Review

Cerebrovascular Diseases

Cerebrovasc Dis 2016;41:119–138
DOI: 10.1159/000442678

Received: September 8, 2015
Accepted: November 17, 2015
Published online: January 12, 2016

# ApoE Polymorphisms and the Risk of Different Subtypes of Stroke in the Chinese Population: A Comprehensive Meta-Analysis

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**Key Words**
ApoE · Ischemic stroke · Intracerebral hemorrhage · Subarachnoid hemorrhage · Meta-analysis

**Abstract**
***Background and Purpose:*** Numerous studies have evaluated the association between apolipoprotein E (ApoE) gene polymorphisms and the risk of different subtypes of stroke. However, the results remain uncertain, and few sources of data specific to the Chinese ethnic population contribute to these outstanding questions. Therefore, we performed a meta-analysis to derive a more comprehensive estimate of the association between ApoE polymorphisms and stroke risk in the Chinese population. ***Methods:*** Case–control studies in Chinese and English publications were identified by searching the PubMed, EMBASE, Web of Science, China Nation Knowledge Infrastructure Platform, Wanfang, and VIP databases and by hand-searching relevant journals and the reference lists of the retrieved articles. ORs and 95% CIs were applied to assess the strength of the associations. Subgroup and sensitivity analyses were performed to explore between-study heterogeneity. ***Results:*** Evidence of a significant association was found between the ApoE ε4 allele and different subtypes of stroke (for ischemic stroke (IS): OR 2.19, 95% CI 1.90–2.52, $p < 0.001$; for intracerebral hemorrhage (ICH): OR 2.08, 95% CI 1.57–2.75, $p < 0.001$; and for subarachnoid hemorrhage (SAH): OR 2.03, 95% CI 1.28–3.23, $p = 0.003$) among the Chinese population. In addition, a significant difference in the risk for different subtypes of stroke between ε4 carriers and ε3ε3 genotype carriers was found (for IS: OR 2.41, 95% CI 2.00–2.89, $p < 0.001$; for ICH: OR 2.41, 95% CI 1.68–3.47, $p < 0.001$; and for SAH: OR 2.04, 95% CI 1.21–3.45, $p = 0.008$). ***Conclusion:*** The ApoE ε4 allele may predict an increased risk for different subtypes of stroke, including IS, ICH and SAH, in the Chinese population, and the results of this genotypic analysis may help to identify populations at an increased risk for stroke. Further studies with larger sample sizes are needed to confirm our findings.


## Introduction

Stroke remains one of the most devastating of all neurological diseases and is a common cause of death and gross physical impairment or disability worldwide [1, 2].

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Stroke is generally regarded as a multifactorial disorder associated with genetic and environmental factors [3–6] that can be classified into 3 main pathological types: ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Many candidate genes related to both IS and hemorrhagic stroke have been extensively investigated [7, 8].

Mounting evidence suggests that apolipoprotein E (ApoE) is a candidate gene that is associated with stroke [9]. The ApoE gene, located on chromosome 19q13.2, is polymorphic, consisting of 3 common alleles, ε2, ε3, and ε4, and is able to generate 6 different genotypes (ε2/2, ε2/3, ε2/4, ε3/3, ε3/4, and ε4/4). ApoE is a polymorphic glycoprotein involved in cholesterol transport and injury repair in the brain [10, 11]. Many studies assessing the effect of the ApoE genotype on plasma lipids have indicated that the presence of the ε4 allele is associated with elevated total cholesterol levels but that the presence of the ε2 allele is associated with decreased levels of cholesterol [12]; thus, the ApoE genotype affects the progression of atherosclerosis, which is the main pathology underlying the ischemia-related cerebrovascular disease [11, 13]. Although the exact mechanism responsible for the association between ApoE polymorphisms and ICH risk remains unclear, it appears that the ε4 allele enhances amyloid deposition in blood vessels [14]. Thus, one might expect ε4 carriers to exhibit an increased susceptibility for ICH, especially in a lobar location. Furthermore, the ApoE ε4 allele was associated with an increased risk of developing hypertension [15], which may be another reason for the association of the ε4 allele with an increased ICH risk.

In 2006, a meta-analysis [9] reported that carriers of the ApoE ε4 allele exhibited a significantly increased risk of IS and that the presence of the ε2 allele was associated with an increased ICH risk. Another meta-analysis published in 2014 by Zhang et al. [16] reported that carriers of the ε4 allele exhibited an increased risk of ICH but that ε2 allele carriers showed no significant additional risk of ICH. These 2 meta-analyses had inconsistent results, and few sources of data specific to the Chinese ethnic population contribute to these outstanding questions. Indeed, differences in characteristics such as ethnicity, stroke subtype and sources of controls (SOC) between studies have led to discrepancies in estimates of the effects of specific ApoE polymorphisms on stroke risk. Therefore, we conducted a comprehensive meta-analysis to quantify the overall genetic effects of certain ApoE polymorphisms on the risk of different subtypes of stroke in the Chinese population.

## Materials and Methods

*Literature Search*

This meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses guidelines [17]. We searched related studies from the electronic records of the PubMed, EMBASE, Web of Science, China Nation Knowledge Infrastructure Platform, Wanfang, and VIP databases published through June 2015. The initial keywords for our search were 'apolipoprotein E' OR 'ApoE' AND 'polymorphism' OR 'variant' OR 'mutation' OR 'genotype' AND 'stroke' OR 'ischemic stroke' OR 'cerebral infarction' OR 'cerebral hemorrhage' OR 'intracerebral hemorrhage' OR 'hemorrhagic stroke' OR 'SAH' OR 'subarachnoid hemorrhage' OR 'cerebrovascular disease' OR 'cerebrovascular disorder' OR 'cerebral ischemia'. In addition, the reference lists of the articles identified by the online searches were checked manually to identify additional studies. The literature searches were limited to humans, and only studies published in English or Chinese were included.

*Inclusion Criteria*

Studies were selected according to the following inclusion criteria: (1) studies of the association between ApoE gene polymorphisms and cerebrovascular disease in Chinese populations; (2) studies in which diagnosis of cerebrovascular disease was confirmed based on the results of neurological examination and neuroimaging (MRI or CT) according to domestic or international criteria; (3) case–control studies using a population-based or hospital-based design with sufficient original data for estimating an OR along with 95% CI; (4) studies reported as full-text articles; and (5) for duplicate publications, the more credible or recent study or the study with the larger sample size.

*Data Extraction*

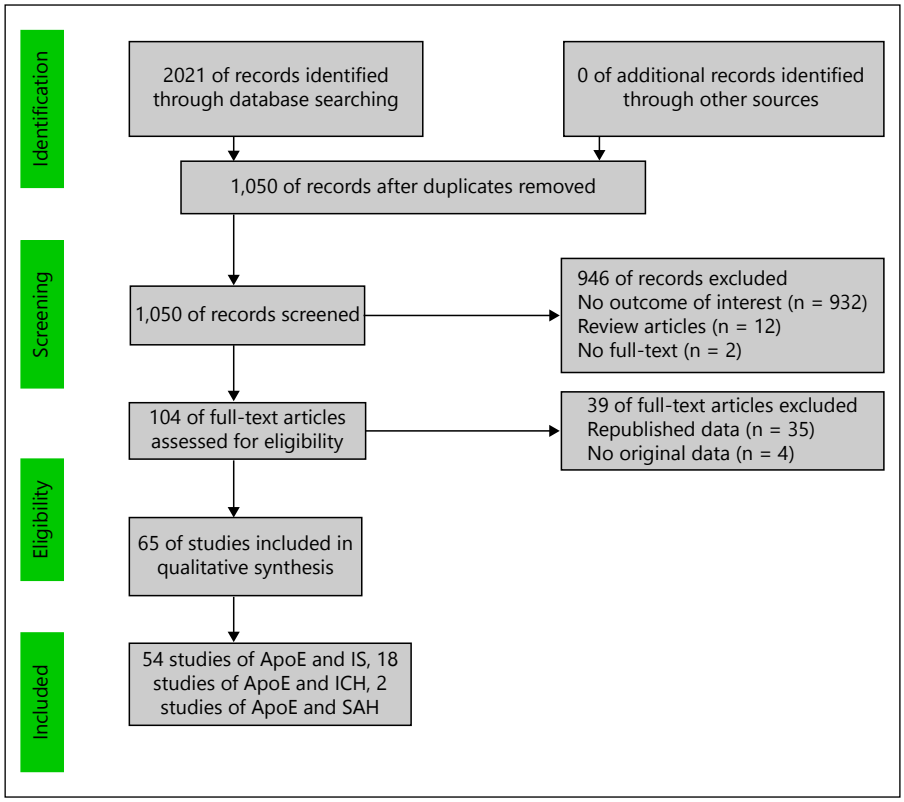
Two investigators independently extracted information from all eligible studies based on the inclusion criteria listed earlier. A consensus was arrived at after discussion of conflicting data or after consultation with a third investigator. From each study, the following information was abstracted: first author, publication year, geographical location of the study population, genotyping method, the number of cases and controls, SOC, the distribution of ApoE genotypes and alleles in both the case and control groups, and the results for Hardy-Weinberg equilibrium (HWE) in the control group using the $\chi^2$ test (a p value <0.05 was considered statistically significant), and the Newcastle Ottawa Scale (NOS) score.

*Quality Score Assessment*

The quality of each included study was independently assessed by the same 2 investigators using the NOS (supp1). The NOS scores ranged from 0 (worst) to 9 (best) based on the factors of selection, comparability, and either exposure (case-control studies) or outcome (cohort studies).

*Statistical Analysis*

The pooled ORs with 95% CIs were used to measure the strengths of the associations of ApoE gene polymorphisms with different subtypes of stroke. Heterogeneity between studies was analyzed using Cochran's Q test and the $I^2$ statistic. Pooled ORs were calculated using a fixed-effects model (considering a Q test




Color version available online

**Fig. 1.** A flow diagram of the selection process for analysis of the association between ApoE polymorphism and the risk for IS, ICH, and SAH in the Chinese population.

p value ($P_Q$) >0.10 and an $I^2$ statistic <50%) or a random-effects model (REM, considering a $P_Q$ <0.10 and an $I^2$ statistic >50%) due to the absence or presence of heterogeneity between the studies, respectively. For IS, subgroup analyses were conducted according to HWE status (yes or no), SOC (population-based or non-population-based) and IS subtype (arteriosclerotic cerebral infarction (ACI) or lacunar infarction (LI)). For ICH, subgroup analyses were conducted according to the HWE status (yes or no) and SOC (population-based or non-population-based). Non-population-based controls included hospital-based and mixed controls. As the ApoE ε3/3 genotype, with a frequency of approximately 67%, is the most common genotype in the population, it is well accepted as the 'wild-type' genotype [18]. Therefore, individuals carrying the ε3/3 genotype or the ε3 allele were designated as the reference group in our study. For separate analyses, ε2 carriers included patients harboring the ε2/2 or ε2/3 genotype, and ε4 carriers included patients harboring the ε3/4 or ε4/4 genotype. Thus, ε2 and ε4 genotype carriers were independently compared with ε3/3 genotype carriers. Moreover, the ε2 and ε4 allele carriers were independently compared with the ε3 allele carriers. Sensitivity analyses were performed by limiting the meta-analysis to studies of high-quality (NOS score >7), studies including population-based controls, studies with results meeting the HWE criteria or studies using polymerase chain reaction (PCR)-based genotyping methods. Potential publication bias was assessed using the Begg's funnel plot and Egger's regression test (significance threshold set at $p < 0.05$). All meta-analyses were conducted using STATA 12.0.

