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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: $P < 0.001$, *OR* 2.05, 95% *CI* 1.40 to 2.99; ε2: $P = 0.04$, *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 significantly increased risk for CP in Chinese individuals with *APOE* ε4 ($P<0.00001$, *OR* 3.71, 95% *CI* 2.37 to 5.78) and in E4 carriers ($P<0.00001$, *OR* 3.95, 95% *CI* 2.38 to 6.53) but not with in those with *APOE* ε2 ($P=0.69$, *OR* 1.09, 95% *CI* 0.72 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

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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 according to ethnicity. On the basis of the *Q*-test, we used the χ^2 test to analyse the heterogeneity, which was thought to be statistically significant at a *P* value <0.05 [28]. To quantify heterogeneity, the I^2 value was calculated and clarified as follows: 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 Mantel-Haenszel (MH) method 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]. 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 perfomed

[33,34]. 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 [35]. 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, χ^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

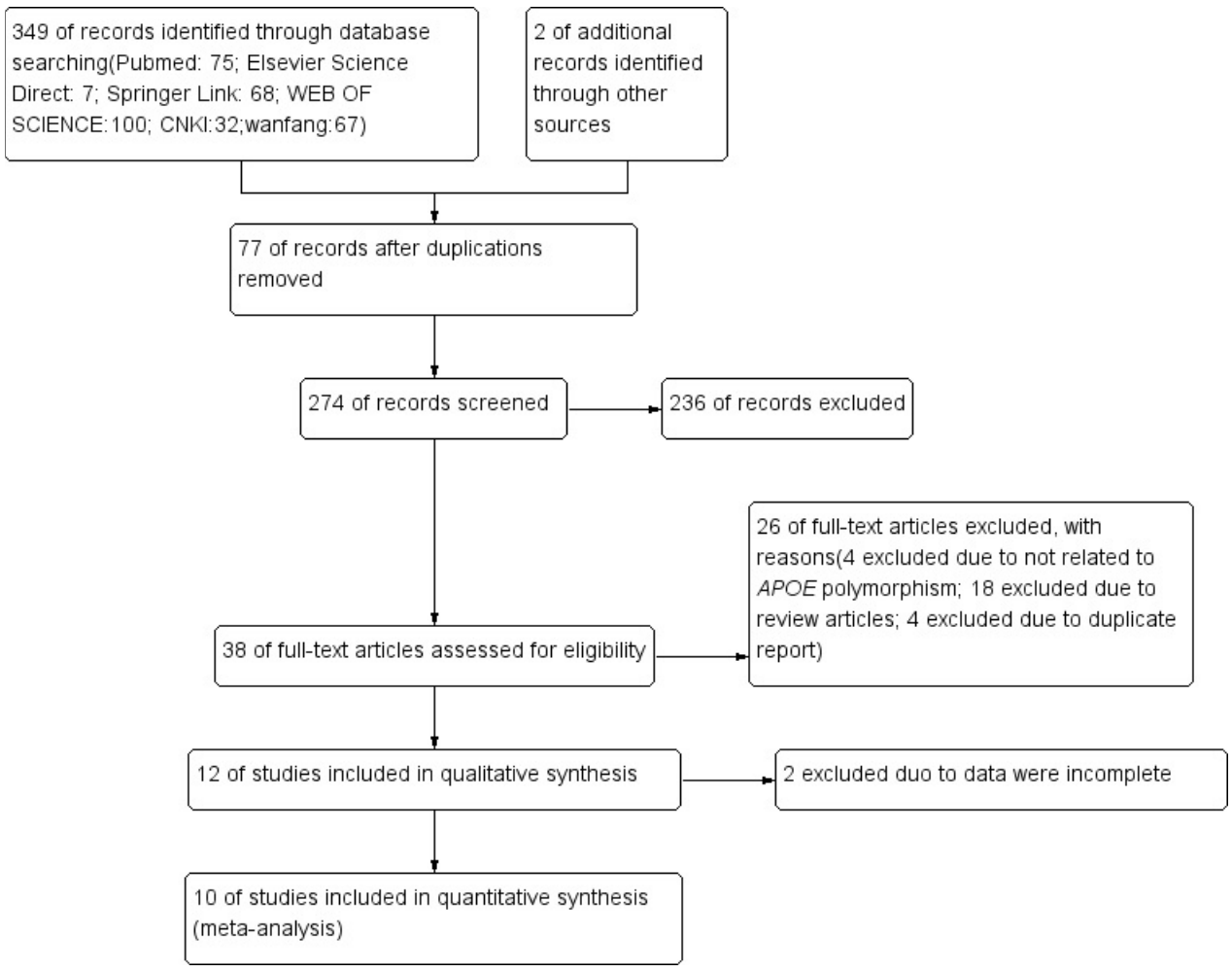

Figure 1: Flow diagram of the study selection process. CNKI, Chinese National Knowledge Infrastructure.

