

Associations between Apolipoprotein E(APOE) polymorphisms and Cerebral Palsy: a meta-analysis

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Abstract

Background Apolipoprotein E (APOE) is one of the main apolipoproteins playing important roles in the central neuronal system. The relationship between polymorphisms and cerebral palsy (CP) is contradictory.

Methods The overall experimental studies of APOE polymorphisms and CP risk were researched. 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 make a systematic review.

Results Totally 10 eligible studies were used to meta-analysis (1570 CP cases and 1982 subjects). Significant associations with CP were observed for APOE polymorphisms in allele ($\epsilon 4$: $P < 0.001$, OR 2.05, 95% CI 1.40 to 2.99; $\epsilon 2$: $P = 0.04$, OR 1.41, 95% CI 1.01 to 1.96) and dominant (E4 carriers: $P = 0.004$, OR 1.90, 95% CI 1.23 to 2.92) models in overall analyses. Interestingly, subgroup analysis indicated a significant increased risk for CP in Chinese patients of CP with APOE $\epsilon 4$ ($P < 0.00001$, OR 3.71, 95% CI 2.37 to 5.78) and E4 carriers ($P < 0.00001$, OR 3.95, 95% CI 2.38 to 6.53), but not with APOE $\epsilon 2$ ($P = 0.69$, OR 1.09, 95% CI 0.72 to 1.65).

Conclusions Combined with the results of our analysis, we concluded that the risk of CP was significantly increased in $\epsilon 4$ individuals. But meta-analysis yielded an incongruent result for the APOE $\epsilon 2$ allele between in multi-ethnic samples and in Chinese subgroup. These conclusions should be confirmed through further studies.

Introduction

Cerebral palsy (CP) is a group of motor and posture development disorders caused by non-progressive injuries of developing fetuses or infants, resulting in a limited activity. CP is a severe disability in children, with the fact that 40 percent of children unable to walk independently, 1/3 have epilepsy, up to 1/3 are non-verbal and about 1/2 have some degree of cognitive impairment.¹⁻

⁶ In recent years, evidence from several high-income countries (United States, Australia, Europe, Canada, Sweden, and Japan) have shown that the prevalence of CP has decreased (mainly in low birth weight and premature infants), but still remains at 2‰ ~ 3‰.⁶ The epidemiological survey results of more than 320,000 children aged 1-6 in 12 provinces and autonomous regions in 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 spend less than \$1 million per person on health care, educational needs, social services, and lost economic opportunities.⁸ The prevalence, severity, as well as the burden of CP is becoming an important public-health problem threatening children's health.

The pathogenesis of CP is multifactorial and various. The causes are premature, inflammatory, anoxic, traumatic, metabolic and genetic. Previous studies on the pathogenesis of CP have focused on the clinical etiology. In recent years, both domestic and foreign studies have found that genetic

factors also involved in the etiology of CP, while apolipoprotein E (*APOE*) genotype as one of the most studied genetic risk factors. Apolipoprotein E plays an important part in the distribution of lipids in peripheral tissues such as peripheral nerve, arterial wall, and brain. The human *APOE* gene produces three protein subtypes: *APOE* ϵ 2 (112Cys/158Cys), *APOE* ϵ 4 (112Arg/158Arg) and wild-type *APOE* ϵ 3 (112Cys/158Arg), and six genotypes (E2/2, E2/3, E2/4, E3/3, E3/4, and E4/4), is found located on chromosome 19q13.2.^{9,10} The gene polymorphism of *APOE* and its relationship with the risk of Parkinson disease has been assured.¹¹ Meanwhile, *APOE* ϵ 4 allele has been reported relate to Alzheimer's disease, age-related cognitive decline and coronary heart disease (CHD).¹²⁻¹⁴ The risk of CHD was increased by 42% in people with *APOE* ϵ 4 allele than in people with the ϵ 3 allele in the previous study.¹⁵

Nowadays, whether there is a link within the *APOE* genotype and the risk of CP has been investigated.¹⁶⁻²⁷ However, the results in existence have been conflicted. Some studies showed that there was a highly significant association between ϵ 2^{20,22} or ϵ 4^{22,23} allele and the risk of CP, whereas others showed 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 the CP risk.

Methods

Search Strategy

We conducted a systematic study of the research articles published up to February 2019 and provided them 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 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 more additional publications. Studies that meet our eligibility standard were involved in the meta-analysis.

Inclusion Criteria

The inclusion standard provides sufficient raw data for: (a) they explained the association between *APOE* gene polymorphism and CP; (b) they offered enough original data of allele frequency or genotype distribution; and (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 chosen.