## Results

### *ApoE and IS in the Chinese Population*

#### Study Characteristics

A total of 54 studies [19–72] containing 6,190 cases and 6,248 controls from China were included in the final meta-analysis of the association of ApoE polymorphisms with IS risk. The selection process is represented in figure 1. The included studies and their main characteristics are presented in table 1. The participants in these studies were recruited from 24 provinces of China, including Anhui, Beijing, Guangdong, Guangxi, Hainan, Hebei, Heilongjiang, Henan, Hubei, Hunan, Hong Kong, Inner Mongolia, Jiangsu, Jilin, Liaoning, Shandong, Shanxi, Shanghai, Sichuan, Taiwan, Tianjin, Xinjiang, Yunnan and Zhejiang. Of the 54 included studies, 52 applied PCR-based methods to detect the ApoE gene polymorphism [19–30, 32–59, 61–72], 48 studies included population-based controls [19–23, 26–41, 43–46, 48–63, 65–71], and 17 studies contained results that did not follow HWE [19, 38, 39, 41, 45, 50, 52, 56, 57, 60, 61, 65–68, 70, 72]. Five of the eligible studies contained data on 2 subtypes of IS, and these data were treated independently [25, 27, 44, 52, 71]. Eight studies examined patients with

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DOI: 10.1159/000442678



**Table 1.** Main characteristics of studies associated with ApoE polymorphism and IS stroke included in this meta-analysis

| Year | Author | Geographical location | Source of controls | Sample size (case/control) | NOS score | ε2/ε2 (case/control) | ε2/ε3 (case/control) | ε2/ε4 (case/control) | ε3/ε3 (case/control) | ε3/ε4 (case/control) | ε4/ε4 (case/control) | ε2 (case/control) | ε3 (case/control) | ε4 (case/control) | HWE | Genotypic method | Subtype |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1997 | Guo et al. [19] | Liaoning | PB | 47/100 | 8 | 1/1 | 4/14 | 1/7 | 28/66 | 13/12 | 0/0 | 7/23 | 73/158 | 14/19 | 0.004 | PCR | ACI |
| 1997 | Yan et al. [20] | Hubei | PB | 50/113 | 8 | 0/0 | 8/19 | 1/2 | 25/78 | 15/13 | 1/1 | 9/21 | 73/188 | 18/17 | 0.678 | PCR | ACI |
| 1997 | Zhou et al. [21] | Hubei | PB | 24/24 | 8 | 0/0 | 3/2 | 3/1 | 12/19 | 4/2 | 2/0 | 6/3 | 31/42 | 11/3 | 0.258 | PCR | ND |
| 1999 | Cao et al. [22] | Heilongjiang | PB | 55/85 | 8 | 0/0 | 2/11 | 0/0 | 47/68 | 6/6 | 0/0 | 2/11 | 102/153 | 6/6 | 0.789 | PCR | ACI |
| 1999 | Liu and Li [23] | Jiangsu | PB | 43/60 | 8 | 0/0 | 5/9 | 1/2 | 22/41 | 13/8 | 2/0 | 6/11 | 62/100 | 18/9 | 0.530 | PCR | ACI |
| 1999 | Peng and Zhao [24] | Hunan | HB | 90/90 | 7 | 0/1 | 13/16 | 1/1 | 55/63 | 19/8 | 2/1 | 14/19 | 142/150 | 24/11 | 0.685 | PCR | ND |
| 2000 | Ding et al. [25] | Guangdong | HB | 58/46 | 7 | 1/0 | 3/2 | 2/1 | 37/38 | 13/5 | 2/0 | 7/3 | 90/83 | 19/6 | 0.287 | PCR | ACI, LI |
| 2000 | Wang et al. [26] | Guangdong | PB | 50/50 | 8 | 0/0 | 6/7 | 1/2 | 36/34 | 7/7 | 0/0 | 7/9 | 85/82 | 8/9 | 0.457 | PCR | ACI |
| 2000 | Yu et al. [27] | Shandong | PB | 63/30 | 8 | 0/0 | 4/3 | 1/0 | 36/23 | 18/4 | 4/0 | 5/3 | 94/53 | 27/4 | 0.914 | PCR | ACI, LI |
| 2001 | Li et al. [28] | Zhejiang | PB | 63/66 | 8 | 0/0 | 9/10 | 0/2 | 37/49 | 14/5 | 3/0 | 9/12 | 97/113 | 20/7 | 0.280 | PCR | ND |
| 2001 | Zhang et al. [29] | Beijing | PB | 116/40 | 7 | 0/0 | 9/8 | 6/1 | 65/28 | 30/3 | 6/0 | 15/9 | 169/67 | 48/4 | 0.719 | PCR | ND |
| 2002 | Shen et al. [30] | Jiangsu | PB | 40/90 | 8 | 0/0 | 4/12 | 4/2 | 20/68 | 11/8 | 1/0 | 8/14 | 55/156 | 17/10 | 0.424 | PCR | ACI |
| 2002 | Xia et al. [31] | Henan | PB | 110/60 | 8 | 2/0 | 19/8 | 5/1 | 58/44 | 16/6 | 10/1 | 28/9 | 151/102 | 41/9 | 0.537 | SIF/IB | ND |
| 2002 | Zhu and Cui [32] | Hubei | PB | 49/108 | 8 | 0/1 | 7/14 | 1/3 | 23/72 | 16/17 | 2/1 | 8/19 | 69/175 | 21/22 | 0.847 | PCR | ND |
| 2003 | Lu [33] | Tianjin | PB | 115/120 | 8 | 1/2 | 8/15 | 3/2 | 85/92 | 16/9 | 2/0 | 13/21 | 194/208 | 23/11 | 0.351 | PCR | ND |
| 2003 | Su et al. [34] | Shandong | PB | 36/40 | 8 | 1/0 | 4/5 | 0/0 | 18/30 | 10/4 | 3/1 | 6/5 | 50/69 | 16/6 | 0.310 | PCR | ND |
| 2003 | Wang et al. [35] | Zhejiang | PB | 40/60 | 8 | 1/0 | 1/3 | 2/1 | 20/43 | 16/13 | 0/0 | 5/4 | 57/102 | 18/14 | 0.649 | PCR | ND |
| 2003 | Zhou [36] | Guangdong | PB | 41/30 | 8 | 0/0 | 3/3 | 4/0 | 13/21 | 21/6 | 0/0 | 7/3 | 50/51 | 25/6 | 0.817 | PCR | ND |
| 2004 | Li et al. [37] | Jiangsu | PB | 66/90 | 8 | 0/0 | 7/12 | 4/2 | 33/68 | 20/8 | 2/0 | 11/14 | 93/156 | 28/10 | 0.424 | PCR | ND |
| 2005 | Xiao et al. [38] | Hunan | PB | 379/351 | 8 | 0/6 | 44/41 | 3/3 | 274/252 | 55/45 | 3/4 | 47/56 | 647/590 | 64/56 | 0.027 | PCR | ND |
| 2004 | Lin et al. [39] | Taiwan | PB | 277/112 | 8 | 1/4 | 17/5 | 10/5 | 180/78 | 18/19 | 1/1 | 29/18 | 445/180 | 80/26 | <0.001 | PCR | ND |
| 2004 | Jin et al. [40] | Shanghai, Zhejiang | PB | 226/201 | 8 | 2/2 | 14/17 | 3/2 | 152/156 | 52/22 | 3/2 | 21/23 | 370/351 | 61/28 | 0.197 | PCR | ND |
| 2004 | He et al. [41] | Xinjiang | PB | 56/104 | 8 | 1/4 | 3/9 | 4/5 | 35/77 | 7/6 | 6/3 | 9/22 | 80/169 | 23/17 | <0.001 | PCR | ND |
| 2006 | Gao et al. [42] | Bejing | HB | 100/100 | 7 | 1/1 | 11/13 | 0/0 | 75/80 | 13/6 | 0/0 | 13/15 | 174/179 | 13/6 | 0.809 | PCR | ND |
| 2006 | Li et al. [43] | Hebei | PB | 51/69 | 8 | 1/0 | 2/4 | 3/2 | 26/53 | 19/10 | 0/0 | 7/6 | 73/120 | 22/12 | 0.161 | PCR | ND |
| 2006 | Ma et al. [44] | Heilongjiang | PB | 109/50 | 8 | 3/0 | 10/6 | 2/1 | 61/38 | 27/5 | 6/0 | 18/7 | 159/87 | 41/6 | 0.744 | PCR | ACI, LI |
| 2006 | Zhang et al. [45] | Sichuan, Yunnan | PB | 120/120 | 8 | 1/1 | 8/5 | 9/2 | 83/100 | 11/10 | 8/2 | 19/9 | 185/215 | 36/16 | 0.003 | PCR | ND |
| 2006 | Wen et al. [46] | Hongkong | PB | 67/134 | 8 | 4/2 | 7/24 | 2/3 | 41/89 | 11/15 | 2/1 | 17/31 | 100/217 | 17/20 | 0.925 | PCR | LI |

