%$, Figure 4A). The results of dominant and recessive models for contrasts of E4, E3, and E2 genotypes are shown in Table 2.

To further address the heterogeneity, we removed studies that showed a substantial departure from the HWE among controls. This fixed effects model was then applied because the heterogeneity was not significant among the pooled 7 studies ($P=44\%$, Figure 2B), and the meta-analysis showed that there was a significant positive correlation between the $\varepsilon 2$ allele and CP risk ($P<0.00001$, OR 1.63, 95% CI 1.21 to 2.19, Figure 2B) [16,20,23-27].

### APOE polymorphisms and CP susceptibility in Chinese subgroups

We also researched the subgroup of Chinese individuals because we involved four Chinese studies that had never appeared in other meta-analyses. In this paper, four studies of the $\varepsilon 4$ vs. $\varepsilon 3$ alleles were carried out [24-27]. The summary of the data supported a significant increase in the CP risk in individuals with $\varepsilon 4$ alleles compared with that in those with $\varepsilon 3$ alleles ($P<0.00001$, OR 3.70, 95% CI 2.37 to 5.78, Figure 3C). Because there was no heterogeneity between studies ($F=9\%$, Figure 3C), a fixed effects model was then applied. We found that compared with those with $\varepsilon 4$ alleles, individuals with $\varepsilon 2$ alleles did not have a risk for CP development in the Chinese population ($P=0.69$, OR 1.09, 95% CI 0.72 to 1.65, Figure 2C). In addition, the summary data showed that those who were E4 carriers had a high risk of developing CP compared with individuals with the E3/3 genotype ($P=0.00001$, OR 3.95, 95% CI 2.38 to 6.53, Figure 4C). Because there was no heterogeneity between studies ($P^2$}
=13%, Figure 4C), the fixed effects model was used. Table 2 shows the results comparing the dominant and recessive models of E4, E3 and E2 genotypes.

**Evaluation of publication Bias**

First, Begg’s funnel plots were used to evaluate publication bias. Asymmetry and publication bias shown on funnel plots were evaluated by Egger’s test (Table 3). We found that comparisons of both ε4 vs ε3 alleles and E4 carriers vs E3/3 genotypes showed evidence of publication bias (P < 0.05 for both Begg’s test and Egger’s test). In contrast, there was a significant deviation for both comparisons of ε2 vs ε3 alleles and E2 carriers vs E3/3 genotypes (P > 0.05 for both Begg’s test and Egger’s test) (Figure S1A-D). Because of this result, we used the trim and fill method for sensitivity analysis, which conservatively presupposes hypothetical negative unpublished studies to reflect a positive study leading to the asymmetry in the funnel diagram [35]. The collected analysis incorporating the hypothetical studies continued to suggest that both APOE ε4 and E4 carriers act as risk factors for CP (Figure S1E-H).

**Discussion**

This is the first time a meta-analysis has been carried out to research the association between APOE polymorphisms and CP risk. In this meta-analysis, 10 qualified studies were included, of which 5 studies showed that the APOE ε4 allele is a risk factor [23-27], 1 study indicated that the APOE ε2 allele is a risk factor [22], 2 studies indicated that both APOE ε2 and ε4 alleles act as risk factors [16,22], and 1 study suggested that APOE allelic and genotypic frequencies did not differ between patients and controls [21]. To reconcile
these contradictory findings with a larger sample size, we have conducted a systematic review of the published studies. In this meta-analysis, a total of 1570 CP patients and 1982 healthy subjects were used to assess the relationship between APOE polymorphism and CP. This meta-analysis indicated that individuals carrying the APOE ε4 allele, especially in the Chinese population, had an increased risk of CP (Figure 3A and 3C). We also found a highly significant association between E4 carriers and CP development risk, especially in the Chinese population (Figure 4A and 4C).

The APOE ε2 allele also appeared to be related to an increased risk of CP, but not appeared in the Chinese population (Figure 2A and 2C). However, in addition to E4 carriers, we found no significant associations between other APOE polymorphisms and the risk of CP development. The results of our study suggested that APOE ε4 is an important genetic risk factor for the development of CP.