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 and population-based), *APOE* genotype and allele distribution. The Newcastle Ottawa Scale (NOS) was used to assess the quality of the studies in the meta-analysis. The genotype distribution reported in percentages were calculated to figures. Hardy-Weinberg equilibrium (HWE) in the control groups was evaluated by the chi-square test ($p < 0.05$ was considered significant). Extracted data were contrasted, if there were discrepancies, it 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 odd ratio (OR) was adopted to evaluate the intensity of the correlation between the *APOE* polymorphism and the 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 according to ethnicity. On the basis of the Q-test, We used χ^2 test to make an analysis of the heterogeneity, which was thought to be that there has statistical significance at P value < 0.05 .²⁸ In order to quantify heterogeneity, the I^2 value was calculated and clarified in the following: no heterogeneity, $I^2 = 0\%$; low heterogeneity, $I^2 = 25\%$, moderate heterogeneity, $I^2 = 50\%$ and high heterogeneity, $I^2 = 75\%$.^{29,30} The summary OR was derived by using the method of Mantel-Haenszel (MH) with the assumptions of a fixed-effects model as well as by using the DerSimonian and Laird method with the assumptions of a random-effects model.^{31,32} And the value of OR was also evaluated using the Z test, and p value < 0.05 was thought to be statistical significance.

The 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 analysis was performed.^{33,34} We have also implemented the Duval and Tweedie nonparametric "trim and fill" process to moreover evaluate the possible impact of publication bias in our meta-analysis.³⁵ The whole statistical analysis were 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 of title and abstract (Figure 1). After reading the full text of these papers, 18 studies were excluded, as they were review articles and the other 8 studies were excluded because the overlapping population was analyzed or the data were not related to the *APOE* polymorphism. Then 12 studies were involved in the meta-analysis, while two studies were removed because the data was incomplete. Finally, 10 eligible studies were identified, published from 1995 to 2019, that reported on genotypes of *APOE* and risk of CP, in which four were published in Chinese²⁴⁻²⁷ and the other six studies 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 cases and 1982 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 study.^{17,21,22}

Overall analyses of the association between *APOE* polymorphisms and CP Susceptibility

Firstly, the meta-analysis of the *APOE* alleles and the CP risk was analyzed. The overall 10 studies were used to evaluate the effect of *APOE* alleles on the CP risk.^{16,17,20-27} The comparison of the presence of $\epsilon 2$ vs. $\epsilon 3$ 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 $\epsilon 2$ allele conferred CP a risk ($p=0.04$, OR

1.41, 95% CI 1.01 to 1.96, Figure 2A). What is more, the presence of $\epsilon 4$ vs. $\epsilon 3$ alleles between CP cases and control groups was estimated. Because of the heterogeneity within the studies ($p < 0.00001$, $\chi^2 = 41.01$, $I^2 = 78\%$, Figure 3A), the random-effects model was used. The meta-analysis showed that there was a significant positive correlation between $\epsilon 4$ 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 the E4 carriers showed significantly increased CP risk, contrasted with those with E3/3 genotype ($p = 0.004$, OR 1.90, 95% CI 1.23 to 2.92, Figure 4A). The random-effect model was adopted due to heterogeneity in 10 studies ($p < 0.0001$, $\chi^2 = 34.68$, $I^2 = 74\%$, Figure 4A). The results of dominant and recessive models for contrasts of E4, E3, and E2 genotypes were shown in Table 2. To further exclude heterogeneity, we removed studies with substantial departure from HWE among controls. This time fixed-effects model was then applied, because the heterogeneity was not significant among the pooled 7 studies ($I^2 = 44\%$, Figure 2B),^{16,20,23-27} and the meta-analysis showed that there was a significant positive correlation between $\epsilon 2$ allele and CP risk ($p = 0.001$, OR 1.63, 95% CI 1.21 to 2.19, Figure 2B).

APOE Polymorphisms and CP Susceptibility in Chinese Subgroups

We also researched the subgroup of Chinese because we involved four Chinese studies that had never appeared in other meta-analyses. In this paper, four studies of the $\epsilon 4$ vs. $\epsilon 3$ alleles were carried out.²⁴⁻²⁷ The summary of the data supported a significant increase in the CP risk in individuals with $\epsilon 4$ alleles contrasted with those with $\epsilon 3$ alleles ($p < 0.00001$, OR 3.70, 95% CI 2.37 to 5.78, Figure 3C). Because there was no heterogeneity between studies ($I^2 = 9\%$, Figure 3C), the fixed-effects model was then applied. We found that, comparison with those with $\epsilon 4$ alleles, individuals with $\epsilon 2$ alleles haven't 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 with E4 carriers had a high risk of developing CP compared with the individuals with 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 ($I^2 = 13\%$, Figure 4C), the fixed-effects model was then used. What is more, Table 2 shows the results for comparing the dominant and recessive models of the E4, E3 and E2 genotypes.

