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Association between apolipoprotein E gene polymorphism and mild cognitive impairment: a meta-analysis

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Abstract: A number of published case–control studies reported that the apolipoprotein E (ApoE) gene polymorphism was associated with the mild cognitive impairment (MCI). However, previous reports still remain conflicting. To estimate the association between ApoE polymorphism and MCI susceptibility, we searched the electronic databases including PubMed, Wanfang, CNKI (China National Knowledge Infrastructure), VIP, and EMBASE to retrieve all available studies. A total of 18 studies with 2,004 cases and 3,705 controls were included in this meta-analysis. The pooled analysis based on selected studies showed that statistically significant risk association was found between ApoE gene polymorphism and MCI in overall population ($\varepsilon4$ vs $\varepsilon3$: odds ratio [OR] =2.38, 95% confidence interval [CI]: 2.11–2.68; $\varepsilon4/\varepsilon4$ vs $\varepsilon3/\varepsilon3$: OR =4.45, 95% CI: 3.06–6.48; $\varepsilon2/\varepsilon4$ vs $\varepsilon3/\varepsilon3$: OR =2.57, 95% CI: 1.77–3.73; $\varepsilon3/\varepsilon4$ vs $\varepsilon3/\varepsilon3$: OR =2.31, 95% CI: 1.99–2.69). However, no significant association was detected in two genetic models: $\varepsilon2$ versus $\varepsilon3$ (OR =0.90, 95% CI: 0.77–1.05) and $\varepsilon2/\varepsilon2$ versus $\varepsilon3/\varepsilon3$ (OR =0.91, 95% CI: 0.50–1.65). Furthermore, ApoE $\varepsilon2/\varepsilon3$ genotype provided a slight protection for MCI in overall population ($\varepsilon2/\varepsilon3$ vs $\varepsilon3/\varepsilon3$: OR =0.80, 95% CI: 0.66–0.97). In the stratified analysis based on ethnicity, similar results were also observed in Chinese population (significant risk: $\varepsilon4$ vs $\varepsilon3$: OR =2.52, 95% CI: 2.19–2.90; $\varepsilon4/\varepsilon4$ vs $\varepsilon3/\varepsilon3$: OR =5.45, 95% CI: 3.41–8.70; $\varepsilon2/\varepsilon4$ vs $\varepsilon3/\varepsilon3$: OR =2.59, 95% CI: 1.74–3.86; $\varepsilon3/\varepsilon4$ vs $\varepsilon3/\varepsilon3$: OR =2.34, 95% CI: 1.97–2.79; slight protection: $\varepsilon2/\varepsilon3$ vs $\varepsilon3/\varepsilon3$: OR =0.79, 95% CI: 0.64–0.98; no association: $\varepsilon2$ vs $\varepsilon3$: OR =0.92, 95% CI: 0.78–1.09; and $\varepsilon2/\varepsilon2$ vs $\varepsilon3/\varepsilon3$: OR =1.04, 95% CI: 0.55–1.99). In summary, this meta-analysis of 5,709 subjects suggested that ApoE $\varepsilon4$ allele was associated with an increased risk of MCI. In addition, ApoE $\varepsilon2/\varepsilon3$ genotype provided a slight protection for MCI.

Keywords: mild cognitive impairment, apolipoprotein E, polymorphism, meta-analysis

Introduction

Mild cognitive impairment (MCI) is a transitional state between normal aging and Alzheimer's disease (AD).[1,2] Approximately 18.5% of Chinese people over the age of 55 years were estimated to have MCI.[3] In fact, patients with MCI represented a conversion rate of 10%–15% per year for developing AD.[4,5] Therefore, discussing the associations between the risk factors and MCI susceptibility is of great significance.

The apolipoprotein E (ApoE) gene, located on the chromosome 19q13, is closely related to MCI and AD.[6,7] ApoE protein plays a vital role in the transport of lipid and cholesterol in the central nervous system (CNS).[8] ApoE gene polymorphism has three common alleles: $\varepsilon2$, $\varepsilon3$, and $\varepsilon4$, which determine three homozygous ($\varepsilon2/\varepsilon2$, $\varepsilon3/\varepsilon3$, and $\varepsilon4/\varepsilon4$) and heterozygous ($\varepsilon2/\varepsilon4$, $\varepsilon3/\varepsilon4$, and $\varepsilon2/\varepsilon3$) genotypes.[9] Of those, ApoE $\varepsilon3$ allele is the most prevalent, followed by $\varepsilon4$ and $\varepsilon2$ alleles.[10] The ApoE $\varepsilon4$ allele has been

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highly associated with MCI;[11,12] its presence is associated with the elevated serum β-amyloid and age-related cognitive decline.[13,14] In addition, it is well known that $\varepsilon 4$ allele was associated with an increased risk of AD.[15]

To date, numerous studies have been conducted to estimate the association between ApoE polymorphism and MCI susceptibility. However, the reports still conflict. The sample sizes of the published studies have been relatively small, and individual study may lack powerful power to obtain a more reliable conclusion. In addition, no meta-analysis was performed to explore those associations. Therefore, we conducted a comprehensive meta-analysis to clarify those varying associations.

