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

Chunli Chen Zhiping Hu

Department of Neurology, Second Xiangya Hospital of Central South University, Changsha, Hunan, PR China

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 E4 al-

KARGER

© 2016 S. Karger AG, Basel 1015–9770/16/0414–0119\$39.50/0

E-Mail karger@karger.com www.karger.com/ced lele 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 £4 carriers and £3£3 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. © 2016 S. Karger AG, Basel

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].

Zhiping Hu

Department of Neurology, Second Xiangya Hospital of Central South University 139 Renmin Road, Changsha, Hunan 410011 (PR China) E-Mail liyatou.hi@163.com

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, £2, £3, and ϵ 4, and is able to generate 6 different genotypes (ϵ 2/2, $\varepsilon 2/3$, $\varepsilon 2/4$, $\varepsilon 3/3$, $\varepsilon 3/4$, and $\varepsilon 4/4$). 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 $\varepsilon 4$ 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 £4 allele enhances amyloid deposition in blood vessels [14]. Thus, one might expect £4 carriers to exhibit an increased susceptibility for ICH, especially in a lobar location. Furthermore, the ApoE ɛ4 allele was associated with an increased risk of developing hypertension [15], which may be another reason for the association of the ɛ4 allele with an increased ICH risk.

In 2006, a meta-analysis [9] reported that carriers of the ApoE ɛ4 allele exhibited a significantly increased risk of IS and that the presence of the $\varepsilon 2$ allele was associated with an increased ICH risk. Another meta-analysis published in 2014 by Zhang et al. [16] reported that carriers of the ɛ4 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 χ^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 I² statistic. Pooled ORs were calculated using a fixed-effects model (considering a Q test

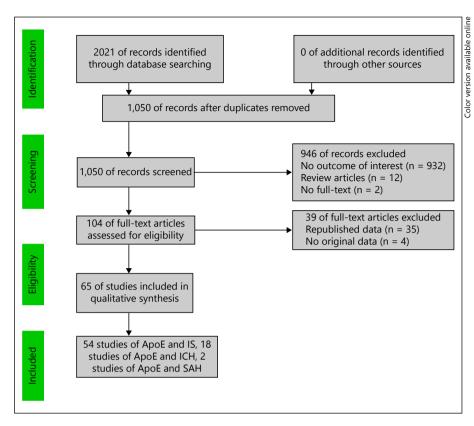


Fig. 1. A flow diagram of the selection process for analysis of the association between ApoE polymorphism and the risk for IS, ICH, and SAH in the Chinese population.

p value (P_{O}) >0.10 and an I² 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 $\varepsilon 3/3$ 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 $\varepsilon 3/3$ genotype or the $\varepsilon 3$ allele were designated as the reference group in our study. For separate analyses, ε_2 carriers included patients harboring the $\varepsilon_2/2$ or $\varepsilon_2/3$ genotype, and $\varepsilon 4$ carriers included patients harboring the $\varepsilon 3/4$ or ε4/4 genotype. Thus, ε2 and ε4 genotype carriers were independently compared with $\varepsilon 3/3$ genotype carriers. Moreover, the $\varepsilon 2$ and $\varepsilon 4$ allele carriers were independently compared with the $\varepsilon 3$ 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

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)	ɛ4 (case/ control)	HWE	Genotypic method	c 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	~	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	~	0/0	3/2	3/1	12/19	4/2	2/0	6/3	31/42	11/3	0.258	PCR	QN
1999	Cao et al. [22]	Heilongjiang	PB	55/85	~	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	~	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	06/06	~	0/1	13/16	1/1	55/63	19/8	2/1	14/19	142/150	24/11	0.685	PCR	QN
2000	Ding et al. [25]	Guangdong	HB	58/46	~	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	717	0/0	6/2	85/82	8/9	0.457	PCR	ACI
2000	Yu et al. [27]	Shandong	PB	63/30	×	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	~	0/0	9/10	0/2	37/49	14/5	3/0	9/12	97/113	20/7	0.280	PCR	ŊŊ
2001	Zhang et al. [29]	Beijing	PB	116/40	~	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	×	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	×	1/2	8/15	3/2	85/92	16/9	2/0	13/21	194/208	23/11	0.351	PCR	QN
2003	Su et al. [34]	Shandong	PB	36/40	œ	1/0	4/5	0/0	18/30	10/4	3/1	6/5	50/69	16/6	0.310	PCR	QN
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	ŊŊ
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	×	0/0	7/12	4/2	33/68	20/8	2/0	11/14	93/156	28/10	0.424	PCR	ΟN
2005	Xiao et al. [38]	Hunan	PB	379/351	×	9/0	44/41	3/3	274/252	55/45	3/4	47/56	647/590	64/56	0.027	PCR	ΟN
2004	Lin et al. [39]	Taiwan	PB	277/112	œ	1/4	17/5	10/5	180/78	18/19	1/1	29/18	445/180	80/26	<0.001	PCR	QN
2004	Jin et al. [40]	Shanghai, Zhejiang	PB	226/201	×	2/2	14/17	3/2	152/156	52/22	3/2	21/23	370/351	61/28	0.197	PCR	ΟN
2004	He et al. [41]	Xinjiang	PB	56/104	×	1/4	3/9	4/5	35/77	7/6	6/3	9/22	80/169	23/17	<0.001	PCR	ΟN
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	QN
2006	Li et al. [43]	Hebei	PB	51/69	×	1/0	2/4	3/2	26/53	19/10	0/0	7/6	73/120	22/12	0.161	PCR	QN
2006	Ma et al. [44]	Heilongjiang	PB	109/50	œ	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	œ	1/1	8/5	9/2	83/100	11/10	8/2	19/9	185/215	36/16	0.003	PCR	QN
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	ΓI