Evaluation of Publication Bias

Firstly, Begg's funnel plots were used to evaluate the publication bias. Asymmetry and publication bias showed on funnel plots were evaluated by Egger's tests (Table 3). We found that both $\epsilon 4$ vs $\epsilon 3$ alleles and E4 carriers vs E3/3 genotypes has the evidence of publication bias ($P < 0.05$ for both Begg's test and Egger's test). In contrast, there was a significant deviation both for $\epsilon 2$ vs $\epsilon 3$ 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, we used the trim and fill method for sensitivity analysis, which conservatively presupposes hypothetical negative unpublished studies to reflect the positive study that leads to the asymmetry of the funnel diagram.³⁵ The collected analysis incorporating the hypothetical studies continued to suggest both *APOE* $\epsilon 4$ and E4 carriers acts as a risk factor for CP (Figure S1E-H).

Table 3 Publication bias of *APOE* polymorphisms and the risk of CP

Publication bias by Egger's test					
Variables	Coefficient	SE	z	p Value	95% CI
$\epsilon 2$ vs $\epsilon 3$ alleles	4.983226	1.93	2.575458	0.089	-.9557911 to 10.92224
E2 carriers vs E3/3	4.906202	3.225086	1.52	0.167	-2.530861 to 12.34326
$\epsilon 4$ vs $\epsilon 3$ alleles	8.115601	1.398786	5.80	0.000	4.889996 to 11.34121
E4 carriers vs E3/3	7.736085	1.921866	4.03	0.004	3.304254 to 12.16792

Discussion

It is the first time a meta-analysis has been carried out in order to research the association between *APOE* polymorphisms and CP risk. In this meta-analysis, 10 qualified studies were determined, of which 5 studies showed that *APOE* $\epsilon 4$ is a risk factor,²³⁻²⁷ 1 study of them indicated that *APOE* $\epsilon 2$ is a risk factor,²² 2 studies of them indicated both *APOE* $\epsilon 2$ and $\epsilon 4$ acts as a risk factor,^{16,22} and 1 study suggested *APOE* allelic and genotypic frequencies did not differ between cases and controls.²¹ To solve this contradiction with a larger sample size, we have made a systematic review of the published studies. In this meta-analysis, a total of 1570 CP cases and 1982 subjects were used to assess the relationship between *APOE* polymorphism and CP. This meta-analysis indicated that individuals carrying *APOE* $\epsilon 4$ allele, especially in the Chinese population, increased the risk of CP (Figure 3A and 3C). We found a highly significant association between E4 carriers and CP development risk as well, especially in the Chinese population too (Figure 4A and 4C).

The *APOE* $\epsilon 2$ 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 $\epsilon 4$ carriers, we found no significant associations between other *APOE* polymorphisms and the risk of CP development. The results of our study suggested that *APOE* $\epsilon 4$ is an important genetic risk factor for the development of CP.

Apolipoprotein E is one of the main apolipoproteins of the central neuronal system playing important roles in neurobiology. Between the *APOE* $\epsilon 4$ allele and CP, the existence of an association was defined in many studies.^{16,22,23-27} Disturbance in neurobehavioral functions and the brain healing process along with reduced ischemia tolerance have all been implicated with possessing the ApoE $\epsilon 4$ allele in a number of studies.^{17,36} Interestingly, against poor prognosis and unfavorable clinical outcomes stemmed from $\epsilon 4$ allele, some studies suggest that having the ApoE $\epsilon 3$ allele renders a favorable response to traumatic and hypoxic injury in developing brain.³⁷ A meta-analysis of 2,000 adults aged 45-89 years found that *APOE* $\epsilon 4$ resulted in poor executive function in cognitive assessment. It is suggested that the efficiency of nerve cell repair is low in allele $\epsilon 4$ carriers.³⁸ Combined with the results of our analysis, we concluded that the risk of CP was significantly increased in $\epsilon 4$ individuals.

The relationship between *APOE* $\epsilon 2$ allele and CP is contradictory. BRAGA *et al*²⁰ found that the frequency distribution of $\epsilon 2$ allele in the individuals with CP was significantly higher than control group. The other study conducted by McMichael *et al*²¹ reported an association between $\epsilon 2$ allele and low birth weight as well as prematurity. Our data show that *APOE* $\epsilon 2$ increases the risk of CP slightly in multi-ethnic samples, but this trend is not obvious in the Chinese population. Because of the different ethnic, race or environmental elements of the sample population, which might be part of the reason why the literature produces contradictory results on the $\epsilon 2$ allele and CP.

Some limitations of this research should be discussed. First, the meta-analysis was on the basis of unadjusted data due to lack of the individual original data, and more accurate analysis of hierarchical environmental factors or clinical manifestations is not carried out. Second, in some studies, the distribution of genotypes in the control group did not show HWE, which may affect the effectiveness of the conclusion. Third, funnel plot analysis shows some asymmetrical phenomena, indicating the existence of publication bias. The sensitivity analysis was carried out by the trim and fill method, and the results show that this association is not an artifact of unpublished negative

studies (Figure S1). However, this approach does not completely rule out this possibility. Fourth, although we detected an association of *APOE* genetic polymorphisms ($\epsilon 2$ vs. $\epsilon 3$ alleles; $\epsilon 4$ vs. $\epsilon 3$ alleles; E4 carriers vs. E3/3 genotypes) with CP, the result should be explained with caution because the number of participants was small.

