



## OPEN

# Apolipoprotein E gene polymorphism and Alzheimer's disease in Chinese population: a meta-analysis

SUBJECT AREAS:  
HEALTH CARE  
ALZHEIMER'S DISEASE

Mengying Liu<sup>1,2</sup>, Chen Bian<sup>1</sup>, Jiqiang Zhang<sup>1</sup> & Feng Wen<sup>3</sup>

Received  
14 January 2014

Accepted  
20 February 2014

Published  
17 March 2014

Correspondence and requests for materials should be addressed to J.Q.Z. (zhangjqtmu@yahoo.com) or F.W. (wenfengjlu@163.com)

<sup>1</sup>Department of Neurobiology, Chongqing Key Laboratory of Neurobiology, Third Military Medical University, Chongqing 400038, China, <sup>2</sup>Student Camp Seven, Third Military Medical University, Chongqing 400038, China, <sup>3</sup>Systems Biology Laboratory, Department of Basic Sciences, College of Veterinary Medicine, Mississippi State University, Mississippi State, MS 39762, USA.

The relationship between Apolipoprotein E (ApoE) genotype and the risk of Alzheimer's disease (AD) is relatively well established in Caucasians, but less established in other ethnicities. To examine the association between ApoE polymorphism and the onset of AD in Chinese population, we searched the commonly used electronic databases between January 2000 and November 2013 for relevant studies. Total 20 studies, including 1576 cases and 1741 controls, were retrieved. The results showed statistically significant positive association between risk factor  $\epsilon 4$  allele carriers and AD in Chinese population (OR = 3.93, 95% CI = 3.37–4.58,  $P < 0.00001$ ). Genotype ApoE  $\epsilon 4/\epsilon 4$  and  $\epsilon 4/\epsilon 3$  have statistically significant association with AD as well ( $\epsilon 4/\epsilon 4$ : OR = 11.76, 95% CI = 6.38–21.47,  $P < 0.00001$ ;  $\epsilon 4/\epsilon 3$ : OR = 3.08, 95% CI = 2.57–3.69,  $P < 0.00001$ ). Furthermore, the frequency of the ApoE  $\epsilon 3$  is lower in AD than that in the health controls, and the difference of  $\epsilon 3$  allele is also statistically significant (OR = 0.42, 95% CI = 0.37–0.47,  $P < 0.00001$ ). No significant heterogeneity was observed among all studies. This meta-analysis suggests that the subject with at least one ApoE  $\epsilon 4$  allele has higher risk suffering from AD than controls in Chinese population. The results also provide a support for the protection effect of ApoE  $\epsilon 3$  allele in developing AD.

Alzheimer's disease (AD) is a progressive and fatal brain disorder that causes memory loss, steady deterioration of cognition, and dementia<sup>1</sup>. It is the sixth leading cause of all deaths in the United States, and deaths increased by 66% between 2000 and 2008<sup>2</sup>. Approximately 13% of people over the age of 65 years and 45% over the age of 85 years are estimated to have AD<sup>3</sup>. Therefore, discussing the risk factors and pathogenesis of AD, is of great significance for early detection, prevention and control of the susceptible population.

During the last two decades, researchers have found that Apolipoprotein E (ApoE) gene, located on chromosome 19, is closely associated with the onset of AD<sup>4,5</sup>. ApoE is a 299-amino acid protein encoded by the ApoE gene and has a molecular mass of ~34 kDa<sup>6</sup>. It is a major cholesterol carrier that supports lipid transport and injury repair in the brain<sup>7</sup>. Three common polymorphisms in the ApoE gene,  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ , including 6 genotypes, three homozygote ( $\epsilon 2/\epsilon 2$ ,  $\epsilon 3/\epsilon 3$ ,  $\epsilon 4/\epsilon 4$ ) and three heterozygote ( $\epsilon 3/\epsilon 2$ ,  $\epsilon 4/\epsilon 2$ ,  $\epsilon 4/\epsilon 3$ )<sup>8</sup>, result in a single amino acid change in the ApoE protein. Differences between the three ApoE isoforms are limited to amino acid residues 112 and 158<sup>9</sup>. Of these, the  $\epsilon 3$  allele is the most common, followed by  $\epsilon 4$  and  $\epsilon 2$ , although these frequencies vary between populations. ApoE polymorphic alleles are the main genetic determinants of AD risk: individuals carrying the  $\epsilon 4$  allele are at increased risk of AD compared with those carrying the more common  $\epsilon 3$  allele, whereas the  $\epsilon 2$  allele decreases risk<sup>10</sup>. Moreover, the  $\epsilon 4$  allele is most highly associated with AD at a large range of ages and in all ethnic groups; its presence is related with increased risk of cerebral amyloid angiopathy and age-associated cognitive decline during normal ageing<sup>11,12</sup>; It is also associated with hyperlipidaemia and hypercholesterolaemia, which lead to atherosclerosis, coronary heart disease and stroke<sup>13</sup>. The effects of ApoE genotype on risk of these diseases are likely to be mediated by differential effects of ApoE on amyloid- $\beta$  accumulation in the brain and its vasculature<sup>14,15</sup>. Response to treatment for AD might differ according to ApoE genotype<sup>16</sup>.

Although numerous studies have demonstrated the association, inconsistency was presented for different allele frequencies among study populations, particularly in different ethnic and geographical groups. The purpose of conducting this meta-analysis is to reduce heterogeneity and summarize the published evidence on the prevalence of the ApoE polymorphism among patients diagnosed with AD in Chinese population.