Materials and methods

Search strategy

All published studies assessing the association of ApoE polymorphism with MCI susceptibility were identified by comprehensive literature searches of the PubMed, EMBASE, Wanfang, VIP, and CNKI (China National Knowledge Infrastructure) databases from May 2002 to October 2016. The key terms used for searching are ("MCI" OR "mild cognitive impairment") AND ("ApoE" OR "apolipoprotein E") AND ("polymorphism" OR "variant"). Moreover, the references in all selected studies were searched for other potential studies.

Inclusion and exclusion criteria

Studies included in our meta-analysis must meet the following criteria: 1) case–control or cohort study; 2) estimate the association between ApoE polymorphism and MCI susceptibility; 3) allelic and genotype frequencies are available for calculating odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs); 4) genotype distribution of control must be in Hardy–Weinberg equilibrium (HWE); 5) not overlapping samples; and 6) studies with full-text. The exclusion criteria for the studies were as follows: case reports, reviews, in vitro studies, clinical trials, incomplete genotype data, and meta-analysis.

Data extraction

Relevant data from each selected studies, including the first author, publication year, country of region, genotyping methods, sample size, genotype distributions and allele frequencies of cases and controls, and the diagnosis criteria of MCI, were extracted independently by two investigators (TH and WSD).

Statistical analysis

The ORs and corresponding 95% CIs were used to evaluate the relationship between ApoE polymorphism and MCI susceptibility. The risk of variant genotypes $\varepsilon 2/\varepsilon 2$, $\varepsilon 2/\varepsilon 3$, $\varepsilon 2/\varepsilon 4$, $\varepsilon 3/\varepsilon 4$, and $\varepsilon 4/\varepsilon 4$ was evaluated compared with the $\varepsilon 3/\varepsilon 3$ genotype. In addition, $\varepsilon 2$ versus $\varepsilon 3$ and $\varepsilon 4$ versus $\varepsilon 3$ were also analyzed. The test of heterogeneity for selected studies was assessed by I^2-statistics.[16,17] When a significant heterogeneity (no heterogeneity: $I^2<25\%$; moderate heterogeneity: $I^2=25\%–50\%$; significant heterogeneity: $I^2\geq 50\%$) appeared across the selected studies, the random effects model was used.[18,19] Otherwise, the fixed effects model was adopted. To estimate whether our results were stable, a sensitivity analysis was performed by sequentially omitting each individual study and recalculating the remaining studies. The potential publication bias was examined by Begg's tests and funnel plot.[20] Statistical tests were carried out by Stata software v12.0 (Stata Corp, College Station, TX, USA).

Results

Characteristics of eligible studies

The initial search identified 721 references. Of those, 18 publications[21–38] with 2,004 cases and 3,705 controls were included in our meta-analysis. The study selection process was shown in Figure 1. Of all eligible studies focusing on the association between ApoE polymorphism and MCI susceptibility, 14 studies were performed in China,[21,23–35] two in Caucasians,[22,37] one in Brazil,[36] and one in India.[38] The genotype distributions of all control samples are consistent with the HWE. The detailed characteristics of selected studies are summarized in Table 1.

Quantitative synthesis

The overall results showed that ApoE variants were associated with an increased risk of MCI in the following genetic models: $\varepsilon 4$ versus $\varepsilon 3$: OR =2.38, 95% CI: 2.11–2.68; $\varepsilon 4/\varepsilon 4$ versus $\varepsilon 3/\varepsilon 3$: OR =4.45, 95% CI: 3.06–6.48; $\varepsilon 2/\varepsilon 4$ versus $\varepsilon 3/\varepsilon 3$: OR =2.57, 95% CI: 1.77–3.73; $\varepsilon 3/\varepsilon 4$ versus $\varepsilon 3/\varepsilon 3$: OR =2.31, 95% CI: 1.99–2.69 (Figure 2 and Table 2). The results also showed that a slight protection was observed in $\varepsilon 2/\varepsilon 3$ versus $\varepsilon 3/\varepsilon 3$ analysis (OR =0.80, 95% CI: 0.66–0.97, Table 2). However, no association was detected in $\varepsilon 2$ versus $\varepsilon 3$ (OR =0.90, 95% CI: 0.77–1.05, Figure 3 and Table 2) and $\varepsilon 2/\varepsilon 2$ versus $\varepsilon 3/\varepsilon 3$ models (OR =0.91, 95% CI: 0.50–1.65, Table 2). In the stratified analysis based on ethnicity, we only analyzed the Chinese population due to rare publications on other ethnicities. Stratified analysis indicated that ApoE