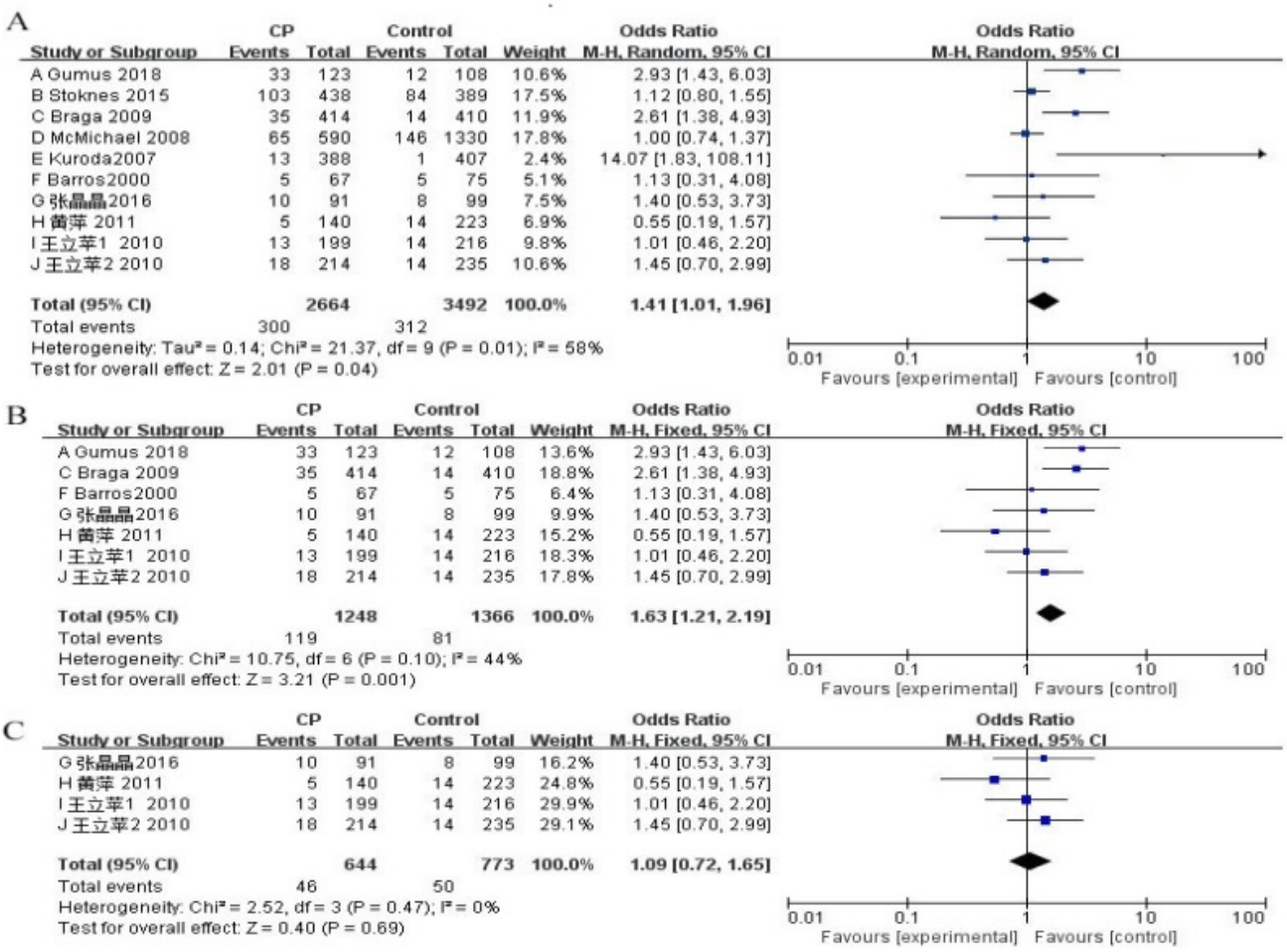

Figure 2: Forest plots describing the association of *APOE* polymorphism with cerebral palsy (CP) (ε2 allele versus ε3 allele). A: Overall analyses; B: Overall analyses (P_{HWE}>0.05); C: Chinese subgroups analyses.