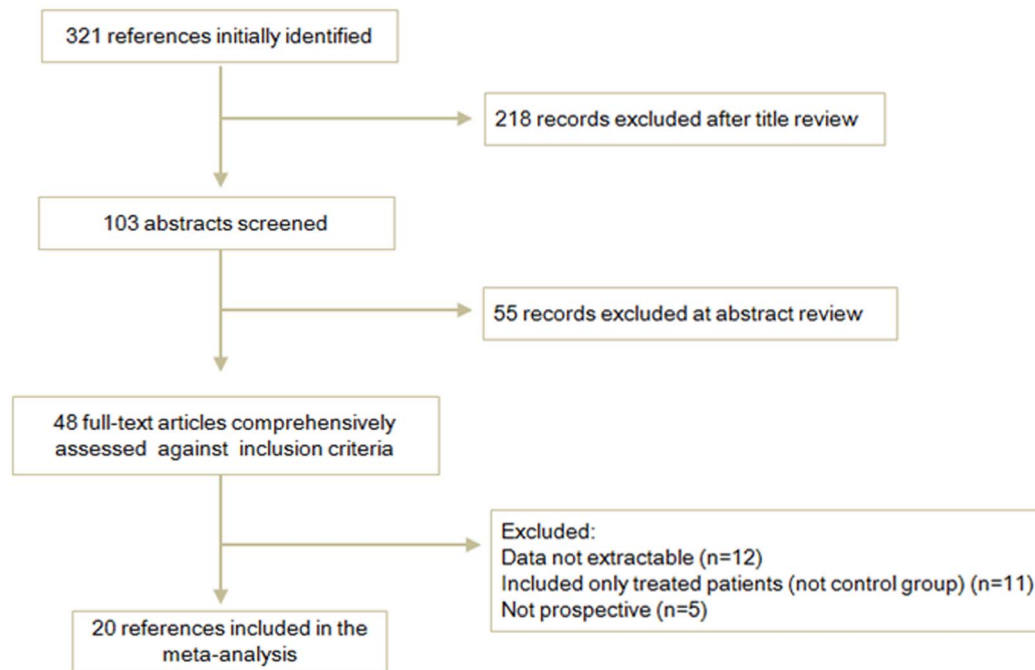


Figure 1 | Flow chart of literature screening.

## Results

**Study selection and characteristics.** The electronic database search identified 312 references. Of those, 218 records excluded after title review and 103 articles were judged potentially relevant. Following abstracts screened for relevance, 48 full-text articles comprehensively assessed against inclusion criteria. Overall, the initial search with the keywords and the subject terms identified 20 publications, including 1576 cases and 1741 controls that met the inclusion criteria and were eligible for review. Figure 1 shows the study flow.

Of the 20 reports focusing on the relationship between ApoE polymorphism and AD, 18 were from mainland<sup>17–34</sup>, two were from Taiwan<sup>35,36</sup>. The distribution of the genotypes in the control group was consistent with Hardy-Weinberg equilibrium (HWE). The detailed characteristics of the included studies were shown in

Table 1. The distributions of genotypes in the individual studies were presented in Table 2.

**Association between ApoE allele and AD.** The results of each allele and genotypes of ApoE in this meta-analysis were listed in Table 3. The heterogeneity between studies was not significant excepting the allele  $\epsilon 2$ . The fixed effect model or the random effect model was employed for calculating the pooled OR. Overall, this meta-analysis showed that the frequency of ApoE  $\epsilon 4$  allele is higher in AD than that in the health controls, and demonstrated statistically significant positive association between risk factor  $\epsilon 4$  allele carriers and AD in Chinese population (OR = 3.93, 95% CI = 3.37–4.58,  $P < 0.00001$ ), as shown in Figure 2. The frequency of the ApoE  $\epsilon 3$  is lower in AD than that in the health controls and the difference is also

Table 1 | Main characteristics of the eligible studies

First author-published year	Geographical location	Total no. of		diagnostic criteria	Mean-age	
		cases	controls		Cases	Controls
Zhu-2000	Shandong	36	36	NINCDS-ADRDA	-	-
Huang-2001	Guangzhou	41	85	DSM-III-R	80.8	59.6
Jia-2002	Beijing	58	60	NINCDS-ADRDA	68.6 ± 7.6	65.9 ± 8.5
Huang H-2002	Taiwan	99	96	NINCDS-ADRDA	76.3 ± 6.9	72.2 ± 6.9
Bi-2002	Haerbin	42	40	NINCDS-ADRDA	70.4 ± 6.6	68.1 ± 4.3
Zhou-2003	Wulumuqi	51	52	NINCDS-ADRDA	74.1 ± 9.7	69.4 ± 11.4
Chen-2003	Beijing/Shanxi	160	195	NINCDS-ADRDA	69.4 ± 9.5	69.8 ± 7.8
Zhang-2004	Shandong	32	40	CCMD-2-R	74.1 ± 7.3	63.9 ± 7.3
He-2005	Beijing	27	67	NINCDS-ADRDA	82.9 ± 7.9	-
Wang-2006	Taiwan	151	161	DSM-IV	74.8 ± 7.9	62.5 ± 8.7
Li-2006	Guizhou	30	30	DSM-IV	70.2 ± 11.6	71.4 ± 10.5
Yang J-2008	Yunnan	58	96	NINCDS-ADRDA	74.0 ± 8.48	74.2 ± 4.72
Yang L-2008	Henan	102	98	NINCDS-ADRDA	78.5 ± 7.3	76.5 ± 9.3
Wu-2009	Shanghai	262	118	NINCDS-ADRDA	76.91 ± 5.10	60.72 ± 4.88
Duan-2009	Henan	32	76	DSM-IV-R	70.6 ± 9.8	63.5 ± 6.7
Mai-2010	Guangdong	88	97	DSM-IV-R	79.6 ± 9.2	79.7 ± 8.6
Jiang-2010	Guangxi	79	156	NINCDS-ADRDA	72.8 ± 9.5	71.2 ± 9.3
Zhou C-2012	Chongqing	68	72	DSM-IV-TR	70.6 ± 6.8	71.2 ± 6.6
Lv-2012	Shanghai	100	106	NINCDS-ADRDA	77.0 ± 4.8	79.5 ± 5.0
Dong-2013	Liaoning	60	60	NINCDS-ADRDA	-	-



statistically significant (OR = 0.42, 95% CI = 0.37–0.47,  $P < 0.00001$ ), implying the protection effect of  $\epsilon 3$  allele in developing AD. No significant association was found between ApoE  $\epsilon 2$  allele and AD (OR = 0.93, 95% CI = 0.66–1.29,  $P = 0.65$ ) in a random-effect model.