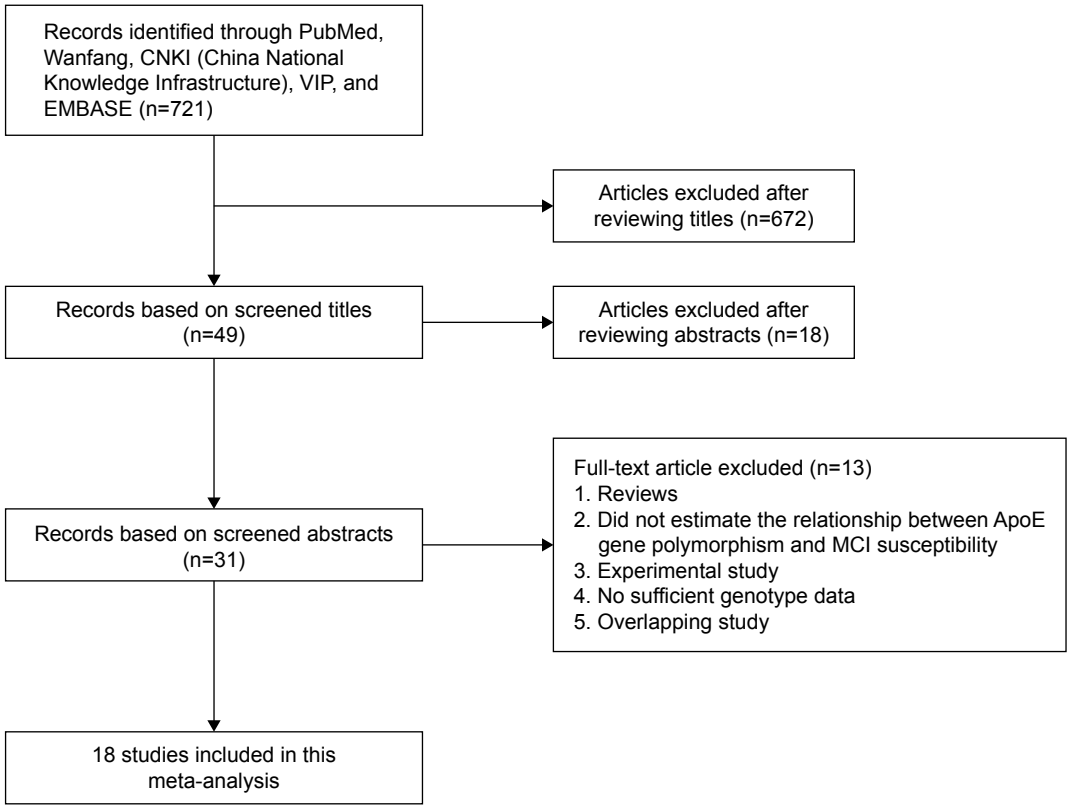

Figure 1 Flow diagram of the article selection process.

variants contributed to increase the risk of MCI in Chinese population (ε4 versus ε3: OR =2.52, 95% CI: 2.19–2.90; ε4/ε4 versus ε3/ε3: OR =5.45, 95% CI: 3.41–8.70; ε2/ε4 versus ε3/ε3: OR =2.59, 95% CI: 1.74–3.86; ε3/ε4 versus ε3/ε3: OR =2.34, 95% CI: 1.97–2.79, Table 2). No significant association was observed in two genetic models in Chinese population (ε2 versus ε3: OR =0.92, 95% CI: 0.78–1.09 and ε2/ε2 versus ε3/ε3: OR =1.04, 95% CI: 0.55–1.99, Table 2). It is noted that only slight protection was found under the comparison of ε2/ε3 versus ε3/ε3 genotype (OR =0.79, 95% CI: 0.64–0.98, Table 2) in Chinese population. In addition, no significant heterogeneity was detected in all genetic models (Table 2).

Sensitivity analysis and publication bias

The stability of results is assessed by sequential omission of one study in turn. The pooled ORs are not materially altered (Figures 4 and 5), indicating that no single study could influence the stability of the results of this meta-analysis.

To assess the potential publications bias of studies, Begg's test was performed. For ε2 versus ε3, the funnel plot seemed nearly symmetry (Figure 6), and the *P*-value for Begg's test ($P=0.820$) suggests no obvious publication bias. With regard to ε4 versus ε3 model, the funnel plot seemed asymmetry (Figure 7), and the *P*-value ($P<0.05$) revealed that a significant publication existed. By using the trim and fill method, six studies are filled for ε4 versus ε3 model, in order to balance the funnel plot. The adjusted risk estimate for ε4 versus ε3 was 2.255 (95% CI: 2.141–2.370, $P<0.001$), remaining statistically significant, suggesting that the results of our meta-analysis was stable.