Conclusions

In a word, the pooled data indicate a high correlation between *APOE* polymorphisms and CP. Contrasted with individuals carrying *APOE* $\epsilon 3$ allele, the risk of CP was significantly increased in individuals carrying $\epsilon 4$ allele. In addition, compared with individuals with *APOE* E3/3 genotype, E4 carriers have significantly increased risk suffering from CP. Because of the fewer studies, further well-designed studies are still warranted to confirm whether *APOE* $\epsilon 2$ increase the susceptibility to CP. Additionally, the mechanism of apolipoprotein E involved in CP is not clear and needs to be further studied.

Declarations

Abbreviations

APOE: Apolipoprotein E; CP: cerebral palsy; CHD: coronary heart disease; CNKI: Chinese National Knowledge Infrastructure; HWE: Hardy–Weinberg equilibrium; MH: Mantel-Haenszel

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Not applicable.

Authors' contributions

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. Revised the manuscript critically, and approved of the final version. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used for the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1 Characteristics of studies investigating the association of *APOE* polymorphisms with cerebral palsy ^a

ID	Study	Year	Population	Study type	Types of CP	Source of controls	genotyping methods	Sample size		NOS score
								CP	Control	
1	Gumus <i>et al</i> ¹⁶	2018	Anatolian	case-control	spastic (unilateral, bilateral)/dyskinetic/ ataxic/ unclassified CP	population-based	Real-time PCR	78	60	7
2	Stoknes <i>et al</i> ¹⁷	2015	Norse	case-parent triads	spastic (unilateral, bilateral)/dyskinetic/ ataxic/ unclassified CP	siblings	/	295	256	4
3	Xu <i>et al</i> ¹⁸	2014	Chinese	case-control	spastic/ataxic/ dyskinetic/ mixed/ hypotonic/ unclassified CP	population-based	MassARRAY	350	242	9
4	O'Callaghan <i>et al</i> ¹⁹	2012	Caucasian	case-control	hemiplegia/ diplegia/ quadriplegia/ other CP types	population-based	MassARRAY	587	1154	9
5	Braga <i>et al</i> ²⁰	2009	Brazilian	cross-sectional	Spastic CP	hospital-based	Real-time PCR	243	243	6
6	McMichael <i>et al</i> ²¹	2008	Caucasian	case-control	diplegia/ hemiplegia/ quadriplegia, and all types CP	hospital-based	PCR-RFLP	342	773	8
7	Kuroda <i>et al</i> ²²	2007	American	Cross-sectional	spastic CP	population-based	PCR-RFLP	209	209	7
8	Barros <i>et al</i> ²³	2000	brazilian	case-control	mild or moderate CP	population-based	PCR-RFLP	40	40	4
9	☐☐☐ <i>et al</i> ²⁴	2016	Chinese	case-control	unclassified CP	population-based	PCR-RFLP	50	51	9
10	☐☐ <i>et al</i> ²⁵	2011	Chinese	case-control	unclassified CP	population-based	PCR-RFLP	83	120	9
11	☐☐☐1 <i>et al</i> ²⁶	2010	Chinese	case-control	spastic CP	population-based	PCR-RFLP	110	110	8
12	☐☐☐2 <i>et al</i> ²⁷	2010	Chinese	case-control	unclassified CP	population-based	PCR-RFLP	120	120	9

^a Not including overlapping data; NA, not available; CP, cerebral palsy; HWE, Hardy-Weinberg Equilibrium; RFLP, Restriction Fragment Length Polymorphism;

Table 2 Meta-analysis of the association of *APOE* polymorphisms and cerebral palsy