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DOI: 10.1159/000442678

**Table 1.** (continued)

| Year | Author | Geographical location | Source of controls | Sample size (case/control) | NOS score | ε2/ε2 (case/control) | ε2/ε3 (case/control) | ε2/ε4 (case/control) | ε3/ε3 (case/control) | ε3/ε4 (case/control) | ε4/ε4 (case/control) | ε2 (case/control) | ε3 (case/control) | ε4 (case/control) | HWE | Genotypic method | Subtype |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2006 | Zhou et al. [47] | Heilongjiang | PB + HB | 72/68 | 7 | 2/2 | 11/9 | 2/0 | 52/46 | 5/11 | 0/0 | 17/13 | 120/112 | 7/11 | 0.155 | PCR | ND |
| 2006 | Baum et al. [48] | Hongkong | PB | 243/311 | 8 | 7/2 | 39/60 | 6/6 | 155/203 | 32/39 | 4/1 | 59/70 | 381/505 | 46/47 | 0.659 | PCR | ND |
| 2007 | Deng et al. [49] | Hunan | PB | 105/322 | 8 | 0/5 | 20/40 | 1/3 | 70/233 | 13/37 | 1/4 | 21/53 | 173/543 | 16/48 | 0.058 | PCR | LI |
| 2007 | Lv et al. [50] | Liaoning | PB | 38/98 | 8 | 0/1 | 2/13 | 10/7 | 12/65 | 14/12 | 0/0 | 12/22 | 40/155 | 24/19 | 0.003 | PCR | ND |
| 2007 | Man et al. [51] | Shandong | PB | 40/50 | 8 | 1/1 | 6/6 | 0/0 | 20/38 | 10/4 | 3/1 | 8/8 | 56/86 | 16/6 | 0.109 | PCR | ND |
| 2007 | Lai et al. [52] | Taiwan | PB | 257/112 | 8 | 1/4 | 17/5 | 10/5 | 162/78 | 67/19 | 0/1 | 29/18 | 408/180 | 77/26 | <0.001 | PCR | ACI, LI |
| 2008 | Sun et al. [53] | Inner Mongolia | PB | 78/90 | 8 | 0/0 | 12/10 | 3/2 | 44/71 | 18/7 | 1/0 | 15/12 | 118/159 | 23/9 | 0.256 | PCR | ND |
| 2008 | Xie et al. [54] | Yunnan | PB | 92/50 | 8 | 0/1 | 9/10 | 4/2 | 49/36 | 28/1 | 2/0 | 13/14 | 135/83 | 36/3 | 0.066 | PCR | ACI |
| 2009 | Nie [55] | Yunnan | PB | 40/43 | 8 | 0/1 | 6/7 | 1/1 | 24/32 | 9/2 | 0/0 | 7/9 | 63/74 | 10/3 | 0.576 | PCR | ND |
| 2009 | Wang et al. [56] | Northern area | PB | 396/396 | 8 | 16/33 | 98/116 | 60/41 | 124/164 | 87/39 | 11/3 | 190/223 | 433/483 | 169/86 | <0.001 | PCR | ND |
| 2009 | Zhou et al. [57] | Hainan | PB | 78/74 | 8 | 0/15 | 5/7 | 4/6 | 46/43 | 13/3 | 10/0 | 9/43 | 110/96 | 37/9 | <0.001 | PCR | ND |
| 2010 | Yang et al. [58] | Shanxi | PB | 240/150 | 8 | 3/2 | 37/23 | 5/3 | 157/99 | 35/21 | 3/2 | 48/30 | 386/242 | 46/28 | 0.864 | PCR | ND |
| 2010 | Yuan [59] | Yunan | PB | 58/50 | 8 | 0/0 | 4/3 | 2/2 | 28/39 | 23/6 | 1/0 | 6/5 | 83/87 | 27/8 | 0.059 | PCR | ND |
| 2012 | Li et al. [60] | Hunan | PB | 240/240 | 8 | 4/0 | 38/48 | 5/0 | 149/157 | 39/34 | 5/1 | 51/48 | 375/396 | 54/36 | 0.032 | Gene chip | ACI |
| 2012 | Liu et al. [61] | Anhui | PB | 108/76 | 8 | 2/5 | 11/17 | 0/2 | 77/49 | 15/2 | 3/1 | 15/29 | 180/117 | 21/6 | 0.007 | PCR | ND |
| 2012 | Lv et al. [62] | Guangdong Guangxi | PB | 61/156 | 8 | 1/0 | 8/31 | 5/1 | 29/107 | 13/17 | 5/0 | 15/32 | 79/262 | 28/18 | 0.321 | PCR | ND |
| 2012 | Wang et al. [63] | Hainan | PB | 50/50 | 8 | 1/0 | 0/8 | 0/1 | 34/27 | 13/14 | 2/0 | 2/9 | 80/76 | 17/15 | 0.469 | PCR | ND |
| 2013 | Gu et al. [64] | Guangxi | PB + HB | 166/192 | 7 | 1/1 | 25/21 | 2/2 | 113/141 | 23/26 | 2/1 | 29/25 | 274/329 | 29/30 | 0.994 | PCR | ND |
| 2013 | Jing [65] | Sichuan | PB | 162/120 | 8 | 1/2 | 18/6 | 4/3 | 114/88 | 23/18 | 2/3 | 24/13 | 269/200 | 31/27 | 0.003 | PCR | ND |
| 2013 | Liu [66] | Yunnan | PB | 40/40 | 8 | 0/0 | 3/3 | 2/2 | 19/31 | 15/4 | 1/0 | 5/5 | 56/69 | 19/6 | 0.043 | PCR | ND |
| 2013 | Wang et al. [67] | Hebei | PB | 110/126 | 8 | 4/2 | 15/13 | 7/4 | 51/84 | 21/18 | 12/5 | 30/21 | 138/200 | 52/32 | 0.021 | PCR | ND |
| 2013 | Zhao [68] | Jilin | PB | 200/100 | 8 | 1/2 | 12/7 | 14/3 | 136/79 | 22/5 | 15/4 | 28/14 | 306/170 | 66/16 | <0.001 | PCR | ND |
| 2014 | Huang [69] | Yunnan | PB | 54/56 | 8 | 0/0 | 3/2 | 1/1 | 18/43 | 30/10 | 2/0 | 4/3 | 69/98 | 35/11 | 0.488 | PCR | ND |
| 2014 | Sun [70] | Liaoning | PB | 50/50 | 8 | 3/4 | 5/6 | 2/2 | 26/32 | 12/3 | 2/3 | 13/16 | 69/73 | 18/11 | <0.001 | PCR | ND |
| 2014 | Zhang et al. [71] | Guangdong | PB | 91/105 | 8 | 0/1 | 14/14 | 1/0 | 56/72 | 20/18 | 0/0 | 15/16 | 146/176 | 21/18 | 0.388 | PCR | ACI, LI |
| 2015 | Yan et al. [72] | Henan | HB | 580/580 | 6 | 11/61 | 41/54 | 33/49 | 351/354 | 82/33 | 62/29 | 96/225 | 825/795 | 239/140 | <0.001 | PCR | ND |

PB = Population-based controls; HB = hospital-based controls; IEF/WB = isoelectric focusing/western blotting; ND = not described.

ACI [19, 20, 22, 23, 26, 30, 54, 60], and 2 studies examined LI patients [46, 49]. Of the 15 studies that subtyped the stroke, only one [52] used the Classification of Cerebrovascular Diseases III from the National Institute of Neurological Disorders and Stroke (NINDS) [73]; all other studies used the risk-factor based Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification [74]. The mean NOS score was 7.85; this result indicated that the quality of the included studies was relatively good according to this scale.

Quantitative Synthesis

The forest plots are shown in figure 2a–d, and the main results are presented in table 2.

Main Results of the Allele Comparisons

Compared with the ε3 allele, the ε2 allele was not associated with IS risk (OR 1.01, 95% CI 0.87–1.17, p = 0.938), although moderate heterogeneity was detected between studies ($I^2$ = 57.5%, $P_Q$ = 0.000). Similarly, no significant associations were detected in our subgroup analyses based on the HWE status (yes or no), SOC (population-based or non-population-based) or IS subtype (ACI or LI). However, we found a significant association of the ε4 allele with IS risk compared with the ε3 allele (OR 2.19, 95% CI 1.90–2.52, p < 0.001), although moderate heterogeneity was observed between studies ($I^2$ = 58.5%, $P_Q$ = 0.000). For the subgroup analyses based on SOC (population-based or non-population-based), HWE status (yes or no) and IS subtype (ACI or LI), significant associations were detected between the presence of the ε4 allele and the risk of IS.

Main Results of the Genotype Comparisons

The pooled OR for ε2 carriers vs. ε3ε3 genotype carriers was 0.98 (95% CI 0.88–1.09, p = 0.73), and no heterogeneity was detected between studies ($I^2$ = 0.0%, $P_Q$ = 0.49). In addition, no significant associations were detected in the subgroup analyses based on the HWE status (yes or no), SOC (population-based or non-population-based) or IS subtype (ACI or LI).

In addition, a significant difference in IS risk was detected between ε4 carriers and ε3ε3 genotype carriers (OR 2.41, 95% CI 2.00–2.89, p < 0.001) based on a REM ($I^2$ = 63.2%, $P_Q$ = 0.000). For the subgroup analyses based on SOC (population-based or non-population-based), HWE status (yes or no) or IS subtype (ACI or LI), significant associations were found between the presence of the ε4 allele and the risk of IS.

Sensitivity Analysis

Sensitivity analysis was performed after limiting the included studies to those assigned an NOS score >7. The corresponding pooled ORs of all genetic models were not substantially altered. Furthermore, after limiting the pool to studies containing population-based controls, studies with results meeting HWE and studies using PCR-based genotyping methods, the corresponding pooled ORs were not substantially altered. These data suggested that our results were sensitive and reliable.

Publication Bias

Begg's funnel plots and Egger's regression tests were performed to assess the potential publication bias. The funnel plot of the genetic comparisons (ε2 vs. ε3, ε2 carrier vs. ε3ε3 carrier) did not show any evident asymmetry (fig. 3b, d). Egger's regression test confirmed that no publication bias existed in these analyses (p = 0.14, ε2 vs. ε3; p = 0.441, ε2 carrier vs. ε3ε3 carrier). However, publication bias was detected in other genetic comparisons (ε4 vs. ε3, ε4 carrier vs. ε3ε3 carrier), as revealed by Begg's funnel plots (fig. 3a, c) and Egger's regression tests (ε4 vs. ε3, p = 0.000; ε4 carrier vs. ε3ε3 carrier, p = 0.000).

*ApoE and ICH in the Chinese Population*

A total of 18 studies [24, 28, 33, 35, 36, 43, 53, 58, 59, 75–83] containing 2,018 cases and 2,143 controls from China were included in the final meta-analysis of the association between ApoE polymorphisms and ICH risk. The selection process is shown in figure 1, and the included studies and their main characteristics are presented in table 3. The participants in these studies were recruited from 15 provinces of China, including Anhui, Chongqing, Fujian, Guangdong, Hebei, Hunan, Inner Mongolia, Jiangsu, Liaoning, Shanxi, Shanghai, Taiwan, Tianjin, Yunnan and Zhejiang. ApoE gene polymorphisms were detected using PCR and restriction fragment length polymorphism methods in all included studies. Of the 18 included studies, 16 studies [28, 33, 35, 36, 43, 53, 58, 59, 75–81, 83] contained population-based controls, and 2 studies contained results that did not follow HWE [77, 83]. The mean NOS score was 7.89; this result indicated that the quality of the included studies was relatively good according to this scale.