Discussion

The ApoE gene is one of the most studied genes for associations with MCI susceptibility. The ApoE polymorphism has been associated with an increased risk of several CNS disorders. Although the exact mechanisms by which ApoE variants lead to MCI are still unclear, ApoE may have many important functions for developing MCI. Studies showed that carrying ε4 allele could increase the aggregation and deposition of amyloid β-protein (Aβ) in brain compared to other polymorphisms.[39,40] In addition, higher tau levels, lower CSF Aβ 42 levels, and greater brain atrophy were found in the ε4 allele carriers than noncarriers.[41] ApoE gene

Table 1 Characteristics of the selected studies

Study	Year	Geographical location	Sample size (case/control)	Case								Control								
				ε4ε4	ε4ε3	ε4ε2	ε3ε3	ε3ε2	ε2ε2	ε4	ε3	ε2	ε4ε4	ε4ε3	ε4ε2	ε3ε3	ε3ε2	ε2ε2	ε4	ε3	ε2
Wang et al[21]	2002	China (Heifei)	28/30	2	9	7	6	3	1	20	24	12	1	4	2	18	4	1	8	44	8
Gamarra et al[22]	2015	Spain	124/125	20	66	2	119	9	0	108	313	11	0	49	2	170	22	2	51	411	28
Wang et al[23]	2014	China (Wuzhong)	216/743	1	24	1	135	17	3	27	311	24	6	34	2	580	105	16	48	1,299	139
Borenstein et al[24]	2010	China (Shanghai)	30/32	2	5	2	20	1	0	11	46	3	0	2	1	23	6	0	3	54	7
Wang et al[25]	2014	China (Beijing)	56/75	0	23	1	26	3	3	24	78	10	0	8	3	51	12	1	11	122	17
Chen et al[26]	2016	China (Shanghai)	583/1,149	27	129	16	353	56	2	199	891	76	8	156	21	802	154	8	193	1,914	191
Chen et al[27]	2016	China (Ningbo)	64/54	5	20	0	35	4	0	30	94	4	0	7	0	37	10	0	7	91	10
Hu et al[28]	2005	China (Guangxi)	16/96	1	3	1	10	1	0	6	24	2	0	4	1	79	7	5	5	169	18
Xu et al[29]	2009	China (Guangzhou)	120/120	2	36	1	65	16	0	41	182	17	1	16	1	81	21	0	19	199	22
Lv and Zhong[30]	2012	China (Shanghai)	84/106	3	20	2	52	6	1	28	130	10	0	15	1	76	12	2	16	179	15
He et al[31]	2015	China (Nanchang)	120/120	4	23	1	79	12	1	32	193	15	0	17	1	83	17	2	18	200	22
Ye and Zhang[32]	2008	China (Wuhan)	56/89	2	15	5	31	3	0	24	80	8	1	11	1	64	12	0	14	151	13
He et al[33]	2015	China (Shenyang)	63/60	6	18	1	32	6	0	31	88	7	2	8	1	39	10	0	13	96	11
Yue et al[34]	2013	China (Nanjing)	111/90	4	25	3	66	13	0	36	170	16	0	8	0	69	13	0	8	159	13
Chen et al[35]	2011	China (Guiyang)	76/152	9	18	28	13	6	2	64	50	38	10	29	38	57	14	4	87	157	60
Kerr et al[36]	2016	Brazil	43/144	1	14	1	25	1	1	17	65	4	1	31	2	91	18	1	35	231	22
Lanni et al[37]	2012	Italy	70/248	2	18	2	41	7	0	24	107	9	0	27	0	201	20	0	27	449	20
Jairani et al[38]	2016	India	87/152	4	40	2	35	6	0	50	116	8	20	34	3	82	8	5	81	206	21

polymorphisms also play an important role in the neuronal repair,[42] cerebral glucose metabolism,[43] lipid metabolism,[44] maintaining synaptic plasticity,[45,46] neuroinflammation,[47–49] and neurogenesis.[50–52] Those functions of ApoE may also be involved in the pathology of MCI.

In 1998, Smith et al[53] first demonstrated that ApoE gene ε4 allele was highly associated with an increased risk of MCI. Subsequently, a number of studies were performed to estimate the association of ApoE gene polymorphism with MCI. However, the results were still controversial. To further explore and evaluate the association between ApoE gene polymorphism and MCI susceptibility, we performed a meta-analysis of 2,004 cases and 3,705 controls. Overall, we detected that ApoE polymorphism contributed to increase the risk of MCI under the ε4 versus ε3, ε4/ε4 versus ε3/ε3, ε2/ε4 versus ε3/ε3, and ε3/ε4 versus ε3/ε3 genetic models. However, no association was found under the ε2 versus ε3 and ε2/ε2 versus ε3/ε3 genetic models. Furthermore, a slight protection was discovered under the ε2/ε3 versus ε3/ε3 genetic model. In the stratified analysis, we analyzed only the Chinese population, and the results were similar to overall population. Interestingly, we found that ApoE ε4 allele increased MCI risk in a dose-dependent manner (ε4 versus ε3: OR =2.52, 95% CI: 2.19–2.90; ε4/ε4 versus ε3/ε3: OR =5.45, 95% CI: 3.41–8.70), which was in accordance with several previous studies.[23,24,54,55] No significant heterogeneity was identified in any genetic models.