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

Cerebrovasc Dis 2016;41:119–138 DOI: 10.1159/000442678 Downloaded from http://www.karger.com/ced/article-pdf/41/3-4/119/2353988/000442678.pdf by guest on 20 April 2024

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)	ɛ3 (case/ control)	ɛ4 (case/ control)	HWE	Genotypic method	Subtype
2006	Zhou et al. [47]	Heilongjiang	PB + HB	72/68	~	2/2	11/9	2/0	52/46	5/11	0/0	17/13	120/112	7/11	0.155	PCR	QN
2006	Baum et al. [48]	Hongkong	PB	243/311	~	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	~	0/5	20/40	1/3	70/233	13/37	1/4	21/53	173/543	16/48	0.058	PCR	II
2007	Lv et al. [50]	Liaoning	PB	38/98	~	0/1	2/13	10/7	12/65	14/12	0/0	12/22	40/155	24/19	0.003	PCR	ŊŊ
2007	Man et al. [51]	Shandong	PB	40/50	~	1/1	6/6	0/0	20/38	10/4	3/1	8/8	56/86	16/6	0.109	PCR	ŊŊ
2007	Lai et al. [52]	Taiwan	PB	257/112	~	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	ŊŊ
2008	Xie et al. [54]	Yunnan	PB	92/50	~	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	~	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	~	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	~	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	ŊŊ
2012	Lv et al. [62]	Guangdong Guangxi PB	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	ŊŊ
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	ŊŊ
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	ŊŊ
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	ŊŊ
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	ŊŊ
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	ŊŊ
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	ŊŊ
2014	Sun [70]	Liaoning	PB	50/50	×	3/4	5/6	2/2	26/32	12/3	2/3	13/16	69/73	18/11	<0.001	PCR	ŊŊ
2014	Zhang et al. [71]	Guangdong	PB	91/105	×	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
PF	B = Population-based	PB = Population-based controls; $HB = hospital-based controls$; $IEF/WB = isoelectric focusing/western blotting$; $ND = not described$.	-based contr	ols; IEF/WB	= isoele	ectric focus	sing/wester:	n blotting;	ND = not d	lescribed.							

ApoE Polymorphisms and the Risk of Different Subtypes of Stroke

123

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 ε 3 allele, the ε 2 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 $\varepsilon 4$ allele with IS risk compared with the ϵ 3 allele (OR 2.19, 95% CI 1.90–2.52, p < 0.001), although moderate heterogeneity was observed between studies ($I^2 = 58.5\%$, $P_0 = 0.000$). 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 ɛ4 allele and the risk of IS.

Main Results of the Genotype Comparisons

The pooled OR for $\varepsilon 2$ carriers vs. $\varepsilon 3\varepsilon 3$ genotype carriers was 0.98 (95% CI 0.88–1.09, p = 0.73), and no heterogeneity was detected between studies (I² = 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 $\epsilon4$ carriers and $\epsilon3\epsilon3$ genotype carriers (OR 2.41, 95% CI 2.00–2.89, p < 0.001) based on a REM (I² = 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 $\epsilon4$ 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 ($\epsilon 2 \text{ vs. } \epsilon 3, \epsilon 2 \text{ car$ $rier vs. } \epsilon 3 \epsilon 3 \text{ carrier}$) 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, $\epsilon 2 \text{ vs.}$ $\epsilon 3$; p = 0.441, $\epsilon 2 \text{ carrier vs. } \epsilon 3 \epsilon 3 \text{ carrier}$). However, publication bias was detected in other genetic comparisons ($\epsilon 4 \text{ vs. } \epsilon 3$, $\epsilon 4 \text{ carrier vs. } \epsilon 3 \epsilon 3 \text{ carrier}$), as revealed by Begg's funnel plots (fig. 3a, c) and Egger's regression tests ($\epsilon 4 \text{ vs. } \epsilon 3$, p = 0.000; $\epsilon 4 \text{ carrier vs. } \epsilon 3 \epsilon 3 \text{ carrier}$, 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.