Polymorphisms	Comparisons	Population	Number of studies	Test of association			Test of heterogeneity				
				OR (95% CI)	Z	p value	Model	χ^2	p value	I ² (%)	
$\epsilon 2$	$\epsilon 2$ vs $\epsilon 3$ alleles	Overall*	10	1.41 [1.01, 1.96]	2.01	0.04	R	21.37	0.01	58%	
		Overall [†]	7	1.63 [1.21, 2.19]	3.21	0.001	F	10.75	0.10	44%	
		Chinese [‡]	4	1.09 [0.72, 1.65]	0.40	0.69	F	2.52	0.47	0%	
	E2 carriers vs E3/3	Overall*	10	1.16 [0.92, 1.46]	1.22	0.22	F	15.15	0.09	41%	
		Overall [†]	7	1.17 [0.83, 1.66]	0.88	0.38	F	7.93	0.24	24%	
		Chinese [‡]	4	0.95 [0.59, 1.53]	0.20	0.84	F	2.02	0.57	0%	
	E2/2 vs E2/3+E3/3	Overall*	10	1.13 [0.60, 2.12]	0.37	0.71	F	3.24	0.66	0%	
		Overall [†]	7	2.32 [0.57, 9.39]	1.18	0.24	F	1.65	0.65	0%	
		Chinese [‡]	4	1.66 [0.33, 8.50]	0.61	0.54	F	1.24	0.54	0%	
	E2/2 vs E3/3	Overall*	10	1.12 [0.59, 2.11]	0.34	0.73	F	3.08	0.69	0%	
		Overall [†]	7	2.25 [0.55, 9.16]	1.13	0.26	F	1.56	0.67	0%	
		Chinese [‡]	4	1.68 [0.33, 8.58]	0.62	0.53	F	1.24	0.54	0%	
	$\epsilon 4$	$\epsilon 4$ vs $\epsilon 3$ alleles	Overall*	10	2.05 [1.40, 2.99]	3.71	0.0002	R	41.01	<0.00001	78%
			Overall [†]	7	2.78 [1.51, 5.09]	3.30	0.0010	R	25.29	0.003	76%
			Chinese [‡]	4	3.70 [2.37, 5.78]	5.75	<0.00001	F	3.30	0.35	9%
E4 carriers vs E3/3		Overall*	10	1.90 [1.23, 2.92]	2.90	0.004	R	34.68	<0.0001	74%	
		Overall [†]	7	2.49 [1.23, 5.04]	2.54	0.01	R	24.18	0.0005	75%	
		Chinese [‡]	4	3.95 [2.38, 6.53]	5.34	<0.00001	F	3.44	0.33	13%	
E4/4 vs E3/3+E3/4		Overall*	10	1.22 [0.73, 2.02]	0.76	0.45	F	3.06	0.93	0%	
		Overall [†]	7	1.22 [0.50, 2.95]	0.44	0.66	F	1.97	0.85	0%	

	Chinese ‡	4	2.93 [0.56, 15.35]	1.27	0.20	F	0.00	1.00	0%
E4/4 vs E3/3	Overall*	10	1.27 [0.76, 2.10]	0.91	0.36	F	3.42	0.91	0%
	Overall†	7	1.32 [0.54, 3.19]	0.61	0.54	F	2.16	0.83	0%
	Chinese ‡	4	3.46 [0.66, 18.18]	1.47	0.14	F	0.00	1.00	0%

E2 carrier include E2/2 and E2/3; E4 carrier include E3/4 and E4/4; Overall*, Overall analyses; Overall†, Overall analyses ($P_{HWE} > 0.05$); Chinese ‡, Chinese subgroups analyses; OR, odds ratio; R, random-effects model; F, fixed-effects model