In this meta-analysis, we detected a potential publication bias in the ε4 versus ε3 genetic model, which may generate false-positive results. By using the trim and fill method, the results suggested that six studies were needed to balance the asymmetric funnel plot and the adjusted results for ε4 versus ε3 remained significant (OR =2.255, 95% CI: 2.141–2.370, $P<0.001$), indicating that the results were stable. It was emphasized that the potential publications may partly influence the results, but not deeply.

There are several limitations in the present meta-analysis. First, our meta-analysis was based predominantly on Chinese population. Only one study focused on the African, two studies on Caucasians, and one study on Indian, which might generate a partial result. Second, due to rare publications on other ethnicities, we analyzed only the Chinese population and other ethnicities were not evaluated in our meta-analysis. Finally, MCI is a complex disease. Gene–gene or gene–environment factors play an important role in MCI susceptibility. However, most selected studies did not analyze those interacted factors.

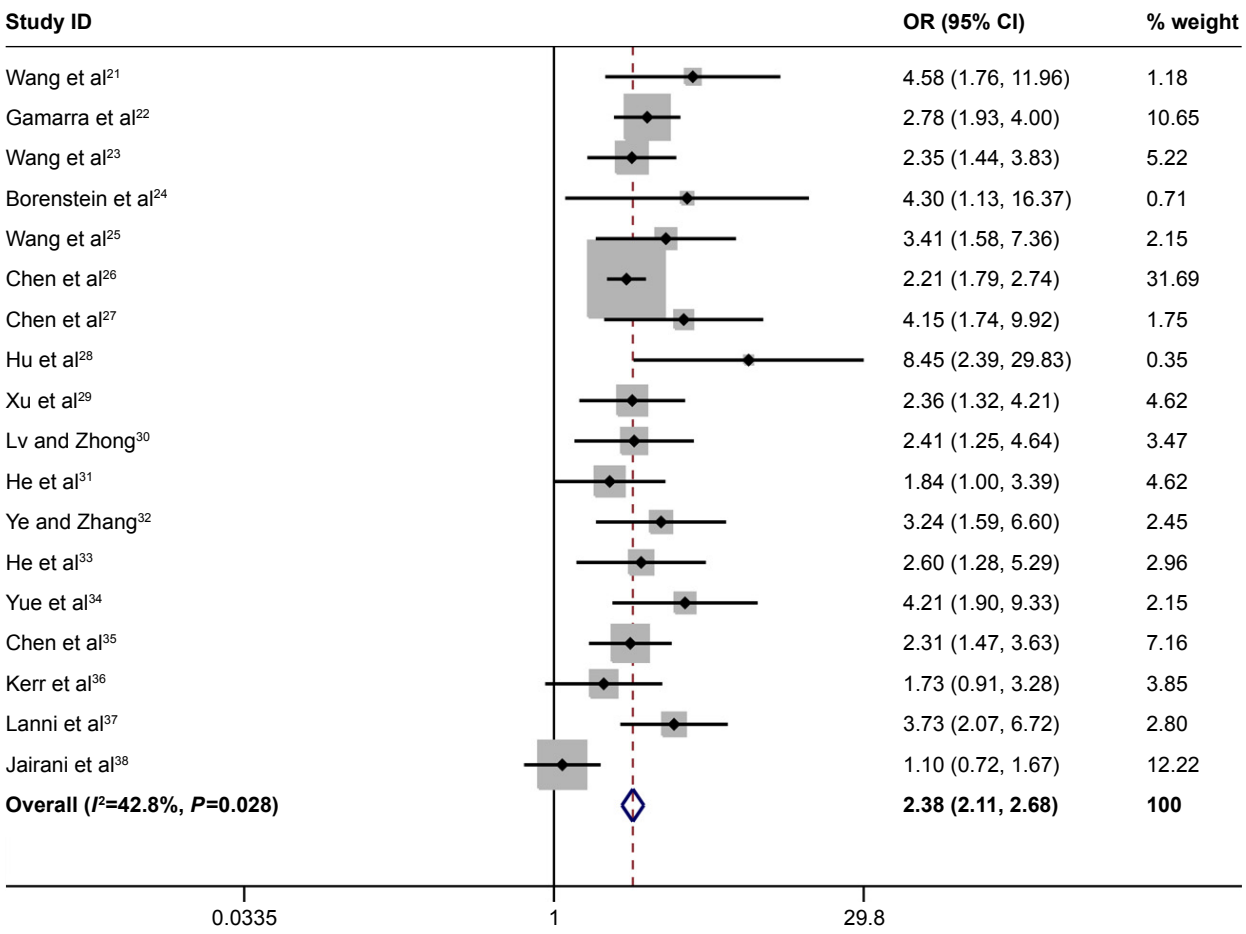

Figure 2 Forest plot for the association of ApoE polymorphism with MCI susceptibility in the overall populations ($\varepsilon4$ vs $\varepsilon3$).
Abbreviations: ApoE, apolipoprotein E; MCI, mild cognitive impairment; OR, odds ratio; CI, confidence interval.