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

the studies (P<0.00001, χ^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 the ε4 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, χ^2=34.68, I^2 =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 (I^2=44%, Figure 2B), and the meta-analysis showed that there was a significant positive correlation between the ε2 allele and CP risk (P=0.001, *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 ε4 vs. ε3 alleles were carried out [24-27]. The summary of the data supported a significant increase in the CP risk in individuals with ε4 alleles compared with that in those with ε3 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), a fixed effects model was then applied. We found that compared with those with ε4 alleles, individuals with ε2 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 *(I^2*

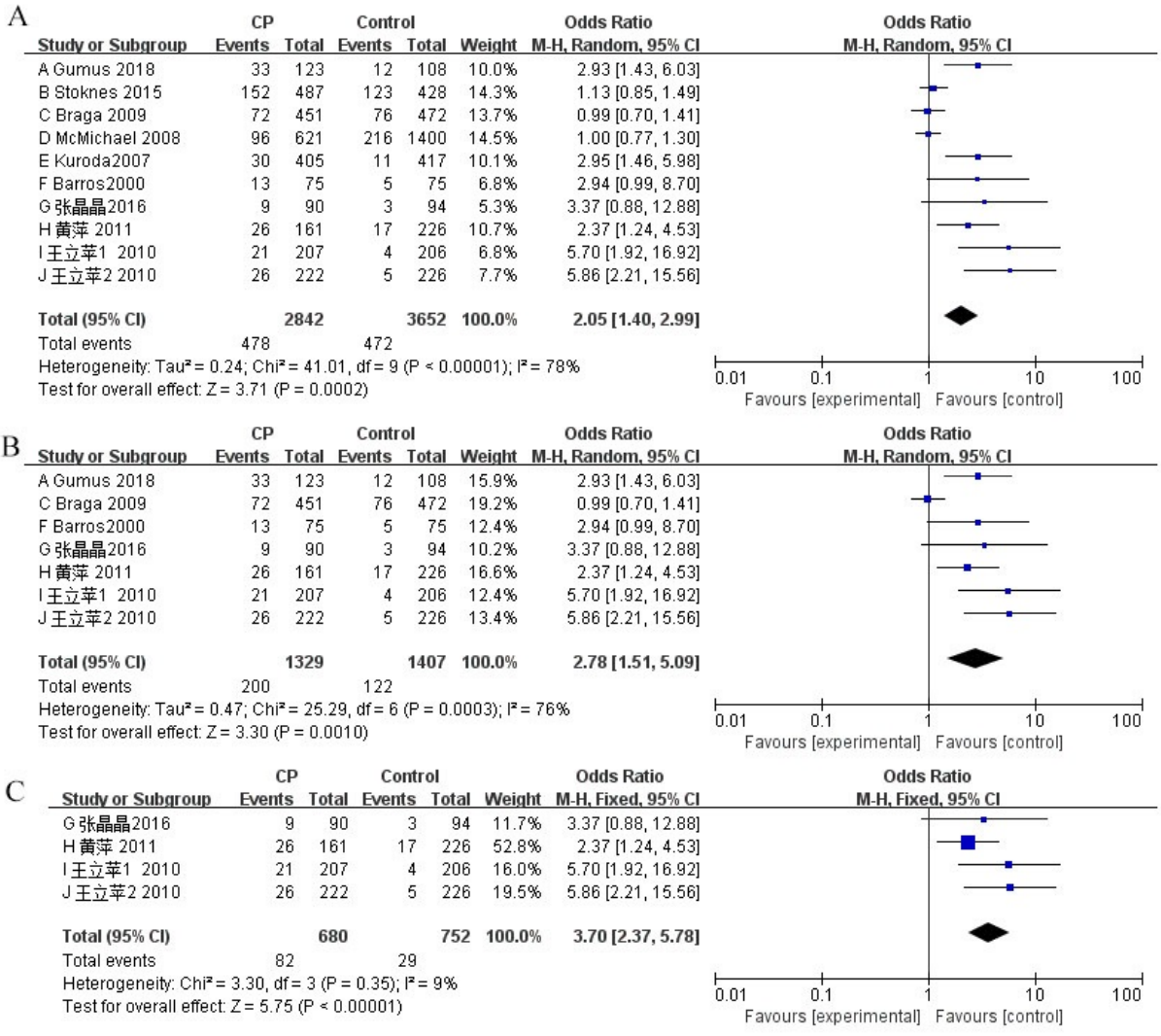

Figure 3: Forest plots describing the association of *APOE* polymorphism with cerebral palsy (CP) (ε4 allele versus ε3 allele). A: Overall analyses; B: Overall analyses (P_{HWE}>0.05); C: Chinese subgroups analyses.