Figures

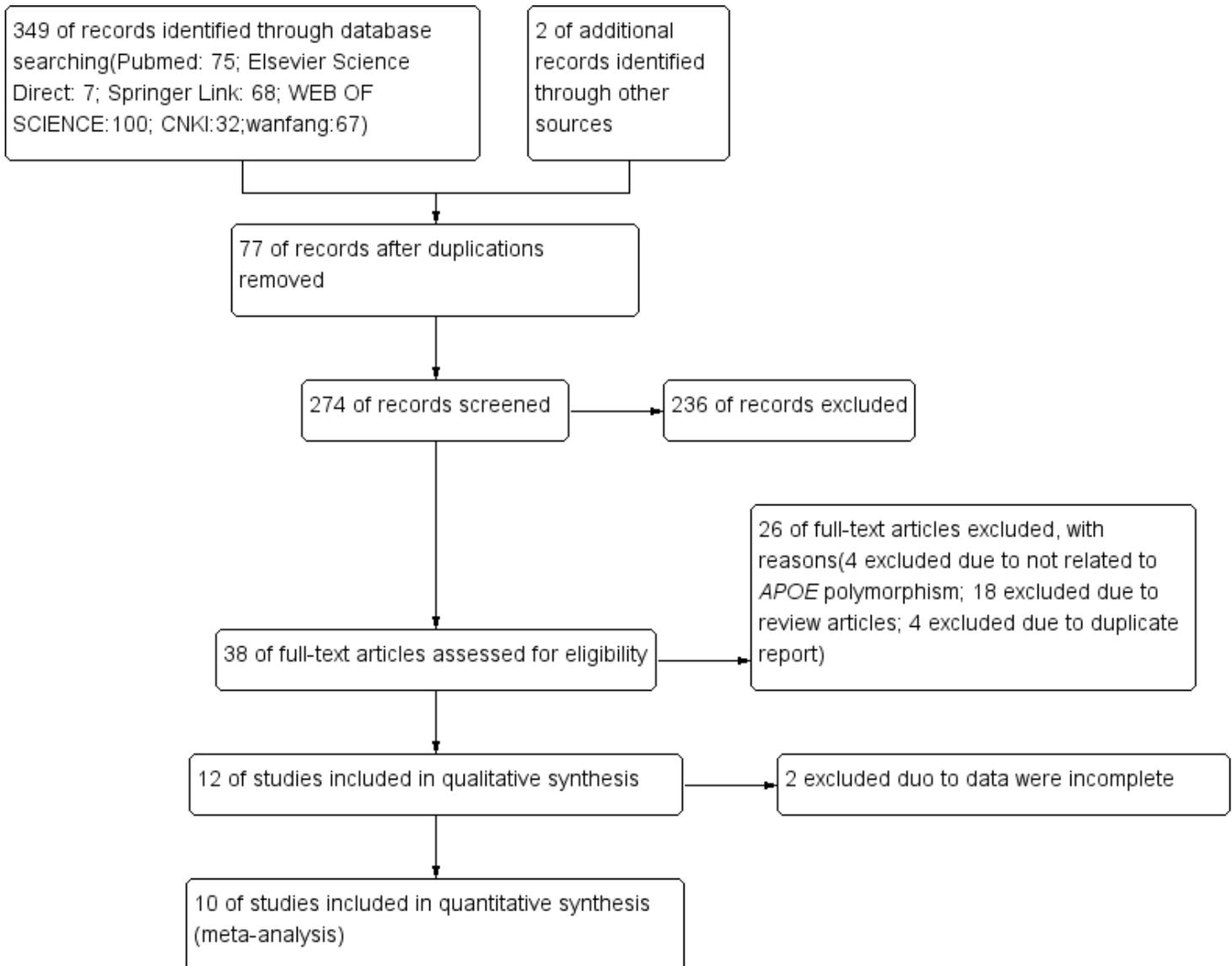


Figure 1

Flow diagram of the study selection process. CNKI, Chinese National Knowledge Infrastructure.