Quantitative Synthesis

The forest plots are shown in figure 4a–d, and the main results are presented in table 4.

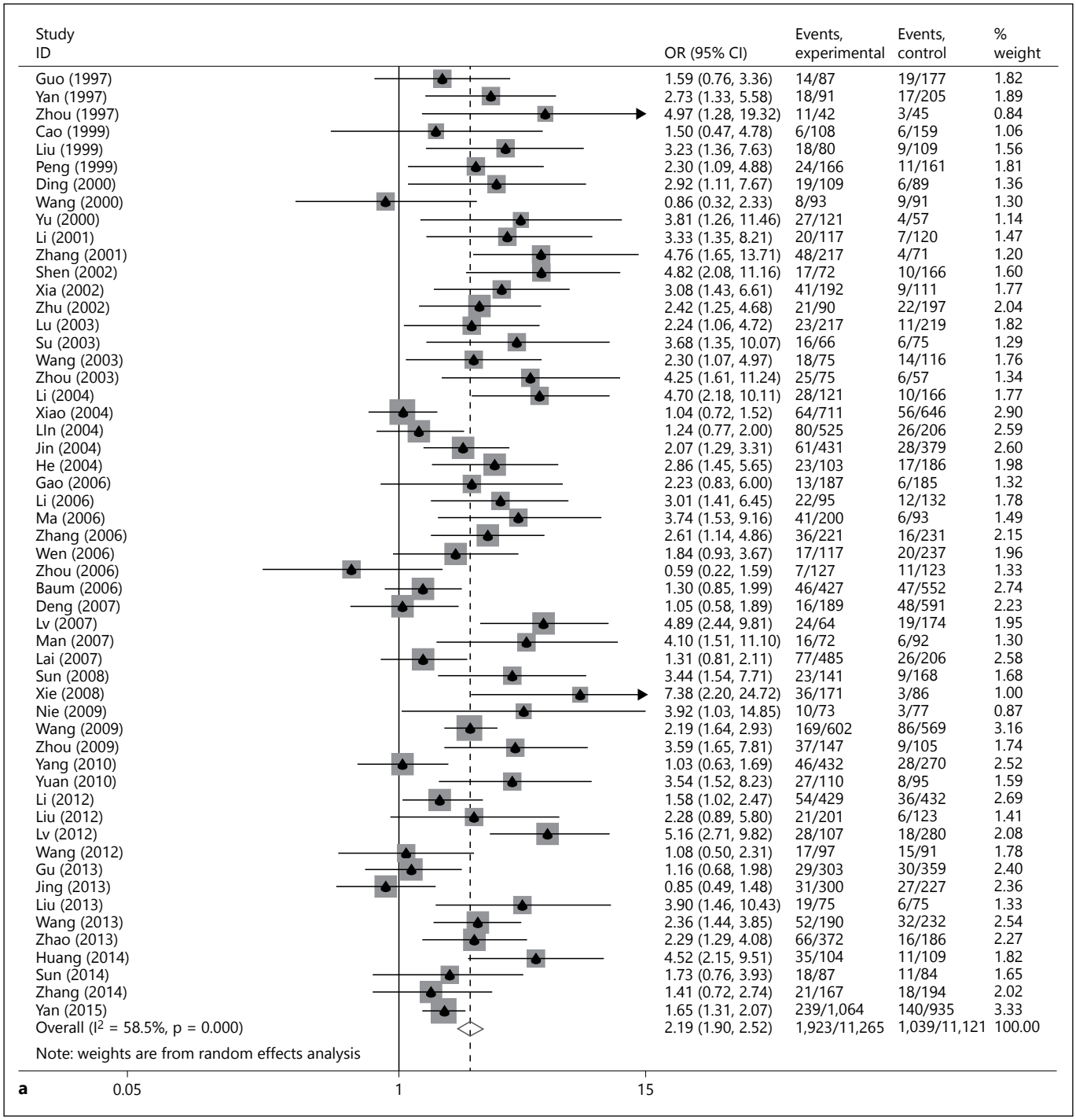
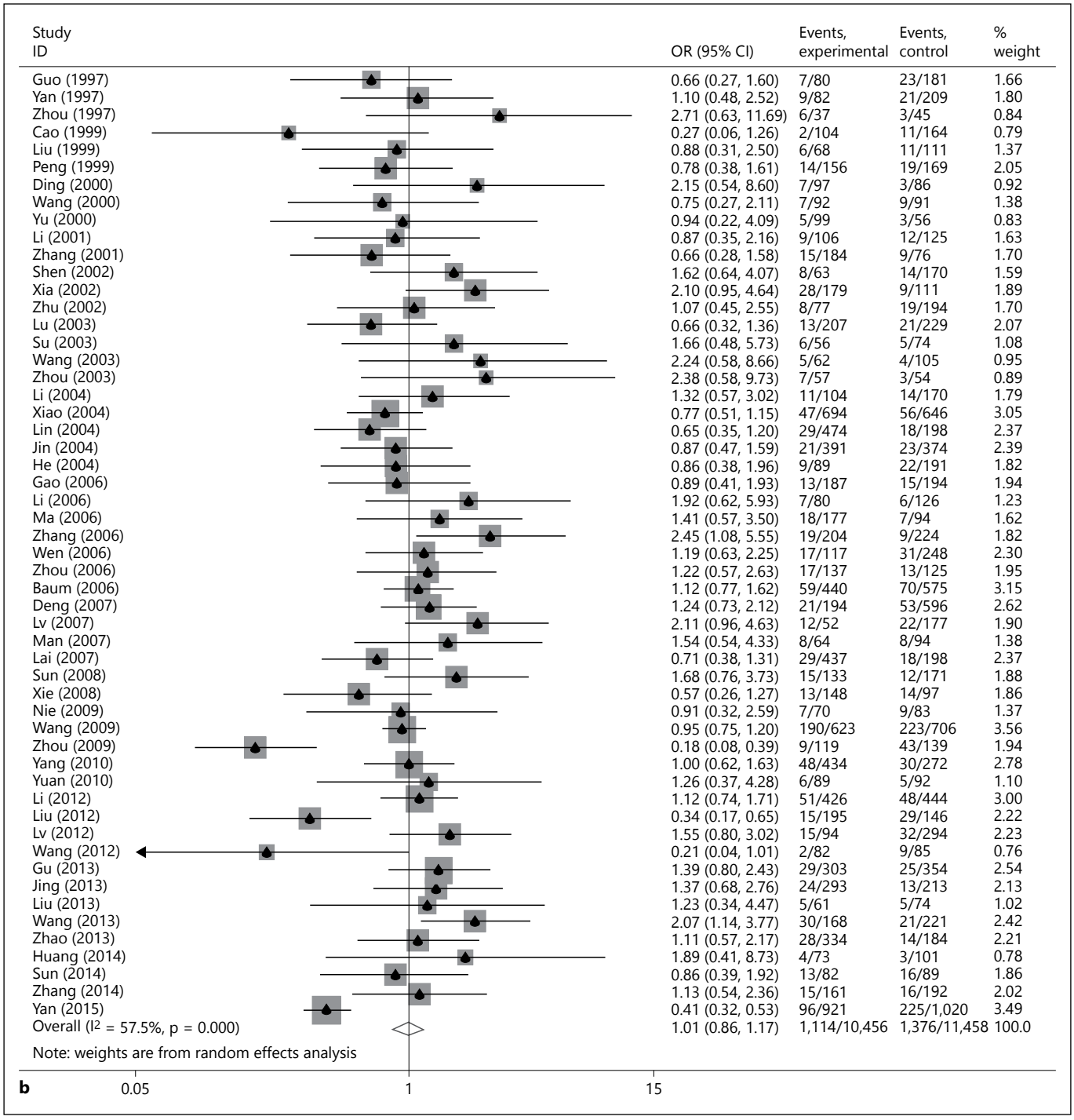


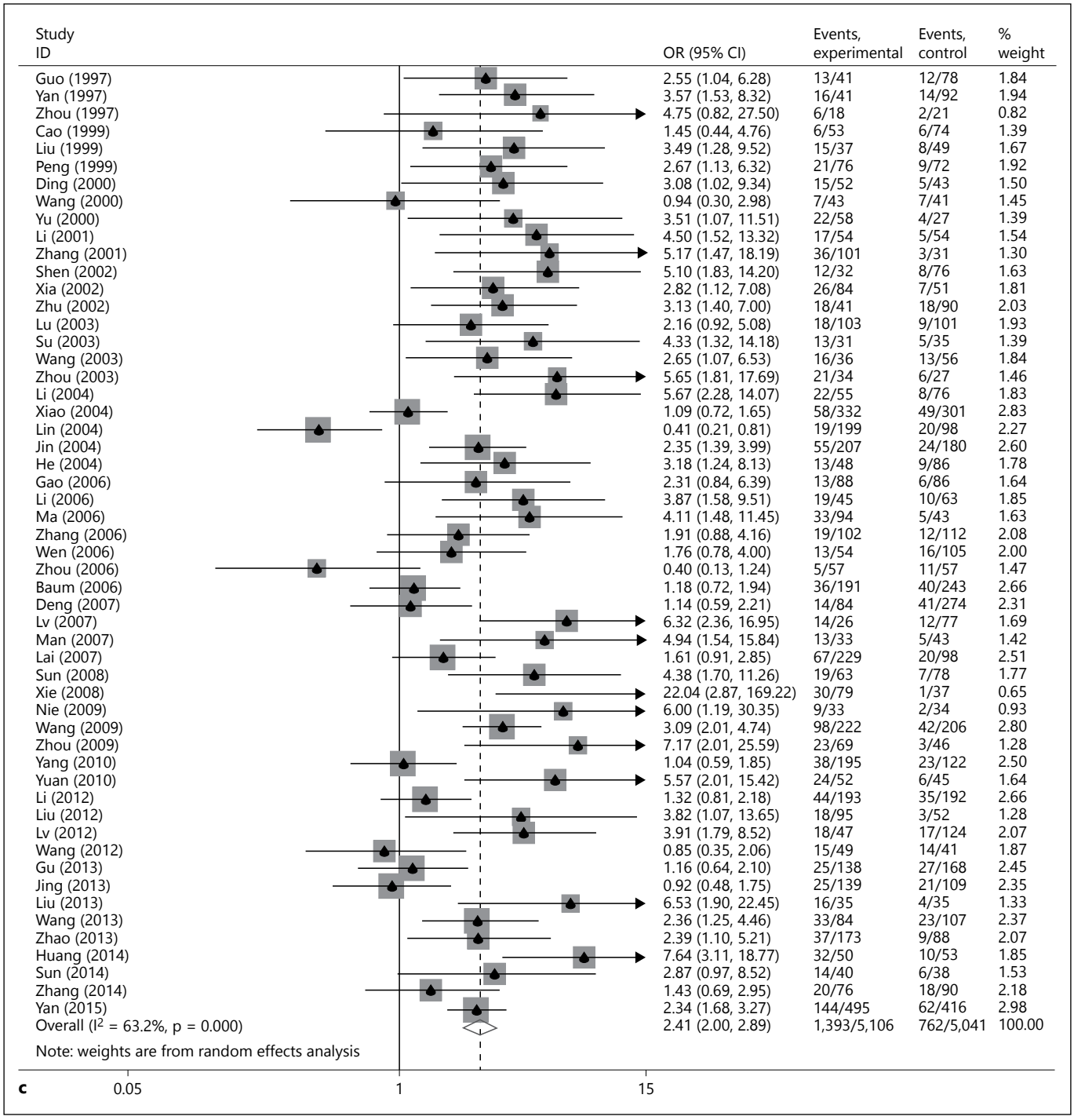

**Fig. 2. a–d** Forest plots of the relationships between ApoE gene polymorphisms and IS risk in the genetic comparisons of the ε4 allele vs. the ε3 allele (**a**); the ε2 allele vs. the ε3 allele (**b**); ε4 carriers vs. ε3ε3 carriers (**c**); and ε2 carriers vs. ε3ε3 carriers (**d**). (*For figure 2b–d see next pages.*)