Apolipoprotein E is one of the main apolipoproteins in the central neuronal system that plays an important role in neurobiology. Between the APOE ε4 allele and CP, the existence of an association has been defined in many studies [16,22,23-27]. Disturbances in neurobehavioral functions and the brain healing process, along with reduced ischaemia tolerance, have all been shown to be related to the possession of these polymorphisms.

### Table 2: Meta-analysis of the association of APOE polymorphisms and cerebral palsy.

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Comparisons</th>
<th>Population</th>
<th>Number of studies</th>
<th>Test of association</th>
<th>Test of heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>Z</td>
</tr>
<tr>
<td>ε2</td>
<td>ε2 vs ε3 alleles</td>
<td>Overall*</td>
<td>10</td>
<td>1.41 [1.01, 1.96]</td>
<td>2.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall†</td>
<td>7</td>
<td>1.63 [1.21, 2.19]</td>
<td>3.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chinese ¹</td>
<td>4</td>
<td>1.09 [0.72, 1.65]</td>
<td>0.40</td>
</tr>
<tr>
<td>E2 carriers vs E3/3</td>
<td>Overall*</td>
<td>10</td>
<td>1.16 [0.92, 1.46]</td>
<td>1.22</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall†</td>
<td>7</td>
<td>1.17 [0.83, 1.66]</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chinese ¹</td>
<td>4</td>
<td>0.95 [0.59, 1.53]</td>
<td>0.20</td>
</tr>
<tr>
<td>E2/2 vs E2/3+E3/3</td>
<td>Overall*</td>
<td>10</td>
<td>1.13 [0.60, 2.12]</td>
<td>0.37</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall†</td>
<td>7</td>
<td>2.32 [0.57, 9.39]</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chinese ¹</td>
<td>4</td>
<td>1.66 [0.33, 8.50]</td>
<td>0.61</td>
</tr>
<tr>
<td>E2/2 vs E3/3</td>
<td>Overall*</td>
<td>10</td>
<td>1.12 [0.59, 2.11]</td>
<td>0.34</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall†</td>
<td>7</td>
<td>2.25 [0.55, 9.16]</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chinese ¹</td>
<td>4</td>
<td>1.68 [0.33, 8.58]</td>
<td>0.62</td>
</tr>
<tr>
<td>ε4</td>
<td>ε4 vs ε3 alleles</td>
<td>Overall*</td>
<td>10</td>
<td>2.05 [1.40, 2.99]</td>
<td>3.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall†</td>
<td>7</td>
<td>2.78 [1.51, 5.09]</td>
<td>3.30</td>
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<td></td>
<td></td>
<td>Chinese ¹</td>
<td>4</td>
<td>3.70 [2.37, 5.78]</td>
<td>5.75</td>
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<tr>
<td>E4 carriers vs E3/3</td>
<td>Overall*</td>
<td>10</td>
<td>1.90 [1.23, 2.92]</td>
<td>2.90</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall†</td>
<td>7</td>
<td>2.49 [1.23, 5.04]</td>
<td>2.54</td>
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<tr>
<td></td>
<td></td>
<td>Chinese ¹</td>
<td>4</td>
<td>3.95 [2.38, 6.53]</td>
<td>5.34</td>
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<tr>
<td>E4/4 vs E3/3+E4/4</td>
<td>Overall*</td>
<td>10</td>
<td>1.22 [0.73, 2.02]</td>
<td>0.76</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall†</td>
<td>7</td>
<td>1.22 [0.50, 2.95]</td>
<td>0.44</td>
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<tr>
<td></td>
<td></td>
<td>Chinese ¹</td>
<td>4</td>
<td>2.93 [0.56, 15.35]</td>
<td>1.27</td>
</tr>
<tr>
<td>E4/4 vs E3/3</td>
<td>Overall*</td>
<td>10</td>
<td>1.27 [0.76, 2.10]</td>
<td>0.91</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall†</td>
<td>7</td>
<td>1.32 [0.54, 3.19]</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chinese ¹</td>
<td>4</td>
<td>3.46 [0.66, 18.18]</td>
<td>1.47</td>
</tr>
<tr>
<td>E2 carrier include E2/2 and E2/3; E4 carrier include E3/4 and E4/4; Overall*, Overall analyses; Overall†, Overall analyses (P_{HWE}&gt;0.05); Chinese ¹, Chinese subgroups analyses; OR, odds ratio; R, random-effects model; F, fixed-effects model</td>
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</table>
of the APOE ε4 allele in a number of studies [17,36]. Interestingly, against poor prognosis and unfavourable clinical outcomes stemming from the ε4 allele, some studies suggest that having the APOE ε3 allele renders a favourable response to traumatic and hypoxic injury in the developing brain [37]. A meta-analysis of 2,000 adults aged 45-89 years found that APOE ε4 resulted in poor executive function in cognitive assessment. It is suggested that the efficiency of nerve cell repair is low in allele ε4 carriers [38]. Combined with the results of our analysis, we concluded that the risk of CP was significantly increased in ε4 allele individuals.