Table 2 Meta-analysis of apolipoprotein E gene polymorphism and MCI risk

Genetic models	Variables	Number of studies	Test of association			Test of heterogeneity	
			OR	95% CI	*P*-value	I^2 (%)	Model
$\varepsilon2/\varepsilon2$ vs $\varepsilon3/\varepsilon3$	Overall	18	0.91	0.50–1.65	0.758	0	F
	Chinese	14	1.04	0.55–1.99	0.902	0	F
$\varepsilon2/\varepsilon4$ vs $\varepsilon3/\varepsilon3$	Overall	18	2.57	1.77–3.73	<0.001	0	F
	Chinese	14	2.59	1.74–3.86	<0.001	0	F
$\varepsilon2/\varepsilon3$ vs $\varepsilon3/\varepsilon3$	Overall	18	0.8	0.66–0.97	0.026	0	F
	Chinese	14	0.79	0.64–0.98	0.03	0	F
$\varepsilon3/\varepsilon4$ vs $\varepsilon3/\varepsilon3$	Overall	18	2.31	1.99–2.69	<0.001	0	F
	Chinese	14	2.34	1.97–2.79	<0.001	5.8	F
$\varepsilon4/\varepsilon4$ vs $\varepsilon3/\varepsilon3$	Overall	18	4.45	3.06–6.48	<0.001	39.6	F
	Chinese	14	5.45	3.41–8.70	<0.001	0	F
$\varepsilon4$ allele vs $\varepsilon3$ allele	Overall	18	2.38	2.11–2.68	<0.001	42.8	F
	Chinese	14	2.52	2.19–2.90	<0.001	0	F
$\varepsilon2$ allele vs $\varepsilon3$ allele	Overall	18	0.9	0.77–1.05	0.179	32.2	F
	Chinese	14	0.92	0.78–1.09	0.346	30.2	F

Note: *P*-value corresponding to the *Z*-test for the summary effect estimate ($P<0.05$ considered statistically significant).
Abbreviations: F, fixed effects model; OR, odds ratio; CI, confidence interval; I^2, heterogeneity index; MCI, mild cognitive impairment.