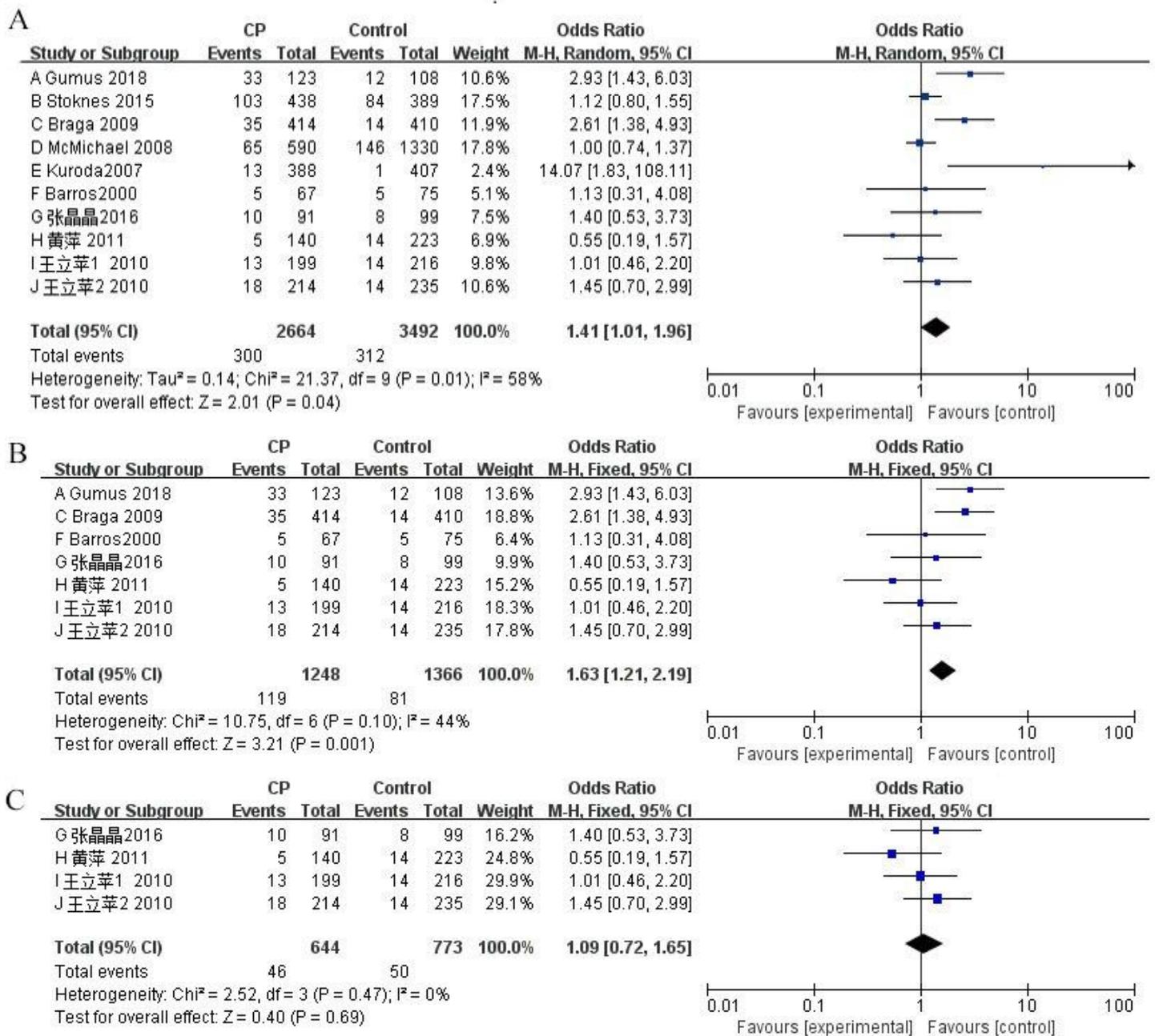


Figure 2

Forest plots describing the association of APOE polymorphism with cerebral palsy (CP) ($\epsilon 2$ allele versus $\epsilon 3$ allele). A: Overall analyses; B: Overall analyses (PHWE>0.05); C: Chinese subgroups analyses.

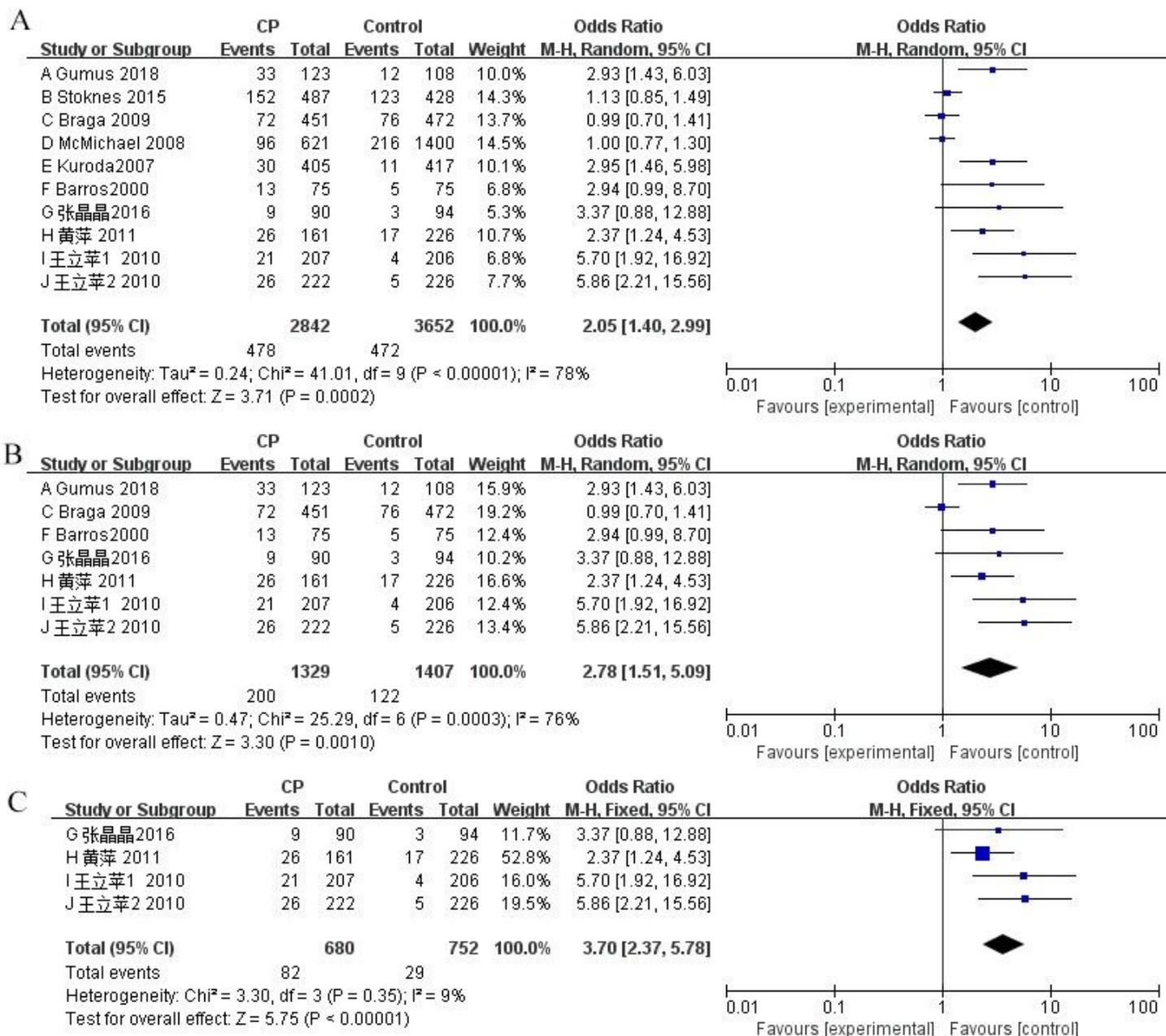


Figure 3

Forest plots describing the association of APOE polymorphism with cerebral palsy (CP) ($\epsilon 4$ allele versus $\epsilon 3$ allele). A: Overall analyses; B: Overall analyses (PHWE>0.05); C: Chinese subgroups analyses.