The relationship between the APOE ε2 allele and CP is contradictory. BRAGA et al found that the frequency distribution of the ε2 allele in individuals with CP was significantly higher than that in the control group [20]. Another study conducted by McMicheal reported an association between the ε2 allele and low birth weight, as well as prematurity [21]. Our data show that the APOE ε2 allele increases the risk of CP slightly in multi-ethnic samples, but this trend is not obvious in the Chinese population. The different ethnicities, races and environments of the sample population might be part of the reason why the literature produces contradictory results regarding the relationship between the ε2 allele and CP.

Some limitations of this research should be discussed. First, the meta-analysis was based on unadjusted data due to a lack of individual original data, and a more accurate analysis of hierarchical environmental factors or clinical manifestations was not carried out. Second, in some studies, the distribution of genotypes in the control group did not align with the HWE, which may affect the validity of the conclusion. Third, funnel plot analysis showed some asymmetrical phenomena, indicating the existence of publication bias. Sensitivity analysis was carried out by the trim and fill method, and the results show that this association is not an artefact of unpublished negative studies (Figure S1). However, this approach does not completely rule out this possibility. Fourth, although we detected an association between APOE genetic polymorphisms (ε2 vs. ε3 alleles; ε4 vs. ε3 alleles; ε4 carriers vs. E3/3 genotypes) and CP, the result should be approached with caution because the number of participants was small.

Conclusion

In summary, the pooled data indicate a high correlation between APOE polymorphisms and CP. In contrast to individuals carrying the APOE ε3 allele, the risk of CP was significantly increased in individuals carrying the ε4 allele. In addition, compared with individuals with the APOE E3/3 genotype, ε4 carriers have a significantly increased risk of CP. Because of the small number studies, further well-designed studies are still warranted to confirm whether the APOE ε2 allele increases susceptibility to CP. Additionally, the mechanism of apolipoprotein E involvement in CP is not clear and needs to be further studied.

Authors’Contribution

HC: Provided contributions to the design of study, extraction of data, analysis and interpretation of data. Drafted and critically revised the manuscript, and approved of the final version. HY and YC: Provided contributions to the extraction and analysis of data. CC: Provided contributions to the revision of the manuscript and approved of the final version. XZ: Provided contributions to the conception and design of study, extraction of data, analysis and interpretation of data. Revisited the manuscript critically, and approved of the final version. All authors read and approved the final manuscript.

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Acknowledgement

Not applicable.

Compliance with Ethical Standards

Conflict of interests

The authors declare that they have no conflict of interests.

Statement of compliance with standards of research involving humans as subjects

Statement of compliance with standards of research involving humans as subjects. All procedures performed in the study with the participation of people corresponded to the ethical standards of the Commission on Bioethics, and the Helsinki Declaration 1964 with its subsequent amendments or comparable ethical norms. All subjects of those study gave their voluntary consent to participate in that study and signed their informed consent.

References