**Association between ApoE genotype and AD.** As shown in table 3, the heterogeneity between studies was not significant ( $I^2 < 50\%$ ) and the fixed effect model was used for calculating the pooled OR. ApoE  $\epsilon 4/\epsilon 4$  and ApoE  $\epsilon 4/\epsilon 3$  have statistically significant association with AD ( $\epsilon 4/\epsilon 4$ : OR = 11.76, 95% CI = 6.38–21.47,  $P < 0.00001$ ;  $\epsilon 4/\epsilon 3$ : OR = 3.08, 95% CI = 2.57–3.69,  $P < 0.00001$ ). Figure 3 showed the association between  $\epsilon 4/\epsilon 4$  and AD in Chinese population. Genotype  $\epsilon 3/\epsilon 3$  also has significant association with AD (OR = 0.39, 95% CI = 0.33–0.45,  $P < 0.00001$ ). ApoE  $\epsilon 3/\epsilon 2$  and ApoE  $\epsilon 4/\epsilon 2$  have slight association with AD. There is no association between  $\epsilon 2/\epsilon 2$  and AD.

**Sensitivity analysis and publication bias.** For this meta-analysis, the influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time, respectively. The risk ratio was not significantly influenced by omitting any single study.

The distribution of the ORs from individual studies in relation to their respective standard deviation in funnel plot, as shown in Figure 4 and Figure 5. The funnel revealed no evidence of asymmetry. Thus, there was no possibility of publication bias risk in the meta-analysis.

## Discussion

ApoE gene, known to mediate the regulation of cholesterol and triglyceride metabolism, is immunochemically localized to the senile plaques, vascular amyloid, and neurofibrillary tangles of AD<sup>37,38</sup>. In 1993, Strittmatter et al. for the first time demonstrated that there was a highly significant association of ApoE  $\epsilon 4$  allele and late-onset familial AD<sup>39</sup>. Subsequently, most studies reported gene frequency of ApoE  $\epsilon 4$  was significantly increased in sporadic AD than in controls. Sando et al. proved that ApoE  $\epsilon 4$  is a very strong risk factor for AD in the population of central Norway, and lowers age at onset of late onset AD (LOAD) significantly<sup>40</sup>; Rhinn et al. identified an ApoE  $\epsilon 4$  associated molecular pathway that promotes LOAD<sup>41</sup>; Genin et al. demonstrated that ApoE  $\epsilon 4$  is a risk factor not only for late-onset but

for early-onset AD as well<sup>42</sup>. Together, these results urge a reappraisal of the impact of ApoE in AD.

Previous meta-analysis demonstrated that ApoE  $\epsilon 4$  genotype prevalence varies among AD patients by region and within each country<sup>43</sup>; the highest estimates were in Northern Europe; the lowest estimates were in Asia and Southern Europe. To further explore and examine the association of prevalence district of ApoE genotype and AD risk, we conducted this meta-analysis only in Chinese population. Overall, our results showed that the risk of developing AD in  $\epsilon 4$  allele carriers was 3.93-fold higher than individuals without  $\epsilon 4$  allele. The risk of developing AD in individuals with  $\epsilon 4/\epsilon 4$  genotype was 11.76-fold higher than individuals without  $\epsilon 4/\epsilon 4$  genotype. There probably exists a dose-dependent association between the number of ApoE  $\epsilon 4/\epsilon 4$  allele and the risk of AD in Chinese population. Furthermore, the frequency of the ApoE  $\epsilon 3$  is lower in AD than that in the health controls and the difference is also statistically significant, implying the protection effect of  $\epsilon 3$  allele in developing AD. No association was found between  $\epsilon 2$  allele and AD risk.

The  $\epsilon 4$  allele of ApoE is the “risk” variant for several phenotypes compared with  $\epsilon 3$  (“neutral”), and  $\epsilon 2$  (generally considered “protective”, although less consistently). The ApoE gene confers differential susceptibility to AD etiology depending on the combination of the 3 alleles as well as the age and ethnicity of the person. The  $\epsilon 4$  allele of ApoE is the strongest genetic risk factor for the development of AD. Although multiple genetic and environmental risk factors are involved in LOAD pathogenesis, overall impairment in A $\beta$  clearance is probably a major contributor to disease development<sup>44</sup>. Accumulation of amyloid- $\beta$  (A $\beta$ ) is hypothesized to initiate synaptic and neuronal dysfunction that ultimately lead to neuronal cell death in AD, and several lines of evidence strongly suggest that the differential effects of ApoE isoforms on A $\beta$  aggregation and/or clearance plays a major role in AD pathogenesis<sup>45,46</sup>. The ApoE isoforms could influence the risk for AD via other mechanisms as well<sup>47</sup>. Relative to the common  $\epsilon 3$  allele, possession of  $\epsilon 4$  increases disease risk and decreases age at onset in a dose-dependent manner<sup>48</sup>. In contrast, possession of the  $\epsilon 2$  allele may confer protection against AD, as carriers of this allele are less likely to develop the disease than  $\epsilon 3$  homozygotes<sup>49</sup>. The ApoE  $\epsilon 4$  allele is associated with greater accumulation of both A $\beta$  plaques and neurofibrillary tangles than the  $\epsilon 3$  allele<sup>50</sup>, while carriers of the  $\epsilon 2$  allele typically develop less AD-related pathology than both  $\epsilon 4$  carriers and  $\epsilon 3$  homozygotes. Pomara et al.