2

Main Results of the Allele Comparisons

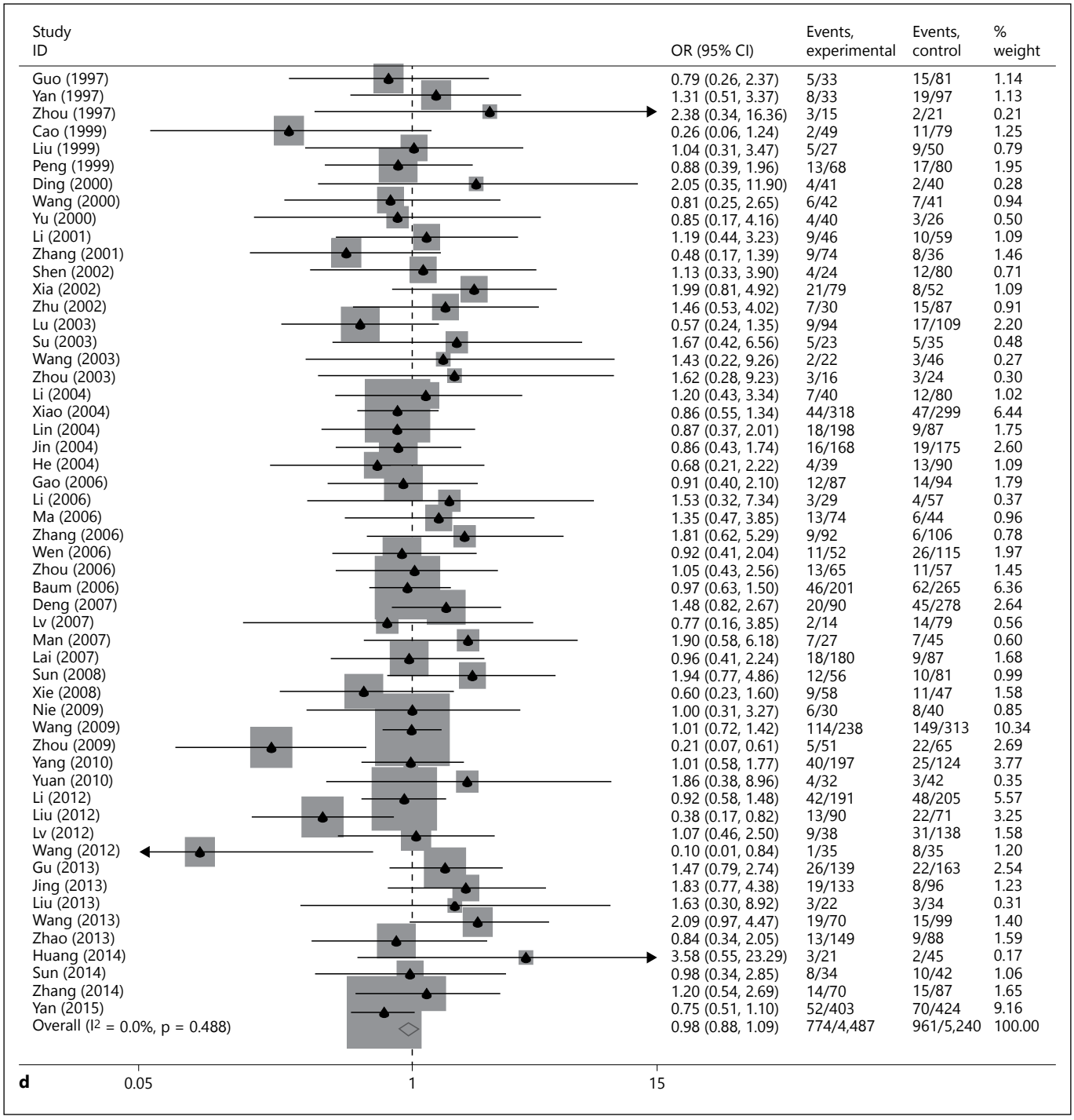
We found a significant association between the ε4 allele and ICH risk compared with the ε3 allele (OR 2.08, 95% CI 1.57–2.75, p < 0.001), although moderate heterogeneity between studies was observed ($I^2 = 61.9\%$, $P_Q = 0.000$). For the subgroup analysis based on SOC (population-based or non-population-based), significant associations were found between the presence of the ε4 allele and the ICH risk. For the subgroup analysis based on HWE status, an increased risk of ICH was noted for the ε4 allele compared to the ε3 allele (OR 2.18, 95% CI 1.64–2.89, p < 0.001), although moderate heterogeneity was observed between




2

studies ($I^2$ = 53.3%, $P_Q$ = 0.006). In contrast, no significant effects were found in the non-HWE subgroup (OR 1.63, 95% CI 0.56–4.74, p = 0.367), although heterogeneity between studies was evident ($I^2$ = 82.3%, $P_Q$ = 0.018).

Furthermore, compared with the ε3 allele, the ε2 allele was not associated with ICH risk (OR 1.13, 95% CI 0.96–1.33, p = 0.133), although mild heterogeneity was observed between studies ($I^2$ = 35.7%, $P_Q$ = 0.067). Similarly, no significant associations were detected in our subgroup analyses based on the HWE status (yes or no) or SOC (population-based or non-population-based).




2

Main Results of the Genotype Comparisons

A significant difference in ICH risk was detected between ε4 carriers and ε3ε3 genotype carriers (OR 2.41, 95% CI 1.68–3.47, p < 0.001) was noted based on a REM ($I^2$ = 70.9%, $P_Q$ <0.000). For the subgroup analyses based on SOC (population-based or non-population-based), significant associations were found between ε4 carrier status and the risk of ICH. However, in the subgroup analysis based on HWE status, this increased risk of ICH remained significant for the ε4 carriers compared with the ε3ε3 genotype carriers in the HWE subgroup (OR 2.50, 95% CI 1.69–3.71, p < 0.001), although moderate

**Table 2.** The main results of studies associated with IS included in this meta-analysis

| Study subgroup | Studies (size/control) | ε4 vs. ε3 | | | ε2 vs. ε3 | | | ε4 carrier vs. ε3ε3 carrier | | | ε2 carrier vs. ε3ε3 carrier | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | $P_Q$ | $I^2$, % | OR (95% CI) | $P_Q$ | $I^2$, % | OR (95% CI) | $P_Q$ | $I^2$, % | OR (95% CI) | $P_Q$ | $I^2$, % |
| IS | 54 (6,190/6,248) | 2.19 (1.90–2.52)* | 0.000 | 58.5 | 1.01 (0.86–1.17) | 0.000 | 57.5 | 2.41 (2.00–2.89)* | 0.000 | 63.2 | 0.99 (0.89–1.11) | 0.488 | 0.0 |
| HWE | | | | | | | | | | | | | |
| Yes | 37 (3,052/3,449) | 2.42 (1.99–2.93)* | 0.000 | 55.4 | 1.12 (0.98–1.28) | 0.751 | 0.0 | 2.61 (2.08–3.28)* | 0.000 | 56.7 | 1.10 (0.94–1.27) | 0.879 | 0.0 |
| No | 17 (3,138/2,799) | 1.87 (1.53–2.29)* | 0.001 | 60.5 | 0.85 (0.63–1.14) | 0.000 | 79.5 | 2.08 (1.53–2.84)* | 0.000 | 72.2 | 0.89 (0.72–1.11) | 0.109 | 31.0 |
| SOC | | | | | | | | | | | | | |
| PB | 48 (5,124/5,172) | 2.29 (1.96–2.68)* | 0.000 | 59.0 | 1.02 (0.89–1.18) | 0.002 | 41.0 | 2.54 (2.07–3.11)* | 0.000 | 64.1 | 1.01 (0.89–1.14) | 0.424 | 2.5 |
| Non-PB | 6 (1,066/1,076) | 1.58 (1.14–2.20)* | 0.146 | 38.9 | 0.92 (0.52–1.64) | 0.000 | 80.0 | 1.73 (1.06–2.84)* | 0.000 | 61.2 | 0.93 (0.71–1.22) | 0.522 | 0.0 |
| Subtype | | | | | | | | | | | | | |
| ACI | 13 (880/1,131) | 2.26 (1.60–3.20)* | 0.008 | 55.3 | 0.98 (0.77–1.23) | 0.545 | 0.0 | 2.47 (1.66–3.67)* | 0.012 | 53.2 | 0.95 (0.72–1.25) | 0.792 | 0.0 |
| LI | 7 (285/372) | 1.61 (1.23–2.12)* | 0.206 | 29.1 | 1.06 (0.78–1.43) | 0.795 | 0.0 | 1.77 (1.29–2.42)* | 0.280 | 19.7 | 1.15 (0.80–1.64) | 0.977 | 0.0 |
| PCR-based | 52 (5,840/5,948) | 2.20 (1.90–2.55)* | 0.000 | 59.4 | 0.99 (0.85–1.16) | 0.000 | 57.3 | 2.45 (2.02–2.96)* | 0.000 | 63.6 | 0.99 (0.88–1.11) | 0.503 | 0.0 |
| High quality | 47 (5,008/5,132) | 2.27 (1.94–2.65)* | 0.000 | 58.9 | 1.03 (0.90–1.19) | 0.002 | 41.6 | 2.51 (2.05–3.08)* | 0.000 | 64.3 | 1.02 (0.90–1.15) | 0.459 | 0.7 |

* $p < 0.05$. $P_Q$ = A p value of the Cochrane's Q test for heterogeneity; $I^2$ = value of $I^2$ statistic for heterogeneity; PB = population-based controls; non-PB = hospital-based controls or mixed controls; PCR-based = PCR based genotypic method; high quality = NOS score >7.

heterogeneity between studies was observed ($I^2$ = 69.8%, $P_Q$ = 0.000). In contrast, no significant effect was found for the non-HWE subgroup (OR 1.92, 95% CI 0.60–6.10, p = 0.271), although moderate heterogeneity was detected between studies ($I^2$ = 72.2%, $P_Q$ = 0.058).