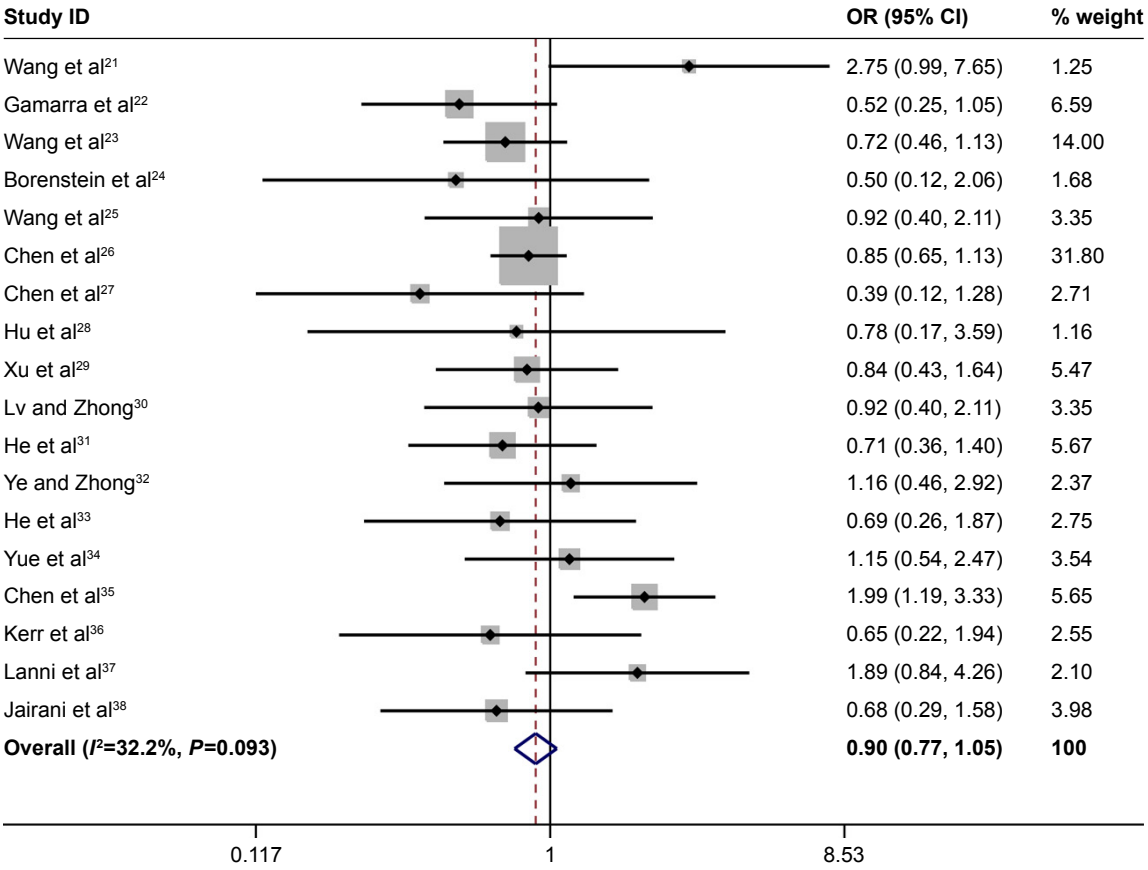

Figure 3 Forest plot for the association of ApoE polymorphism with MCI susceptibility in the overall populations ($\varepsilon 2$ vs $\varepsilon 3$).
Abbreviations: ApoE, apolipoprotein E; MCI, mild cognitive impairment; OR, odds ratio; CI, confidence interval.

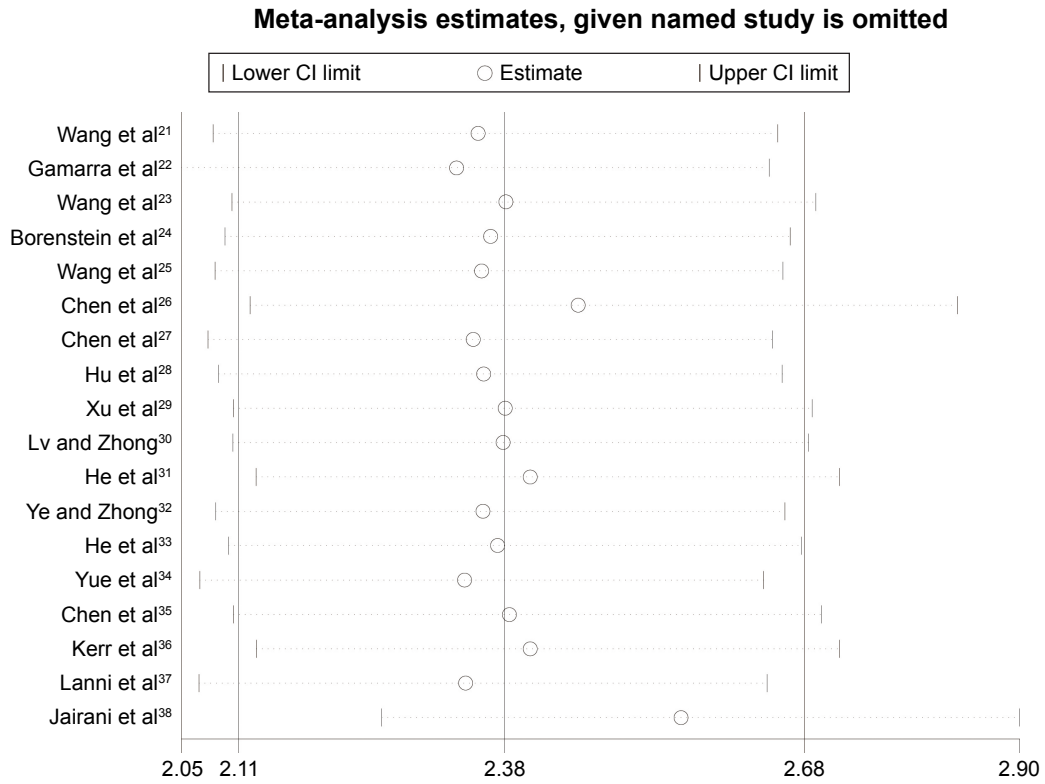

Figure 4 Sensitivity analysis of the summary of OR coefficients in the overall populations ($\varepsilon 4$ vs $\varepsilon 3$).
Abbreviations: OR, odds ratio; CI, confidence interval.