Table 2 | Distribution of genotypes in the individual studies

First author	cases						controls					
	$\epsilon 4/\epsilon 4$	$\epsilon 3/\epsilon 3$	$\epsilon 2/\epsilon 2$	$\epsilon 4/\epsilon 3$	$\epsilon 3/\epsilon 2$	$\epsilon 4/\epsilon 2$	$\epsilon 4/\epsilon 4$	$\epsilon 3/\epsilon 3$	$\epsilon 2/\epsilon 2$	$\epsilon 4/\epsilon 3$	$\epsilon 3/\epsilon 2$	$\epsilon 4/\epsilon 2$
Zhu 2000	3	16	0	12	5	0	0	28	0	4	4	0
Huang 2001	4	20	1	6	7	3	0	62	0	9	0	4
Jia 2002	1	29	0	15	7	6	1	47	0	4	8	0
Huang 2002	6	53	5	23	9	3	0	66	3	15	12	0
Bi 2002	2	20	0	15	2	3	0	28	1	6	3	2
Zhou 2003	1	26	3	19	2	0	0	35	4	4	9	0
Chen 2003	10	85	0	47	11	7	0	137	0	26	29	3
Zhang 2004	1	18	0	9	2	2	0	32	0	3	4	1
He 2005	0	13	0	9	4	1	0	55	0	5	5	0
Wang 2006	13	75	0	54	7	2	0	120	1	27	11	2
Li 2006	2	17	0	9	1	1	0	23	0	1	2	1
Yang L 2008	10	44	1	35	5	7	1	82	0	8	6	1
Yang J 2008	1	40	0	14	3	0	0	75	0	8	11	2
Wu 2009	30	118	0	102	12	1	1	77	2	23	13	2
Duan 2009	5	8	0	12	4	3	1	53	1	9	10	2
Mai 2010	6	45	2	18	14	3	0	65	0	12	16	4
Jiang 2010	2	47	0	20	6	4	0	107	0	17	31	1
Zhou C 2012	5	37	0	17	7	2	0	49	0	9	11	3
Lv 2012	11	44	2	33	10	0	0	76	2	15	12	1
Dong 2013	4	27	0	23	3	2	1	44	0	9	6	0



Table 3 | Meta-analysis of Apolipoprotein E gene polymorphism in Alzheimer's disease

	Fix-effect model				Random-effect model			
	OR (95% CI)	P	$P_h$	$I^2$	OR (95% CI)	P	$P_h$	$I^2$
<b>Allele</b>								
ApoE $\epsilon$ 2	0.88 (0.73, 1.07)	0.20	0.0002	61%	0.93 (0.66, 1.29)	0.65	0.0002	61%
ApoE $\epsilon$ 3	0.42 (0.37, 0.47)	<0.00001	0.07	34%	0.42 (0.36, 0.49)	<0.00001	0.07	34%
ApoE $\epsilon$ 4	3.93 (3.37, 4.58)	<0.00001	0.81	0%	3.89 (3.33, 4.54)	<0.00001	0.81	0%
<b>Genotype</b>								
ApoE $\epsilon$ 4/ $\epsilon$ 4	11.71 (6.38, 21.47)	<0.00001	0.98	0%	9.84 (5.28, 18.34)	<0.00001	0.98	0%
ApoE $\epsilon$ 3/ $\epsilon$ 3	0.39 (0.33, 0.45)	<0.00001	0.25	16%	0.38 (0.33, 0.45)	<0.00001	0.25	16%
ApoE $\epsilon$ 2/ $\epsilon$ 2	1.06 (0.55, 2.06)	0.86	0.60	0%	1.09 (0.52, 2.27)	0.83	0.60	0%
ApoE $\epsilon$ 4/ $\epsilon$ 3	3.08 (2.57, 3.69)	<0.00001	0.06	35%	3.16 (2.48, 4.02)	<0.00001	0.06	35%
ApoE $\epsilon$ 3/ $\epsilon$ 2	0.67 (0.53, 0.85)	0.0008	0.18	23%	0.66 (0.49, 0.88)	0.005	0.18	23%
ApoE $\epsilon$ 4/ $\epsilon$ 2	2.10 (1.35, 3.26)	0.001	0.32	11%	1.92 (1.13, 3.28)	0.02	0.32	11%

$P_h$ , Heterogeneity.

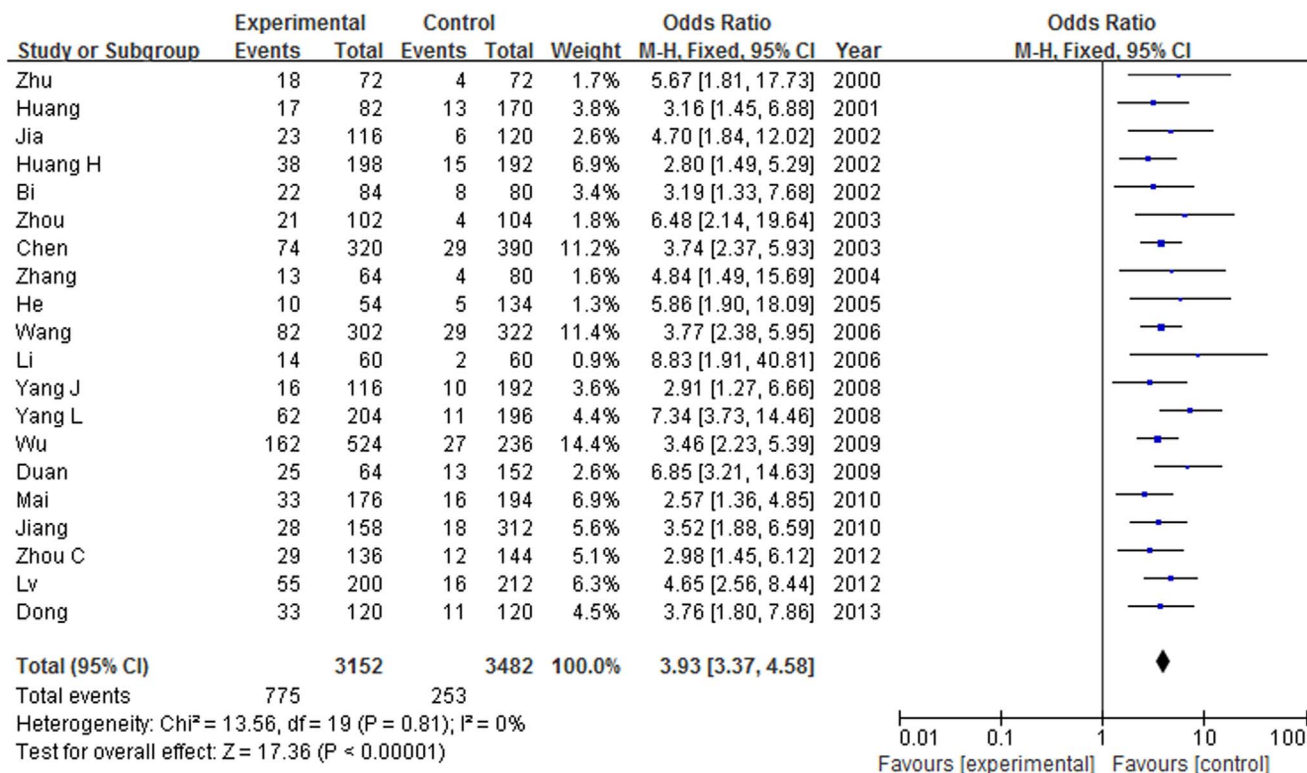
showed a potential effect of the ApoE  $\epsilon$ 2 allele and of family history of Alzheimer's disease on brain amyloid- $\beta$  in normal elderly<sup>51</sup>. Hostage et al. confirmed and extended prior data on the opposing effects of the ApoE  $\epsilon$ 4 and  $\epsilon$ 2 alleles on hippocampal morphology across the spectrum of cognitive aging<sup>48</sup>. This general pattern holds for many physiological phenomena influenced by ApoE genotype, and potentially related to AD, including measures of synaptic plasticity and repair<sup>52</sup>, antioxidant properties, and certain immune responses<sup>53</sup>, and cholesterol levels<sup>54</sup>.