The pooled OR for ε2 carriers compared to ε3ε3 genotype carriers was 1.01 (95% CI 0.84–1.22, p = 0.887), although mild heterogeneity was observed between studies ($I^2$ = 25.7%, $P_Q$ = 0.153). Similarly, no clear evidence for this association was found in our subgroup analyses based on the HWE status (yes or no) or SOC (population-based or non-population-based).

Sensitivity Analysis

Sensitivity analysis was performed after limiting the included studies to those assigned an NOS score >7. The corresponding pooled ORs of all genetic comparisons were not substantially altered. Furthermore, after limiting the studies to those containing population-based controls, those containing results meeting HWE, or those using PCR-based genotype methods, the corresponding pooled ORs were not substantially altered. These data suggested that our results were sensitive and reliable.

Publication Bias

Begg's funnel plots and Egger's regression tests were performed to assess the potential publication bias. No apparent asymmetry was observed in the funnel plots of any genetic comparisons (fig. 5a–d). Egger's regression test confirmed that no publication bias existed (ε4 allele vs. ε3 allele, p = 0.24; ε2 allele vs. ε3 allele, p = 0.18; ε4 carrier vs. ε3ε3 carrier, p = 0.17; ε2 carrier vs. ε3ε3 carrier, p = 0.22).

*ApoE and SAH in the Chinese Population*

Two studies [84, 85] containing 195 cases and 207 controls from China were included in the final meta-analysis of the associations of ApoE polymorphisms with SAH risk. The selection process is outlined in figure 1, and the included studies and their main characteristics are presented in table 3. Pooled analyses showed a significantly increased risk for SAH among ε4 carriers compared with ε3ε3 genotype carriers (OR 2.04, 95% CI 1.21–3.45, p = 0.008), but no association was detected among ε2 carriers compared with ε3ε3 genotype carriers (OR 0.72, 95% CI 0.40–1.31, p = 0.282). Similarly, we found a significant association of the ε4 allele with SAH risk compared with the ε3 allele (OR 2.03, 95% CI 1.28–3.23, p = 0.003), but we failed to detect any association of the ε2 allele with SAH risk compared with the ε3 allele (OR 0.80, 95% CI 0.48–1.32, p = 0.377).

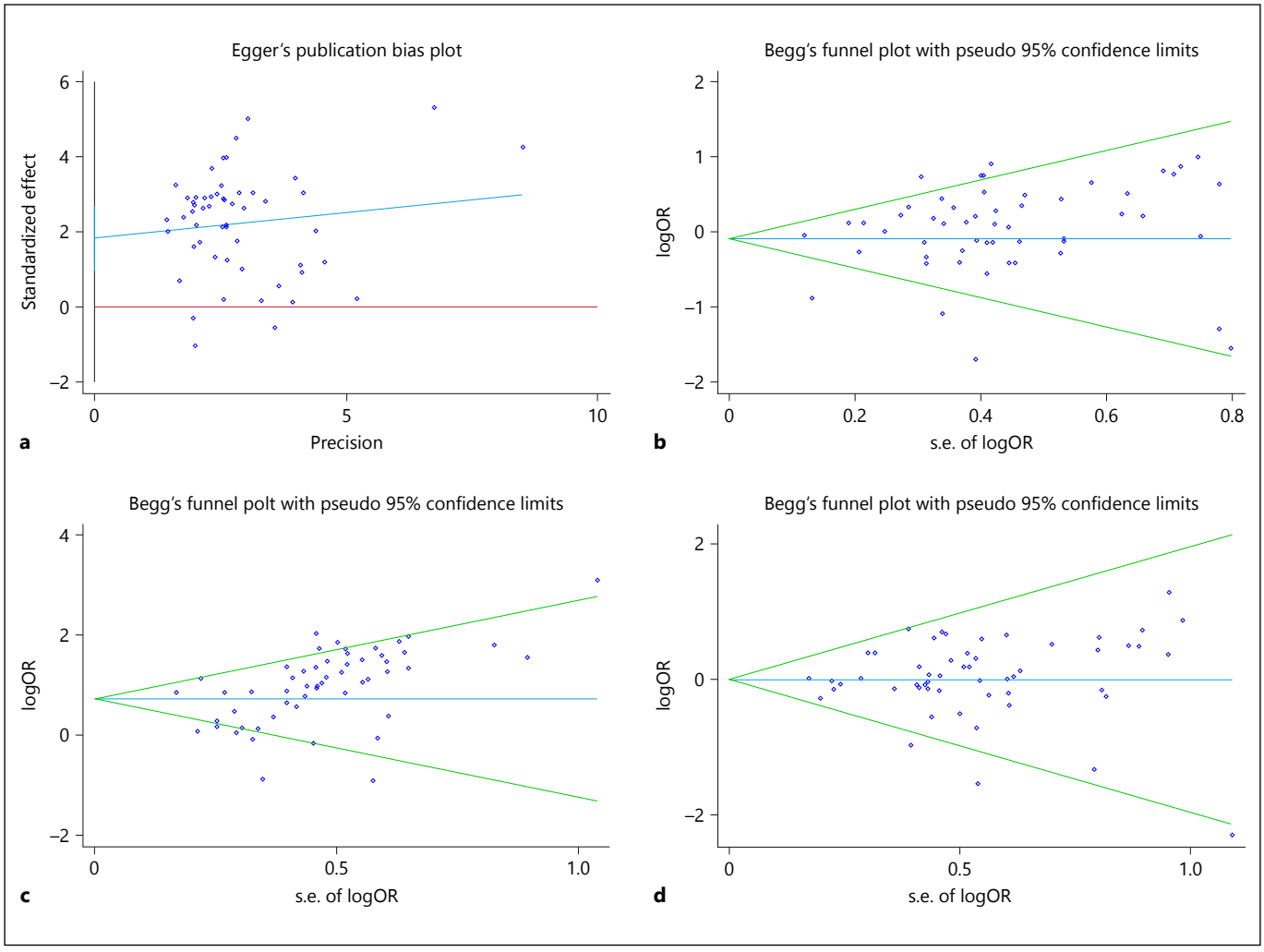



**Fig. 3. a–d** Begg's funnel plots of the relationships between ApoE gene polymorphisms and IS risk in the genetic comparisons of the ε4 allele vs. the ε3 allele (**a**); the ε2 allele vs. the ε3 allele (**b**); ε4 carriers vs. ε3ε3 carriers (**c**); and ε2 carriers vs. ε3ε3 carriers (**d**).

## Discussion

Stroke is a multi-factorial and polygenic disorder disease that is thought to result from complex genetic factors and gene-environment interactions. ApoE polymorphisms have been reported to be associated with various diseases, including type II diabetes, coronary artery disease [86, 87], hypertension [15], Alzheimer's disease [88, 89], and dementia in Parkinson disease [90]. Recently, the associations between ApoE gene polymorphisms and the risk of different subtypes of stroke have been studied extensively [91–93], but the results remain inconclusive, particularly in different ethnic groups and geographical locations. Therefore, this study summarized the published evidence on the association between ApoE gene polymorphisms and stroke risk in the Chinese population.

To determine the relationship between ApoE gene polymorphisms and IS risk, the 54 studies included our meta-analysis, which contained a total of 6,190 IS cases and 6,248 controls. It provided the most comprehensive assessment of the association between ApoE gene polymorphisms and IS risk in the Chinese population to date. Indeed, we found a significant association of the ε4 allele with IS risk compared with the ε3 allele, and ε4 carriers showed a significantly higher risk of developing IS than ε3ε3 genotype carriers. In contrast, the evidence did not support an association of the ε2 allele or ε2 carriers with

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DOI: 10.1159/000442678

**Table 3.** Main characteristics of studies associated with ApoE polymorphism and hemorrhagic stroke included in this meta-analysis

