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 (ε4 vs ε3: odds ratio [OR] =2.38, 95% confidence interval [CI]: 2.11–2.68; ε4/ε4 vs ε3/ε3: OR =4.45, 95% CI: 3.06–6.48; ε2/ε4 vs ε3/ε3: OR =2.57, 95% CI: 1.77–3.73; ε3/ε4 vs ε3/ε3: OR =2.31, 95% CI: 1.99–2.69). However, no significant association was detected in two genetic models: ε2 versus ε3 (OR =0.90, 95% CI: 0.77–1.05) and ε2/ε2 versus ε3/ε3 (OR =0.91, 95% CI: 0.50–1.65). Furthermore, ApoE ε2/ε3 genotype provided a slight protection for MCI in overall population (ε2 vs ε3/ε3: 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: ε4 vs ε3: OR =2.52, 95% CI: 2.19–2.90; ε4/ε4 vs ε3/ε3: OR =5.45, 95% CI: 3.41–8.70; ε2/ε4 vs ε3/ε3: OR =2.59, 95% CI: 1.74–3.86; ε3/ε4 vs ε3/ε3: OR =2.34, 95% CI: 1.97–2.79; slight protection: ε2/ε3 vs ε3/ε3: OR =0.79, 95% CI: 0.64–0.98; no association: ε2 vs ε3: OR =0.92, 95% CI: 0.78–1.09; and ε2/ε2 vs ε3/ε3: OR =1.04, 95% CI: 0.55–1.99). In summary, this meta-analysis of 5,709 subjects suggested that ApoE ε4 allele was associated with an increased risk of MCI. In addition, ApoE ε2/ε3 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). Approximately 18.5% of Chinese people over the age of 55 years were estimated to have MCI. In fact, patients with MCI represented a conversion rate of 10%–15% per year for developing AD. The apolipoprotein E (ApoE) gene, located on the chromosome 19q13, is closely related to MCI and AD. ApoE protein plays a vital role in the transport of lipid and cholesterol in the central nervous system (CNS). ApoE gene polymorphism has three common alleles: ε2, ε3, and ε4, which determine three homozygous (ε2/ε2, ε3/ε3, and ε4/ε4) and heterozygous (ε2/ε4, ε3/ε4, and ε2/ε3) genotypes. Of those, ApoE ε3 allele is the most prevalent, followed by ε4 and ε2 alleles. The ApoE ε4 allele has been commonly identified to be associated with increased risk of AD.
highly associated with MCI, its presence is associated with the elevated serum β-amyloid and age-related cognitive decline. In addition, it is well known that ε4 allele was associated with an increased risk of AD.

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 ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε4, and ε4/ε4 was evaluated compared with the ε3/ε3 genotype. In addition, ε2 versus ε3 and ε4 versus ε3 were also analyzed. The test of heterogeneity for selected studies was assessed by I²-statistics. When a significant heterogeneity (no heterogeneity: I²<25%; moderate heterogeneity: I²=25%–50%; significant heterogeneity: I²≥50%) appeared across the selected studies, the random effects model was used.

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. 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 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, two in Caucasians, one in Brazil, and one in India. 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: ε4 versus ε3: OR =2.38, 95% CI: 2.11–2.68; ε4/ε4 versus ε3/ε3: OR =4.45, 95% CI: 3.06–6.48; ε2/ε4 versus ε3/ε3: OR =2.57, 95% CI: 1.77–3.73; ε3/ε4 versus ε3/ε3: 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 ε2/ε3 versus ε3/ε3 analysis (OR =0.80, 95% CI: 0.66–0.97, Table 2). However, no association was detected in ε2 versus ε3 (OR =0.90, 95% CI: 0.77–1.05, Figure 3 and Table 2) and ε2/ε2 versus ε3/ε3 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
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. In addition, higher tau levels, lower CSF Aβ 42 levels, and greater brain atrophy were found in the ε4 allele carriers than noncarriers. ApoE gene
Table 1 Characteristics of the selected studies