Currently, genetic testing of ApoE  $\epsilon$ 4 carrier status is not routinely considered in clinical practice. As ApoE genotype determines AD risk, and ApoE has crucial roles in cognition<sup>55,56</sup>, ApoE might offer an attractive alternative target for AD therapy. ApoE genotype status could be included in clinical trial enrolment criteria, as some therapies might be effective only in specific ApoE genotypes. In addition,

ApoE is a crucial regulator of the innate immune system, with ApoE  $\epsilon$ 4 promoting pro-inflammatory responses that could exacerbate AD pathogenesis.

Several limitations were presented in this meta-analysis. Firstly, in AD group of retrieved case-control studies, there may exist mixed dementia. It might increase the apparent association of ApoE with AD, since ApoE  $\epsilon$ 4 allele is associated with dementia. Secondly, ApoE polymorphism may interact with other known and unknown risk factors which should be considered. Thirdly, the selected studies may have more subject to bias and artifact than prospective studies.

In conclusion, our meta-analysis suggests that ApoE  $\epsilon$ 4 carrier is associated with AD and provide a support for the protection effect of ApoE  $\epsilon$ 3 allele in developing AD in Chinese population. Although ApoE polymorphism is a well-studied genetic risk factor for developing AD, in some regions most patients do not carry this genotype.

Figure 2 | Forest plot on the association between  $\epsilon$ 4 allele carriers and AD in Chinese population.



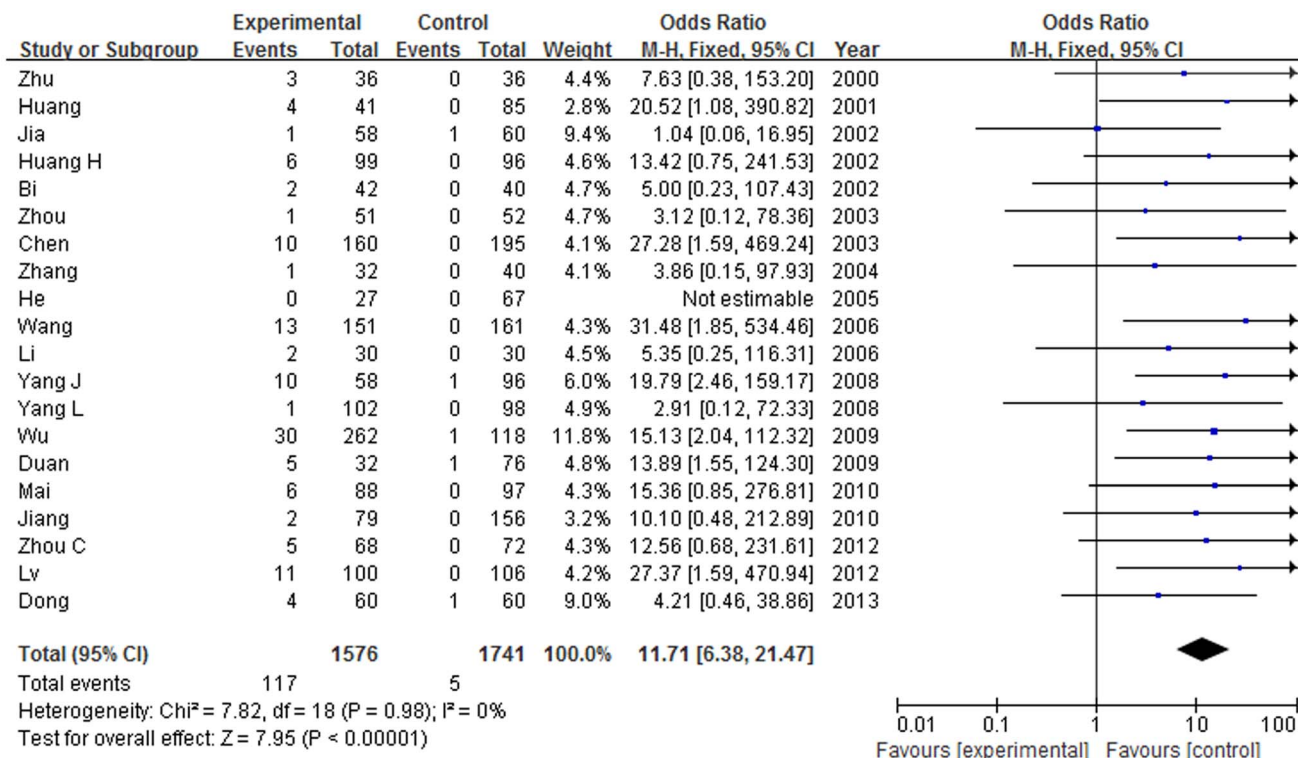


Figure 3 | Forest plot on the association between ε4/ε4 genotype and AD in Chinese population.