| Year | Author | Geographical location | Source of controls | Sample size (case/control) | NOS score | ε2/ε2 (case/control) | ε2/ε3 (case/control) | ε2/ε4 (case/control) | ε3/ε3 (case/control) | ε3/ε4 (case/control) | ε4/ε4 (case/control) | ε2 (case/control) | ε3 (case/control) | ε4 (case/control) | HWE | Subtype |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1999 | Peng and Zhao [24] | Hunan | HB | 90/90 | 7 | 1/1 | 26/15 | 0/1 | 49/63 | 13/9 | 1/1 | 28/18 | 137/150 | 15/12 | 0.790 | ICH |
| 2001 | Cheng and Dong [75] | Jiangsu | PB | 56/30 | 8 | 1/0 | 8/4 | 3/2 | 33/20 | 8/4 | 0/0 | 13/6 | 82/48 | 17/6 | 0.244 | ICH |
| 2001 | Li et al. [28] | Zhejiang | PB | 30/66 | 8 | 0/0 | 2/10 | 7/2 | 6/49 | 12/5 | 3/0 | 9/12 | 26/113 | 25/7 | 0.280 | ICH |
| 2001 | Wu et al. [76] | Shanghai | PB | 225/110 | 8 | 0/0 | 18/23 | 12/3 | 128/70 | 65/13 | 2/0 | 30/26 | 339/178 | 81/16 | 0.396 | ICH |
| 2003 | Wang et al. [35] | Zhejiang | PB | 40/60 | 8 | 1/0 | 4/3 | 1/1 | 22/43 | 12/13 | 0/0 | 7/4 | 60/102 | 13/14 | 0.649 | ICH |
| 2003 | Zhou [36] | Guangdong | PB | 19/30 | 8 | 1/0 | 2/3 | 2/0 | 9/21 | 5/6 | 0/0 | 6/3 | 25/51 | 7/6 | 0.817 | ICH |
| 2003 | Lu [33] | Tianjin | PB | 50/120 | 8 | 0/2 | 7/15 | 0/2 | 39/92 | 3/9 | 1/0 | 7/21 | 88/208 | 5/11 | 0.351 | ICH |
| 2004 | Xiao et al. [77] | Hunan | PB | 313/351 | 8 | 0/6 | 36/41 | 9/3 | 216/252 | 47/45 | 3/4 | 62/56 | 515/590 | 49/56 | 0.027 | ICH |
| 2006 | Li et al. [43] | Hebei | PB | 50/69 | 8 | 1/0 | 5/4 | 1/2 | 28/53 | 15/10 | 0/0 | 8/6 | 76/120 | 16/12 | 0.161 | ICH |
| 2006 | Xu [78] | Jiangsu | PB | 406/216 | 8 | 8/3 | 47/26 | 4/2 | 252/156 | 89/27 | 6/2 | 67/34 | 640/365 | 105/33 | 0.400 | ICH |
| 2008 | Sun et al. [53] | Inner Mongolia | PB | 20/90 | 8 | 0/0 | 2/10 | 1/2 | 14/71 | 31/7 | 0/0 | 3/12 | 33/159 | 4/9 | 0.256 | ICH |
| 2009 | Lin and Zhang [79] | Fujian | PB | 74/80 | 8 | 0/0 | 7/11 | 1/0 | 48/61 | 14/8 | 4/0 | 8/11 | 117/141 | 23/8 | 0.693 | ICH |
| 2009 | Chen et al. [80] | Taiwan | PB | 217/280 | 8 | 1/2 | 25/39 | 6/1 | 150/202 | 34/36 | 1/0 | 33/44 | 359/479 | 42/37 | 0.361 | ICH |
| 2010 | Yang et al. [58] | Shanxi | PB | 60/150 | 8 | 3/2 | 11/23 | 3/3 | 36/99 | 6/21 | 1/2 | 10/30 | 45/242 | 5/28 | 0.864 | ICH |
| 2010 | Yuan [59] | Yunnan | PB | 32/50 | 8 | 0/0 | 2/3 | 2/2 | 24/39 | 4/6 | 0/0 | 4/5 | 54/87 | 6/8 | 0.059 | ICH |
| 2012 | Lv and Qu [81] | Liaoning | PB | 78/80 | 8 | 0/0 | 7/10 | 1/0 | 50/62 | 15/8 | 5/0 | 8/10 | 122/142 | 26/8 | 0.733 | ICH |
| 2012 | Zhang et al. [82] | Chongqing | HB | 180/180 | 7 | 1/1 | 18/20 | 6/4 | 110/140 | 42/14 | 3/1 | 26/26 | 280/314 | 54/20 | 0.114 | ICH |
| 2013 | Huang et al. [83] | Anhui | PB | 78/91 | 8 | 2/6 | 8/20 | 3/3 | 51/58 | 8/2 | 6/2 | 15/35 | 118/138 | 23/9 | <0.001 | ICH |
| 2005 | Dai [84] | Honkong | PB + HB | 133/127 | 7 | 2/2 | 13/20 | 2/1 | 82/85 | 32/19 | 2/0 | 19/25 | 211/209 | 36/20 | 0.539 | SAH |
| 2006 | Wu [85] | Guangzhou | PB | 62/80 | 8 | 1/2 | 5/10 | 3/2 | 38/57 | 13/9 | 2/0 | 10/16 | 94/133 | 20/11 | 0.285 | SAH |

PB = Population-based controls; HB = hospital-based controls.

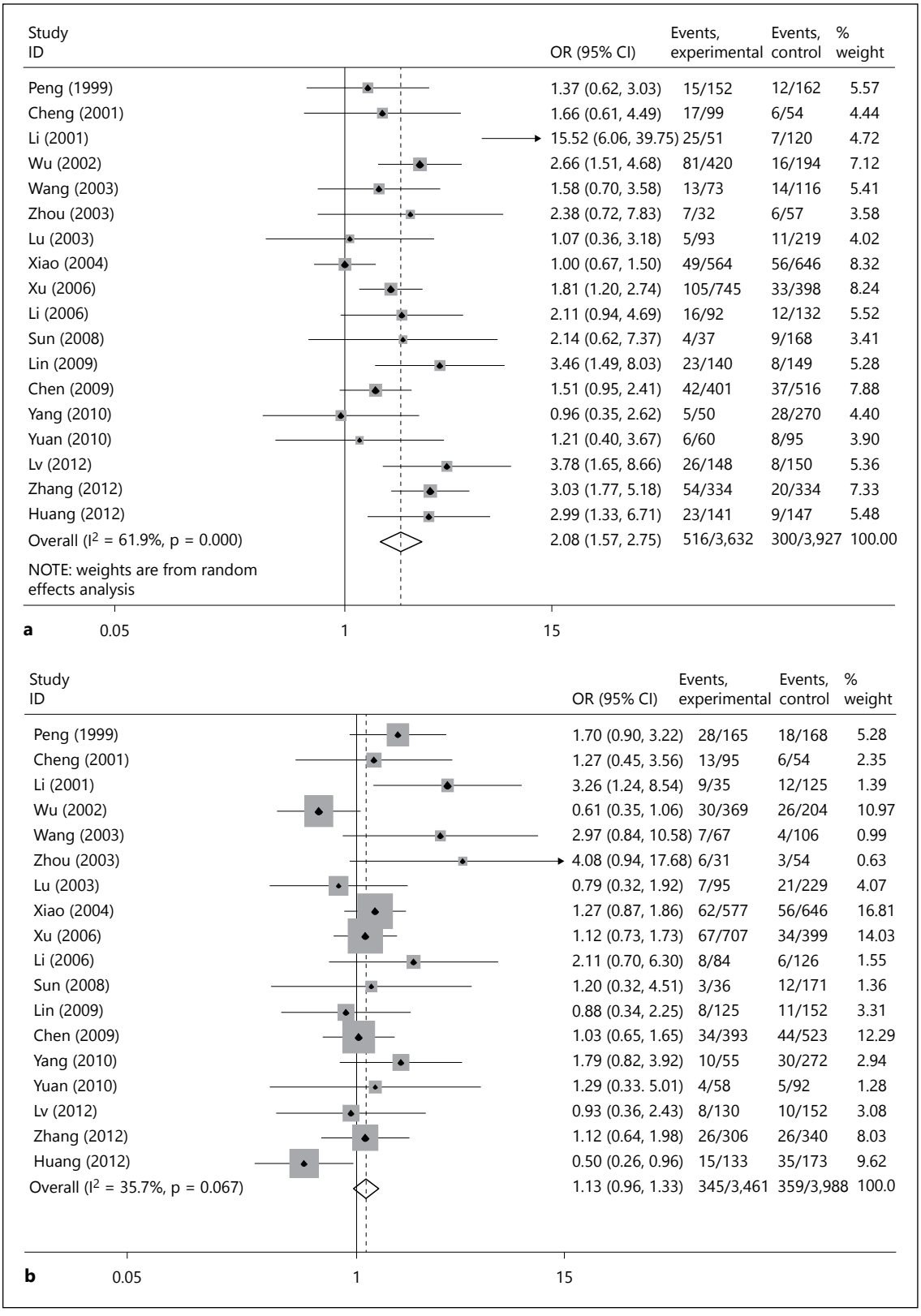


**Fig. 4. a–d** Forest plot of the relationships between ApoE gene polymorphisms and ICH risk in the genetic comparisons of the ε4 allele vs. the ε3 allele (**a**); the ε2 allele vs. the ε3 allele (**b**).

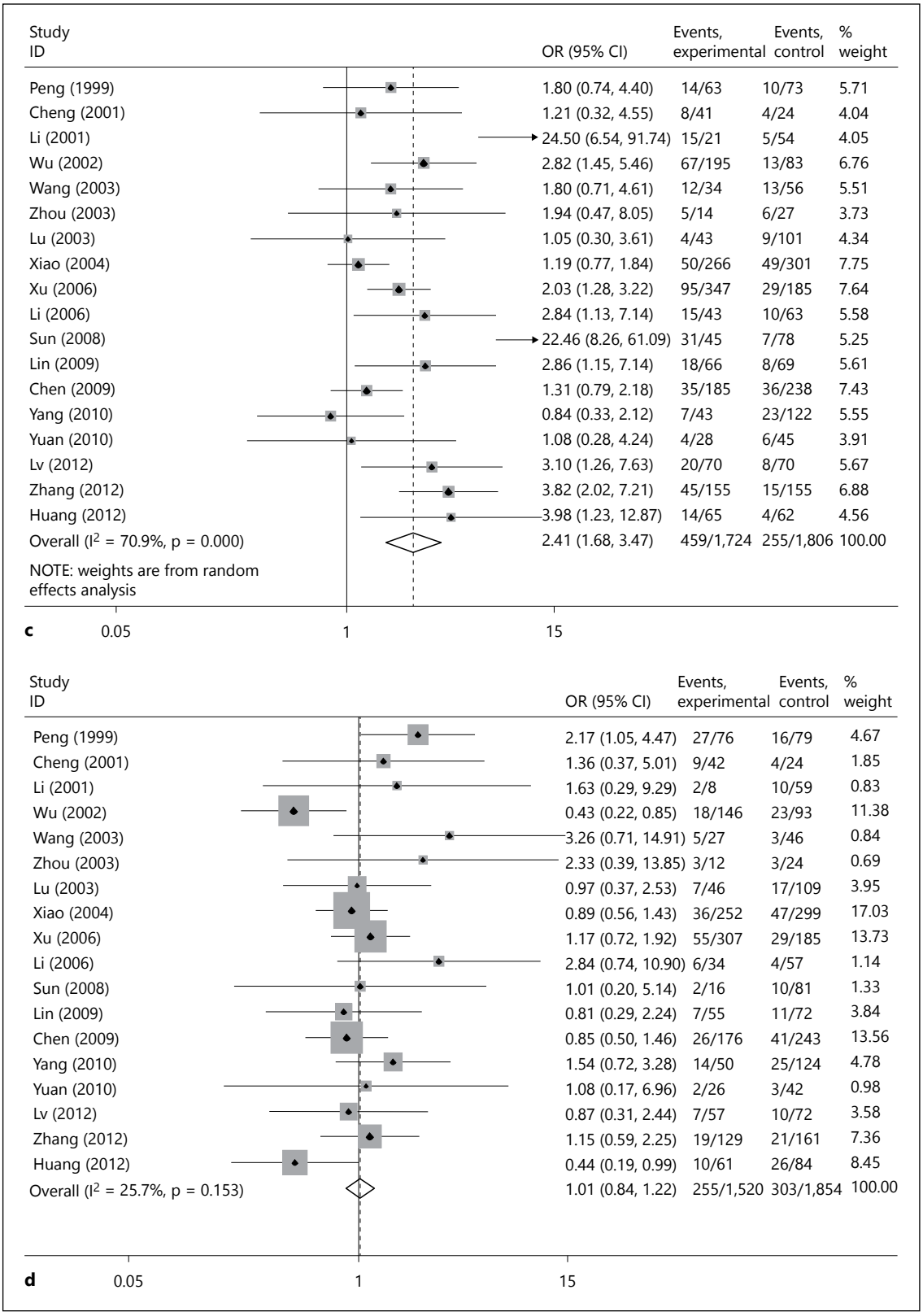


**Fig. 4. a–d** Forest plot of the relationships between ApoE gene polymorphisms and ICH risk in the genetic comparisons of ε4 carriers vs. ε3ε3 carriers (**c**); and ε2 carriers vs. ε3ε3 carriers (**d**).