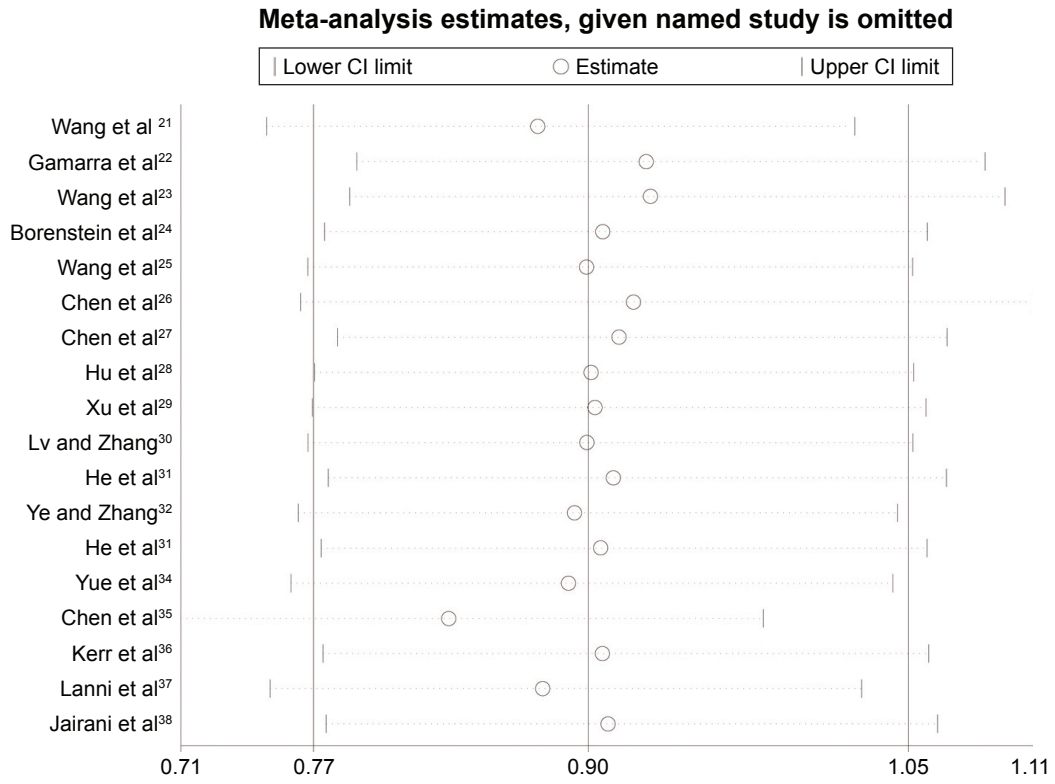

Figure 5 Sensitivity analysis of the summary of OR coefficients in the overall populations ($\varepsilon 2$ vs $\varepsilon 3$).
Abbreviations: OR, odds ratio; CI, confidence interval.

Conclusion

Our meta-analysis first showed that ApoE $\varepsilon 4$ allele, $\varepsilon 4\varepsilon 4$, $\varepsilon 4\varepsilon 3$, and $\varepsilon 2\varepsilon 4$ genotypes were the risk factors of MCI, while $\varepsilon 2\varepsilon 3$ genotype was a protective factor, especially in Chinese population. We boldly supposed that ApoE polymorphism may be used as a useful potential therapeutic target to prevent, delay, or revert the healthy elderly to MCI conversion. Considering several limitations mentioned above, the results should be interpreted with caution. Further well-designed studies with larger sample size are required to validate the association between ApoE polymorphism and MCI risk.

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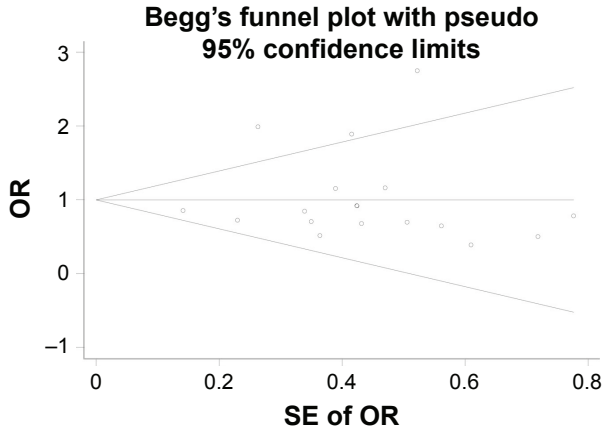

Figure 6 Begg's funnel plot of ApoE polymorphism with MCI susceptibility in overall populations ($\varepsilon 2$ vs $\varepsilon 3$).
Abbreviations: ApoE, apolipoprotein E; MCI, mild cognitive impairment; OR, odds ratio; SE, standard error.

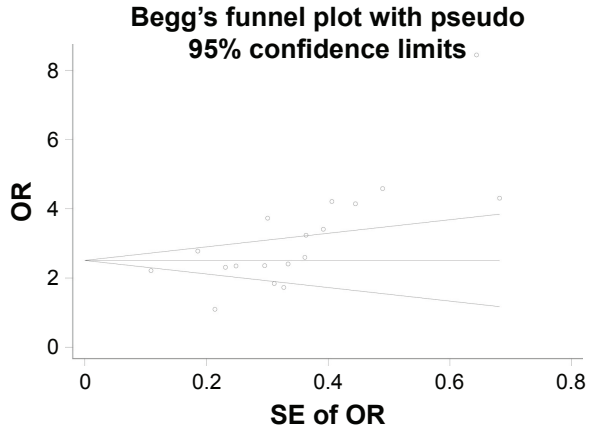

Figure 7 Begg's funnel plot of ApoE polymorphism with MCI susceptibility in overall populations ($\varepsilon 4$ vs $\varepsilon 3$).
Abbreviations: ApoE, apolipoprotein E; MCI, mild cognitive impairment; OR, odds ratio; SE, standard error.

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Disclosure

The authors report no conflicts of interest in this work.

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