Therefore, additional research with well-designed and large sample sizes is needed to be able to understand both other genetic and environmental risk factors in the future.

### Methods

**Identification and eligibility of relevant studies.** We conducted a comprehensive literature search using the electronic database of PubMed, Wanfang database and CNKI (China National Knowledge Infrastructure) for relevant articles assessing the association of ApoE polymorphism and AD in Chinese population from January 2000 to November 2013. The Medical Subject Heading (MeSH) terms “Alzheimer’s disease”, “AD”, “ApoE”, “Apolipoprotein E”, and “polymorphism” were employed as the searching words. The equivalent Chinese terms were used in the Chinese

databases. All studies matching the eligibility criteria were retrieved, and references were checked for other relevant publications.

**Criteria for article screening.** Studies eligible for inclusion in this meta-analysis must meet the following criteria: 1) case-control or cohort study; 2) measure the relationship between ApoE polymorphism and AD; 3) clinical diagnosis of AD based on standards of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) work group<sup>57</sup>; 4) the results were expressed as odds ratio (OR) and corresponding 95 percent confidence interval (95% CI); 5) genotype distribution of control for a certain polymorphism must be in HWE; and 6) when the same authors reported two or more publications on possibly the same patient populations, only the most recent or complete study was included into this meta-analysis.

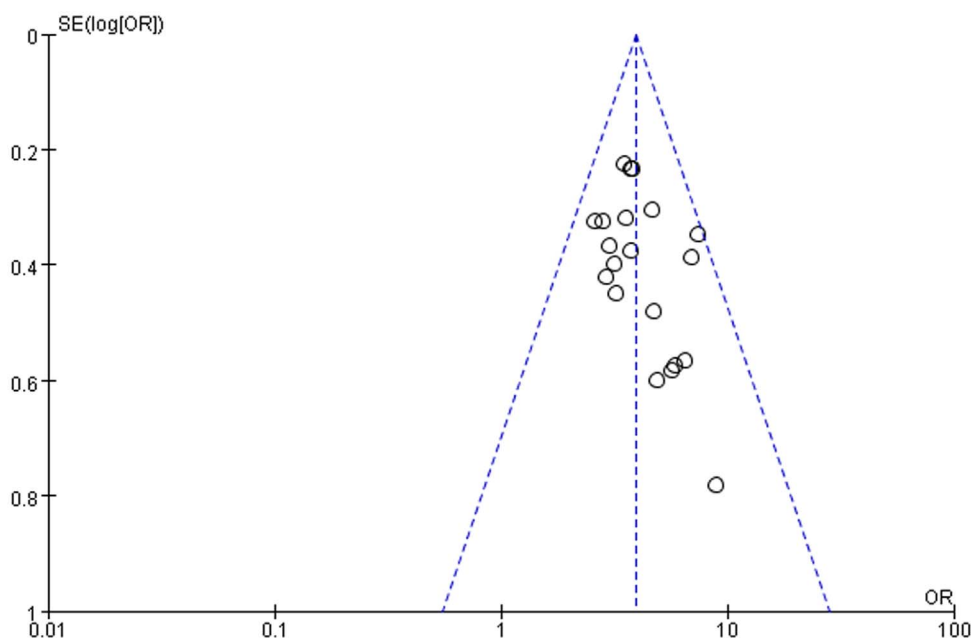
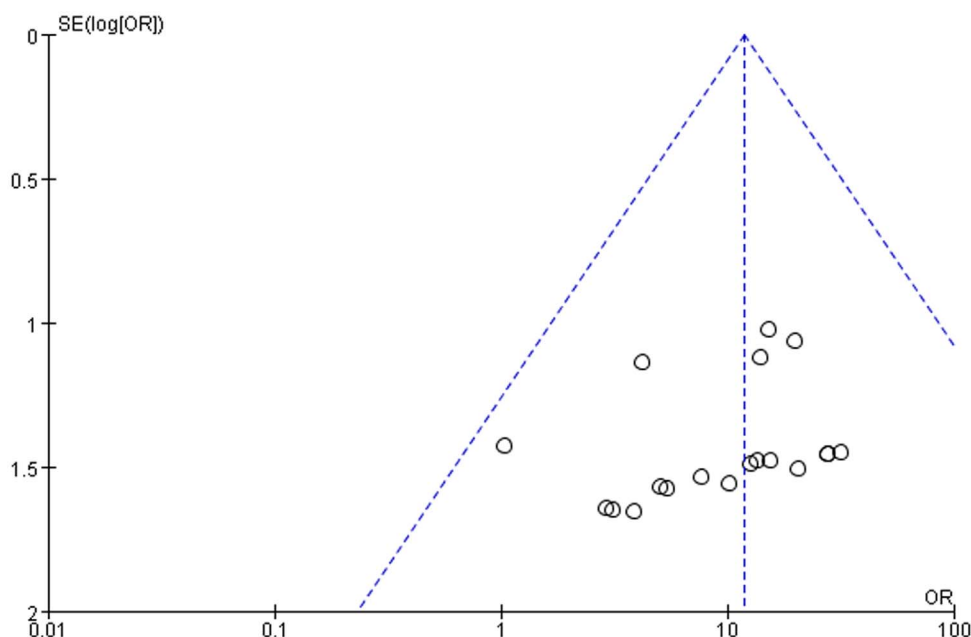


Figure 4 | Funnel plot on the association between ε4 allele carriers and AD.