**Table 4.** The main results of studies associated with IAH included in this meta-analysis

| Study subgroup | Studies (size/control) | ε4 vs. ε3 | | | ε2 vs. ε3 | | | ε4 carrier vs. ε3ε3 carrier | | | ε2 carrier vs. ε3ε3 carrier | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | $P_Q$ | $I^2$, % | OR (95% CI) | $P_Q$ | $I^2$, % | OR (95% CI) | $P_Q$ | $I^2$, % | OR (95% CI) | $P_Q$ | $I^2$, % |
| ICH | 18 (2,018/2,143) | 2.08 (1.57–2.75)* | 0.000 | 61.9 | 1.13 (0.96–1.33) | 0.067 | 35.7 | 2.41 (1.68–3.47)* | 0.000 | 70.9 | 1.01 (0.84–1.22) | 0.153 | 25.7 |
| HWE | | | | | | | | | | | | | |
| Yes | 16 (1,627/1,701) | 2.18 (1.64–2.89)* | 0.006 | 53.3 | 1.18 (0.98–1.42) | 0.177 | 24.5 | 2.50 (1.69–3.71)* | 0.000 | 69.8 | 1.11 (0.89–1.37) | 0.266 | 16.4 |
| No | 2 (391/442) | 1.63 (0.56–4.74) | 0.018 | 82.3 | 0.99 (0.72–1.37) | 0.016 | 82.8 | 1.92 (0.60–6.10) | 0.058 | 72.2 | 0.74 (0.50–1.11) | 0.139 | 54.4 |
| SOC | | | | | | | | | | | | | |
| PB | 16 (1,748/1,873) | 2.07 (1.52–2.82)* | 0.000 | 63.4 | 1.10 (0.92–1.30) | 0.053 | 39.5 | 2.38 (1.59–3.56)* | 0.000 | 72.6 | 0.94 (0.77–1.15) | 0.261 | 16.8 |
| Non-PB | 2 (270/270) | 2.15 (1.00–4.65)* | 0.104 | 62.1 | 1.35 (0.89–2.06) | 0.336 | 0.0 | 2.81 (1.36–5.80)* | 0.179 | 44.7 | 1.55 (0.95–2.52) | 0.207 | 37.1 |
| High quality | 16 (1,748/1,873) | 2.07 (1.52–2.82)* | 0.000 | 63.4 | 1.10 (0.92–1.30) | 0.053 | 39.5 | 2.38 (1.59–3.56)* | 0.000 | 72.6 | 0.94 (0.77–1.15) | 0.261 | 16.8 |

* $p < 0.05$. $P_Q$ = A p value of the Cochrane's Q test for heterogeneity; $I^2$ = value of $I^2$ statistic for heterogeneity; PB = population-based controls; non-PB = hospital-based controls or mixed controls; high quality = NOS score >7.

IS risk. Our results were consistent with those of previous studies [9, 94]. Furthermore, the associations identified in our study were verified by subgroup analyses according to IS subtype (ACI or LI), HWE status (yes or no) and SOC (population-based or non-population-based).

For the relationship between ApoE gene polymorphisms and ICH risk, our meta-analysis of 18 studies, which included a total of 2,018 cases and 2,143 controls, provided the first assessment of the association between ApoE gene polymorphisms and ICH risk in the Chinese population. We found a significant association of the ε4 allele with ICH risk compared with the ε3 allele, and ε4 carriers showed a significantly higher risk of developing ICH than ε3ε3 genotype carriers. Conversely, the evidence did not support an association of ε2 allele or ε2 carriers with ICH risk. In general, the results of our study are in agreement with those reported by Zhang et al. [16] but contrast with those reported by Sudlow et al. [9]. Most study participants included in these 2 meta-analyses were Caucasian, whereas little data were available for Chinese participants. Ethnicity and variation in study design, sample size, and inclusion criteria may have contributed to the differences in results between studies. Thus, we performed subgroup analyses according to SOC (population-based or non-population-based) and the HWE status (HWE or non-HWE). However, no significant difference in ICH risk between ε4 carriers and ε3ε3 genotype carriers or between the ε4 allele and the ε3 allele was found in the non-HWE subgroup. In general, the genetic association results produced from the case–control studies suggested potential selection bias of controls or genotyping errors under circumstances in which the genotype distribution of the controls deviated from HWE. Because the majority of subjects followed HWE, the results for the non-HWE group might be unreliable and should be interpreted with caution.

For the study of the relationship between ApoE gene polymorphisms and SAH risk, pooled analyses showed a significantly increased risk for SAH among ε4 carriers, but not ε2 carriers, compared with ε3ε3 genotype carriers. However, this result was based on small numbers of cases and controls and seemed far more likely to represent the combined effect of publication and reporting bias rather than an actual underlying association.

To aid the interpretation of these results, some limitations of this meta-analysis should be acknowledged. First, between-study heterogeneity in our analysis should be noted, as this factor may have affected the results of the present meta-analysis. Second, subgroup analyses were not performed according to factors such

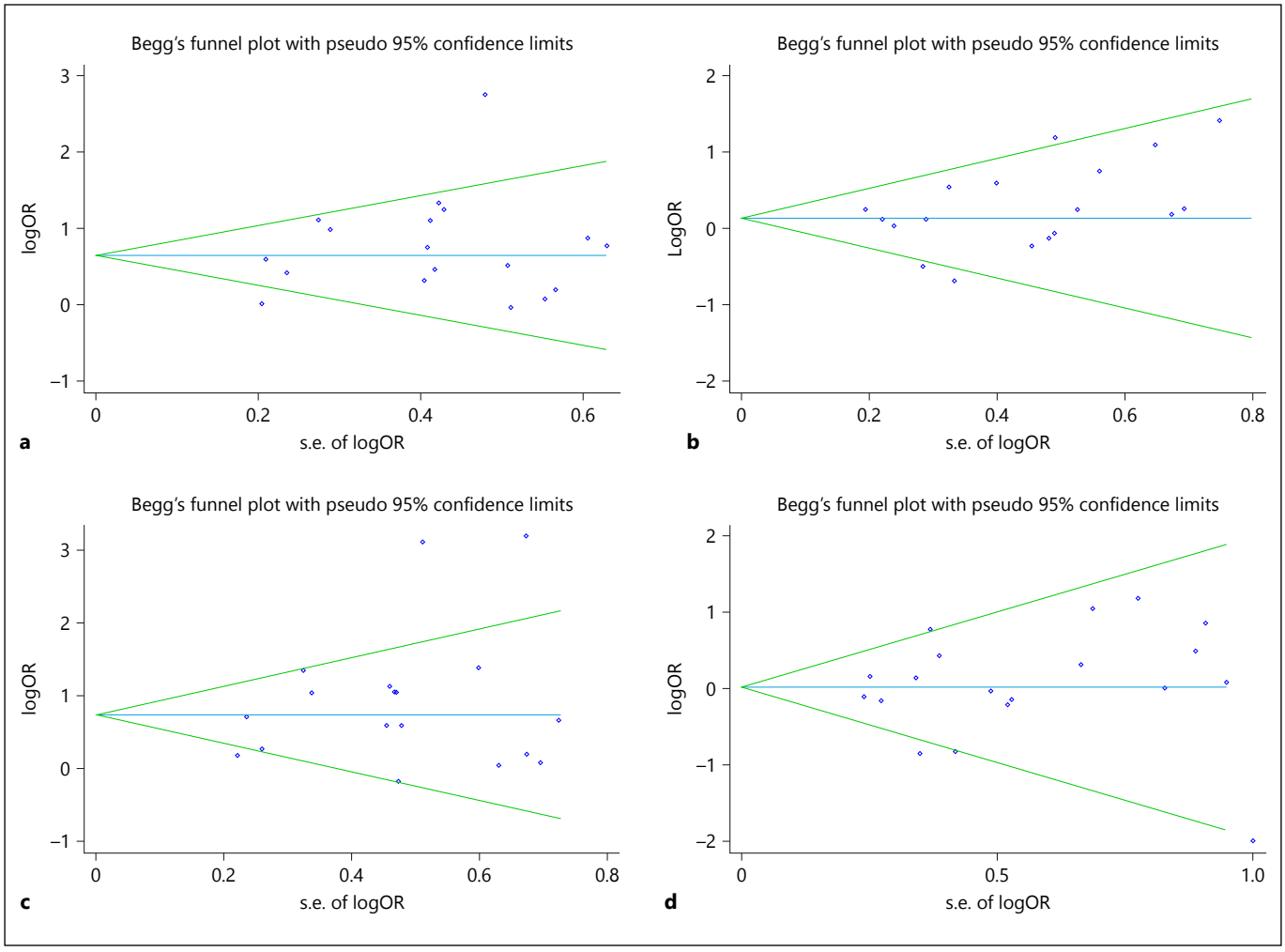


**Fig. 5. a–d** Begg's funnel plots of the relationships between ApoE gene polymorphisms and ICH risk in the genetic comparisons of the ε4 allele vs. the ε3 allele (**a**); the ε2 allele vs. the ε3 allele (**b**); ε4 carriers vs. ε3ε3 carriers (**c**); and ε2 carriers vs. ε3ε3 carriers (**d**).

as gender, age, smoking and alcohol consumption habits because insufficient data were extracted from the primary articles. Third, publication bias and other forms of bias may have existed in our results due to limitations in the inclusion criteria. Finally, the sample size of our meta-analysis was relatively limited considering the massive population and the multiple unique ethnic groups in China.

## Conclusion

In conclusion, the ApoE ε4 allele may predict an increased risk for different subtypes of stroke, including IS, ICH and SAH, as ε4 carriers showed a significantly elevated risk of developing different subtypes of stroke. However, neither the ε2 allele nor ε2 carriers were associated with the risk for stroke. The results of this genotypic analysis may help to identify populations at an increased risk for stroke. Further large-scale studies incorporating various covariates should be performed to further elucidate the association between ApoE gene polymorphisms and the risk for cerebrovascular diseases in the Chinese populations.

## Disclosure Statement

None.

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