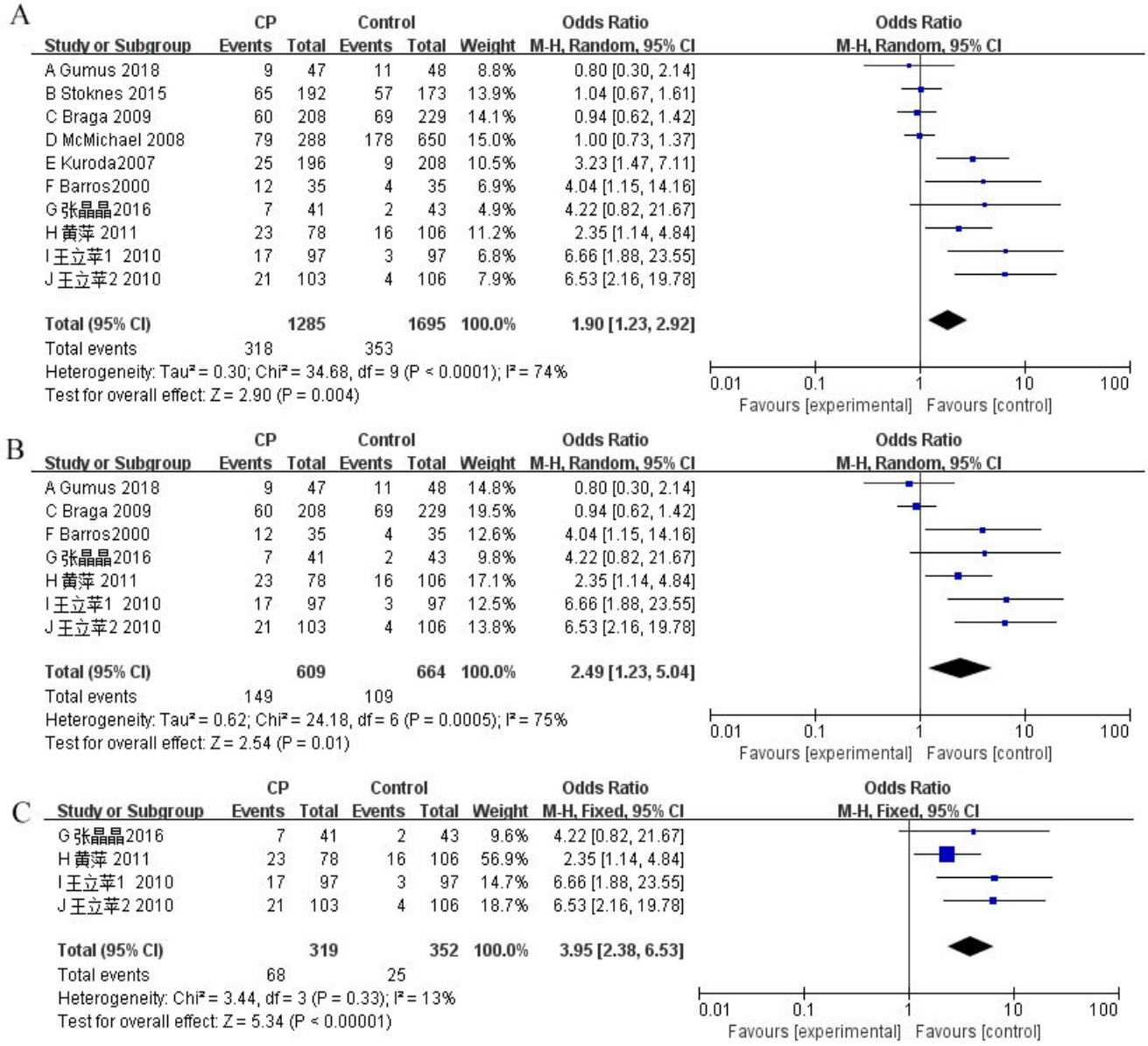

Figure 4: Forest plots describing the association of *APOE* polymorphism with cerebral palsy (CP) (E4 carriers versus E3/3 genotypes). A: Overall analyses; B: Overall analyses (P_{HWE}>0.05); C: Chinese subgroups analyses.

=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

Polymorphisms	Comparisons	Population	Number of studies	Test of association			Test of heterogeneity			
				OR (95% *CI*)	*Z*	*P* value	Model	$\chi 2$	*P* value	I^2(%)
ε2	ε2 vs ε3 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%
ε4	ε4 vs ε3 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%
		Overal[l]†	7	1.32 [0.54, 3.19]	0.61	0.54	F	2.16	0.83	0%
		Chines[e]‡	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

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

Publication bias by Egger's test					
Variables	Coefficient	SE	*Z*	*P* Value	95% *CI*
ε2 vs ε3 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
ε4 vs ε3 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

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

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 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; E4 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, E4 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. Revised the manuscript critically, and approved of the final version. All authors read and approved the final manuscript.

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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.

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