**Figure 5** | Funnel plot on the association between  $\epsilon 4/\epsilon 4$  genotype and AD.

**Quality assessment and data extraction.** Two investigators independently extracted data and reached a consensus on all of the items. Any disagreement was resolved by discussing with the third expert. Data retrieved from the reports included first author, publication year, demographics, number of cases and controls, distribution of genotypes, and the diagnosis criteria of AD.

**Statistical analysis.** The odd ratio (OR) with 95% confidence intervals (95% CI) was used to assess the relationship of ApoE polymorphism and AD. The significance of the pooled OR was determined by the Z test, and a P value less than 0.05 was considered significant. The heterogeneity for the included articles was evaluated using Cochran's Q test and  $I^2$  statistics. P-value less than 0.05 and  $I^2$  less than 50% were considered to be statistically significant. When a significant heterogeneity existed across the included studies ( $I^2 > 50\%$ ), the random effect model was used<sup>58</sup>; When there was no significant heterogeneity across the included studies ( $I^2 < 50\%$ ), the fixed effect model was used<sup>58</sup>. To assess whether our results were substantially influenced by the presence of any individual study, we conducted a sensitivity analysis by systematically removing each study and recalculating the significance of the result. Begg's funnel plot was performed to examine the publication bias. Analyses were carried out using the Review manager 5.2 (The Cochrane Collaboration). All tests were two sided.

- Selkoe, D. J. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev* **81**, 741–766 (2001).
- Thies, W. & Bleiler, L. 2011 Alzheimer's disease facts and figures. *Alzheimers Dement* **7**, 208–244 (2011).
- Alzheimer's, A. 2012 Alzheimer's disease facts and figures. *Alzheimers Dement* **8**, 131–168 (2012).
- Siest, G. *et al.* Apolipoprotein E: an important gene and protein to follow in laboratory medicine. *Clin Chem* **41**, 1068–1086 (1995).
- Levy-Lahad, E. & Bird, T. D. Genetic factors in Alzheimer's disease: a review of recent advances. *Ann Neurol* **40**, 829–840 (1996).
- Mahley, R. W. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* **240**, 622–630 (1988).
- Mahley, R. W. & Rall, S. C. Jr. Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* **1**, 507–537 (2000).
- Zannis, V. I. *et al.* Proposed nomenclature of apoE isoproteins, apoE genotypes, and phenotypes. *J Lipid Res* **23**, 911–914 (1982).
- Morrow, J. A. *et al.* Differences in stability among the human apolipoprotein E isoforms determined by the amino-terminal domain. *Biochemistry* **39**, 11657–11666 (2000).
- Hauser, P. S. & Ryan, R. O. Impact of apolipoprotein E on Alzheimer's disease. *Curr Alzheimer Res* **10**, 809–817 (2013).
- Ghebremedhin, E. *et al.* Gender and age modify the association between APOE and AD-related neuropathology. *Neurology* **56**, 1696–1701 (2001).
- Millar, K., Nicoll, J. A., Thornhill, S., Murray, G. D. & Teasdale, G. M. Long term neuropsychological outcome after head injury: relation to APOE genotype. *J Neurol Neurosurg Psychiatry* **74**, 1047–1052 (2003).
- Lahoz, C. *et al.* Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. *Atherosclerosis* **154**, 529–537 (2001).
- Kim, J. *et al.* Anti-apoE immunotherapy inhibits amyloid accumulation in a transgenic mouse model of Abeta amyloidosis. *J Exp Med* **209**, 2149–2156 (2012).
- Verghese, P. B. *et al.* ApoE influences amyloid-beta (Abeta) clearance despite minimal apoE/Abeta association in physiological conditions. *Proc Natl Acad Sci U S A* **110**, E1807–1816 (2013).
- Claxton, A. *et al.* Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. *J Alzheimers Dis* **35**, 789–797 (2013).
- Chen, D., Zhang, J. & Zhang, Z. Apolipoprotein E Gene Polymorphisms and Alzheimer's Disease. *J G Genomics* **30**, 1167–1170 (2003).
- Zhang, Y., Liu, Z. & Du, Y. Association between Apolipoprotein E gene polymorphism and Vascular dementia and Alzheimer's disease. *Shandong Med J* **22**, 1–2 (2004).
- Mai, Y., Luo, Y., Gu, H., Zhang, L. & LIN, J. Association between Interleukin-8 and Apolipoprotein E gene polymorphism and late-onset Alzheimer's disease. *J sun yat-sen uni* **1**, 118–121 (2010).
- Jia, J., Zhang, J., Xu, M. & Zhou, W. Association between the apolipoprotein E gene polymorphism and the genetic sensitivity of sporadic Alzheimer's disease. *Chin J Geriatrics* **4**, 7–9 (2002).
- Zhu, J., Xu, W. & Gao, Y. The association of apolipoprotein E and Alzheimer's disease. *Practical Geriatrics* **1**, 23–25 (2000).
- Jiang, W., Lv, Z. & Tan, L. Correlation between apolipoprotein E gene polymorphism s and Alzheimer's disease and vascular dementia. *J Clin Neurology* **6**, 408–410 (2010).
- He, S. R., Liu, D. G., Wang, S. & Xia, Y. J. Expression of apolipoprotein E in Alzheimer's disease and its significance. *Chin J Pathology* **34**, 556–560 (2005).
- Zhou, C., Xu, J. & He, J. Genetic correlation study between apolipoprotein E gene and Alzheimer's disease. *Med J NDFNC* **4**, 244–246 (2003).
- Huang, S., Lu, Y. & Chen, S. Inquiring relation between Apolipoprotein E Gene polymorphism and the Alzheimer's disease. *J M Clin Med Bio* **1**, 9–11 (2001).
- Li, G., Zhao, M., Zuo, L., Liu, F. & Kuang, S. Polymorphism in the Apolipoprotein E Gene and Its Association with Sporadic Alzheimer Disease. *J Guiyang Med J*, 24–26 (2006).
- Bi, S. *et al.* The Relationship between ApoE Genotype, Serum Total Cholesterol Level, and Alzheimer's disease. *Chin J neuroimmunology* **1**, 13–16 (2002).
- Wu, P., Guo, Q., Chen, M., Zhou, Y. & Hong, Z. Relationship Between Apolipoprotein E Gene Polymorphism and Early-onset Alzheimer's s Disease. *Chin J Clin Neurosci* **3**, 1168–1170 (2009).
- Zhou, C., Cheng, X. & Xia, X. Relationship between Apolipoprotein E Polymorphism and Alzheimer's Disease in Chongqing. *J Chin GP* **27**, 3115–3117 (2012).
- Yang, J., Yu, F. & Wang, Y. Study of the polymorphisms of APOE gene in Alzheimer's disease and vascular dementia. *Neuro Dis Mental H* **2**, 138–140 (2008).
- Dong, X. The study of the relationship between AD and the ApoE polymorphism. *Chin H Care Nutrition* **2**, 523–524 (2013).
- Yang, L. Study on the association between Apolipoprotein E gene polymorphisms and sporadic Alzheimer's disease. *Chin Mod Doctor* **24**, 89–90 (2008).
- Duan, G., Guo, L. & Yang, L. Study on the Association of Apolipoprotein E-gene Polymorphism with Demented Patients. *J Henan Med C* **6**, 559–561 (2009).