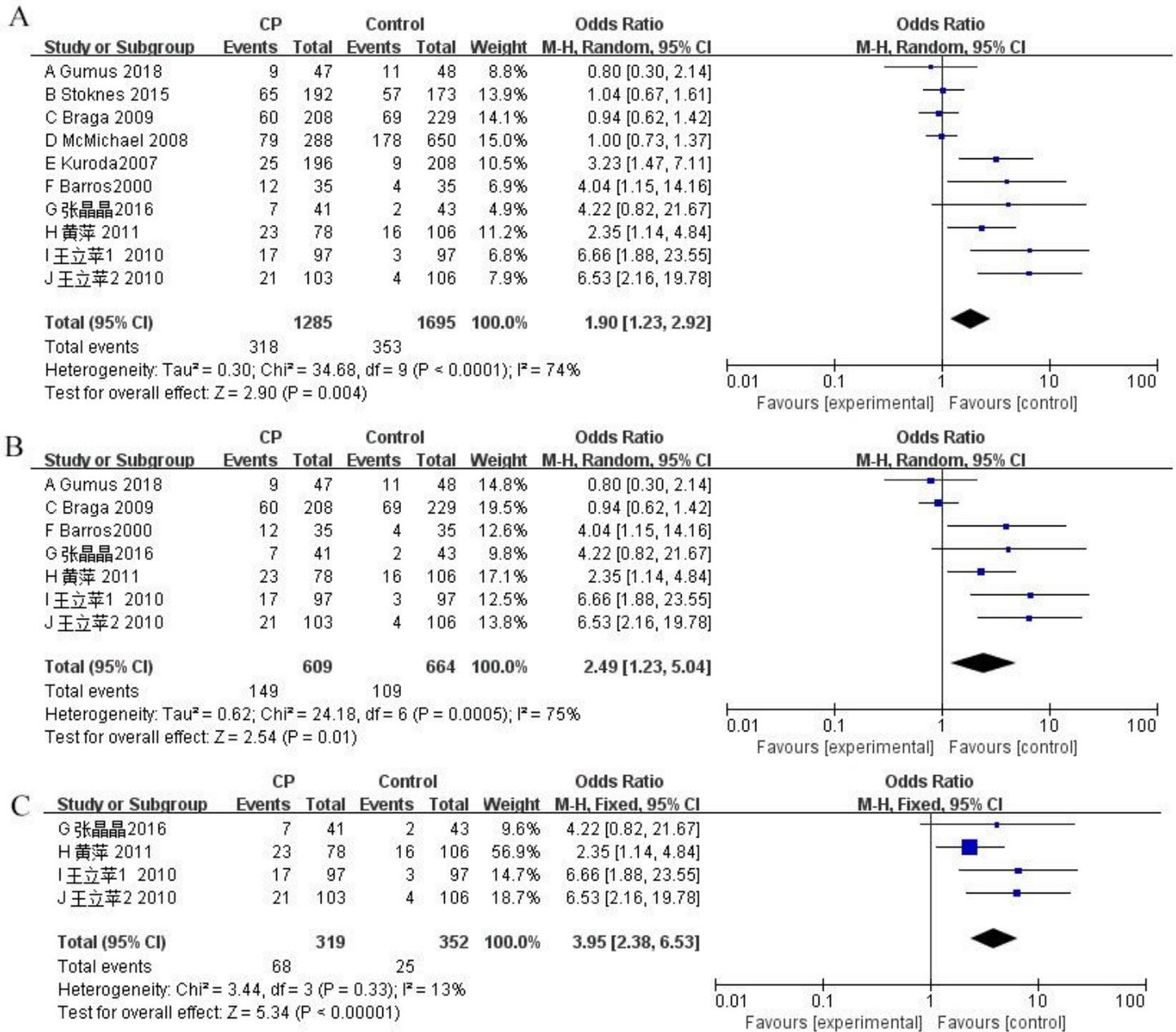


Figure 4

Forest plots describing the association of APOE polymorphism with cerebral palsy (CP) (E4 carriers versus E3/3 genotypes). A: Overall analyses; B: Overall analyses (PHWE>0.05); C: Chinese subgroups analyses.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableS1.docx](#)
- [FigureS1.jpg](#)