| Study | Year | Geographical location | Sample size (case/control) | Case location | Control location |
|-------|------|-----------------------|---------------------------|---------------|-----------------|
| Wang et al | 2002 | China (Hebei) | 284/30 | China (Hebei) | 284/30 |
| Gamara et al | 2015 | Spain | 124/123 | Spain | 124/123 |
| Wang et al | 2014 | China (Wuhan) | 216/243 | China (Wuhan) | 216/243 |
| Wu et al | 2010 | China (Beijing) | 305/91 | China (Beijing) | 305/91 |
| Borjeman et al | 2017 | Italy | 367/75 | Italy | 367/75 |
| Chen et al | 2016 | China (Shanghai) | 27/129 | China (Shanghai) | 27/129 |
| Hu et al | 2008 | China (Nagoya) | 567/54 | China (Nagoya) | 567/54 |
| Chen et al | 2006 | China (Shanghai) | 27/129 | China (Shanghai) | 27/129 |
| Xu et al | 2005 | China (Guangzhou) | 367/75 | China (Guangzhou) | 367/75 |
| Li et al | 2009 | China (Shanghai) | 27/129 | China (Shanghai) | 27/129 |
| He et al | 2013 | China (Shanghai) | 567/54 | China (Shanghai) | 567/54 |
| Ye et al | 2012 | China (Shanghai) | 27/129 | China (Shanghai) | 27/129 |
| Chen et al | 2015 | China (Shanghai) | 567/54 | China (Shanghai) | 567/54 |
| Kong et al | 2016 | China (Shanghai) | 567/54 | China (Shanghai) | 567/54 |
| Li et al | 2015 | China (Shanghai) | 567/54 | China (Shanghai) | 567/54 |
| Lan et al | 2010 | China (Shanghai) | 567/54 | China (Shanghai) | 567/54 |
| Jia et al | 2010 | China (Shanghai) | 567/54 | China (Shanghai) | 567/54 |

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–environment factors play an important role in MCI susceptibility. However, most selected studies did not analyze those interacted factors.

polymorphisms also play an important role in the neuronal repair, cerebral glucose metabolism, maintaining synaptic plasticity, neuroinflammation, and neurogenesis. Those functions of ApoE may also be involved in the pathology of MCI.

In 1998, Smith et al 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. 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 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–environment factors play an important role in MCI susceptibility. However, most selected studies did not analyze those interacted factors.
### 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      | I² (%)  | Model |
| ε2/ε2 vs ε3/ε3       | Overall       | 18                | 0.91                | 0.50–1.65             | 0.758       | 0       | F     |
|                       | Chinese       | 14                | 1.04                | 0.55–1.99             | 0.902       | 0       | F     |
| ε2/ε4 vs ε3/ε3       | Overall       | 18                | 2.57                | 1.77–3.73             | <0.0001     | 0       | F     |
|                       | Chinese       | 14                | 2.59                | 1.74–3.86             | <0.0001     | 0       | F     |
| ε2/ε3 vs ε3/ε3       | Overall       | 18                | 0.8                 | 0.66–0.97             | 0.026       | 0       | F     |
|                       | Chinese       | 14                | 0.79                | 0.64–0.98             | 0.03        | 0       | F     |
| ε3/ε4 vs ε3/ε3       | Overall       | 18                | 2.31                | 1.99–2.69             | <0.0001     | 0       | F     |
|                       | Chinese       | 14                | 2.34                | 1.97–2.79             | <0.0001     | 5.8     | F     |
| ε4/ε4 vs ε3/ε3       | Overall       | 18                | 4.45                | 3.06–6.48             | <0.0001     | 39.6    | F     |
|                       | Chinese       | 14                | 5.45                | 3.41–8.70             | <0.0001     | 0       | F     |
| ε4 allele vs ε3 allele| Overall    | 18                | 2.38                | 2.11–2.68             | <0.0001     | 42.8    | F     |
|                       | Chinese       | 14                | 2.52                | 2.19–2.90             | <0.0001     | 0       | F     |
| ε2 allele vs ε3 allele| Overall    | 18                | 0.8                 | 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; I², heterogeneity index; MCI, mild cognitive impairment.

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**Figure 2:** Forest plot for the association of ApoE polymorphism with MCI susceptibility in the overall populations (ε4 vs ε3).

**Abbreviations:** ApoE, apolipoprotein E; MCI, mild cognitive impairment; OR, odds ratio; CI, confidence interval.
Figure 3 Forest plot for the association of ApoE polymorphism with MCI susceptibility in the overall populations (ε2 vs ε3).
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 (ε4 vs ε3).
Abbreviations: OR, odds ratio; CI, confidence interval.
Association between ApoE gene polymorphism and MCI

Conclusion
Our meta-analysis first showed that ApoE ε4 allele, ε4ε4, ε4ε3, and ε2ε4 genotypes were the risk factors of MCI, while ε2ε3 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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Disclosure

The authors report no conflicts of interest in this work.

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