34. Lv, X. & Zhong, Y. Study on the relationship between apolipoprotein E gene polymorphism and mild cognitive impairment and Alzheimer's disease. *Chin J Gerontology* **5**, 917–919 (2012).
35. Huang, H. M., Kuo, Y. M., Ou, H. C., Lin, C. C. & Chuo, L. J. Apolipoprotein E polymorphism in various dementias in Taiwan Chinese population. *J Neural Transm* **109**, 1415–1421 (2002).
36. Wang, H. K. *et al.* Apolipoprotein E, angiotensin-converting enzyme and kallikrein gene polymorphisms and the risk of Alzheimer's disease and vascular dementia. *J Neural Transm* **113**, 1499–1509 (2006).
37. Saunders, A. M. *et al.* Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43**, 1467–1472 (1993).
38. Schmechel, D. E. *et al.* Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proc Natl Acad Sci U S A* **90**, 9649–9653 (1993).
39. Strittmatter, W. J. *et al.* Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A* **90**, 1977–1981 (1993).
40. Sando, S. B. *et al.* APOE epsilon 4 lowers age at onset and is a high risk factor for Alzheimer's disease; a case control study from central Norway. *BMC Neurol* **8**, 9 (2008).
41. Rhinn, H. *et al.* Integrative genomics identifies APOE epsilon4 effectors in Alzheimer's disease. *Nature* **500**, 45–50 (2013).
42. Genin, E. *et al.* APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry* **16**, 903–907 (2011).
43. Ward, A. *et al.* Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/e4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. *Neuroepidemiology* **38**, 1–17 (2012).
44. Mawuenyega, K. G. *et al.* Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science* **330**, 1774 (2010).
45. Koffie, R. M. *et al.* Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-beta. *Brain* **135**, 2155–2168 (2012).
46. Kim, J., Basak, J. M. & Holtzman, D. M. The role of apolipoprotein E in Alzheimer's disease. *Neuron* **63**, 287–303 (2009).
47. Castellano, J. M. *et al.* Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. *Sci Transl Med* **3**, 89ra57 (2011).
48. Hostage, C. A., Roy Choudhury, K., Doraiswamy, P. M., Petrella, J. R. & Alzheimer's Disease Neuroimaging, I. Dissecting the gene dose-effects of the APOE epsilon4 and epsilon2 alleles on hippocampal volumes in aging and Alzheimer's disease. *PLoS One* **8**, e54483 (2013).
49. Berlau, D. J., Corrada, M. M., Head, E. & Kawas, C. H. APOE epsilon2 is associated with intact cognition but increased Alzheimer pathology in the oldest old. *Neurology* **72**, 829–834 (2009).
50. Reiman, E. M. *et al.* Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* **106**, 6820–6825 (2009).
51. Pomara, N. & Bruno, D. Potential effects of the APOE epsilon2 allele and of family history of Alzheimer's disease on brain amyloid-beta in normal elderly. *Proc Natl Acad Sci U S A* **108**, E1007; author reply E1008 (2011).
52. Jofre-Monseny, L., Minihane, A. M. & Rimbach, G. Impact of apoE genotype on oxidative stress, inflammation and disease risk. *Mol Nutr Food Res* **52**, 131–145 (2008).
53. Smith, J. D. Apolipoproteins and aging: emerging mechanisms. *Ageing Res Rev* **1**, 345–365 (2002).
54. Jack, C. R. Jr. *et al.* Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain* **132**, 1355–1365 (2009).
55. McKhann, G. *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939–944 (1984).
56. Kim, S. M. *et al.* Regional cerebral perfusion in patients with Alzheimer's disease and mild cognitive impairment: effect of APOE epsilon4 allele. *Neuroradiology* **55**, 25–34 (2013).
57. DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. *Control Clin Trials* **7**, 177–188 (1986).
58. Mantel, N. & Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* **22**, 719–748 (1959).

## Acknowledgments

This study was supported by the National Science Foundation of China (NSFC, No. 81171035).

## Author contributions

Conceived and designed the study: J.Q.Z. and F.W.; Performed the experiments: M.Y.L., C.B., J.Q.Z. and F.W.; Contributed material/analysis tools: M.Y.L., J.Q.Z. and F.W.; Statistical analyses and paper writing, revising: M.Y.L., C.B., J.Q.Z. and F.W.

## Additional information

**Competing financial interests:** The authors declare no competing financial interests.

**How to cite this article:** Liu, M.Y., Bian, C., Zhang, J.Q. & Wen, F. Apolipoprotein E gene polymorphism and Alzheimer's disease in Chinese population: a meta-analysis. *Sci. Rep.* **4**, 4383; DOI:10.1038/srep04383 (2014).



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported license. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/3.0>