Study ID		OR (95% CI)	Events, experimental	Events, control	% weight
Guo (1997)		1.59 (0.76, 3.36)	14/87	19/177	1.82
Yan (1997)		2.73 (1.33, 5.58)	18/91	17/205	1.89
Zhou (1997)		→ 4.97 (1.28, 19.32)	11/42	3/45	0.84
Cao (1999)		1.50 (0.47, 4.78)	6/108	6/159	1.06
Liu (1999)		3.23 (1.36, 7.63)	18/80	9/109	1.56
Peng (1999)		2.30 (1.09, 4.88)	24/166	11/161	1.81
Ding (2000)		2.92 (1.11, 7.67)	19/109	6/89	1.36
Wang (2000)		0.86 (0.32, 2.33)	8/93	9/91	1.30
Yu (2000)		3.81 (1.26, 11.46)	27/121	4/57	1.14
Li (2001)		3.33 (1.35, 8.21)	20/117	7/120	1.47
Zhang (2001)		4.76 (1.65, 13.71)	48/217	4/71	1.20
Shen (2002)	<u> </u>	4.82 (2.08, 11.16)	17/72	10/166	1.60
Xia (2002)		- 3.08 (1.43, 6.61)	41/192	9/111	1.77
Zhu (2002)		2.42 (1.25, 4.68)	21/90	22/197	2.04
Lu (2003)		2.24 (1.06, 4.72)	23/217	11/219	1.82
Su (2003)		3.68 (1.35, 10.07)	16/66	6/75	1.29
Wang (2003)		2.30 (1.07, 4.97)	18/75	14/116	1.76
Zhou (2003)		4.25 (1.61, 11.24)	25/75	6/57	1.34
Li (2004)		4.70 (2.18, 10.11)	28/121	10/166	1.77
Xiao (2004)		1.04 (0.72, 1.52)	64/711	56/646	2.90
Lin (2004)		1.24 (0.77, 2.00)	80/525	26/206	2.59
Jin (2004)		2.07 (1.29, 3.31)	61/431	28/379	2.60
He (2004)		2.86 (1.45, 5.65)	23/103	17/186	1.98
Gao (2006)		- 2.23 (0.83, 6.00)	13/187	6/185	1.32
Li (2006)		- 3.01 (1.41, 6.45)	22/95	12/132	1.78
Ma (2006)		3.74 (1.53, 9.16)	41/200	6/93	1.49
Zhang (2006)		2.61 (1.14, 4.86)	36/221	16/231	2.15
Wen (2006)		1.84 (0.93, 3.67)	17/117	20/237	1.96
Zhou (2006) -		0.59 (0.22, 1.59)	7/127	11/123	1.33
Baum (2006)		1.30 (0.85, 1.99)	46/427	47/552	2.74
Deng (2007)		1.05 (0.58, 1.89)	16/189	48/591	2.23
Lv (2007)	· · · · · · · · · · · · · · · · · · ·	4.89 (2.44, 9.81)	24/64	19/174	1.95
Man (2007)		4.10 (1.51, 11.10)	16/72	6/92	1.30
Lai (2007)		1.31 (0.81, 2.11)	77/485	26/206	2.58
Sun (2008)		3.44 (1.54, 7.71)	23/141	9/168	1.68
Xie (2008)		→ 7.38 (2.20, 24.72)	36/171	3/86	1.00
Nie (2009)	·	3.92 (1.03, 14.85)	10/73	3/77	0.87
Wang (2009)		2.19 (1.64, 2.93)	169/602	86/569	3.16
Zhou (2009)			37/147	9/105	1.74
Yang (2010)		1.03 (0.63, 1.69)	46/432	28/270	2.52
Yuan (2010)		3.54 (1.52, 8.23)	27/110	8/95	1.59
Li (2012)		1.58 (1.02, 2.47)	54/429	36/432	2.69
Liu (2012)		2.28 (0.89, 5.80)	21/201	6/123	1.41
Lv (2012)	· · · · · · · · · · · · · · · · · · ·	5.16 (2.71, 9.82)	28/107	18/280	2.08
Wang (2012)		1.08 (0.50, 2.31)	17/97	15/91	1.78
Gu (2013)		1.16 (0.68, 1.98)	29/303	30/359	2.40
Jing (2013)		0.85 (0.49, 1.48)	31/300	27/227	2.36
Liu (2013)		3.90 (1.46, 10.43)	19/75	6/75	1.33
Wang (2013)		2.36 (1.44, 3.85)	52/190	32/232	2.54
Zhao (2013)		2.29 (1.29, 4.08)	66/372	16/186	2.27
Huang (2014)		4.52 (2.15, 9.51)	35/104	11/109	1.82
Sun (2014)		1.73 (0.76, 3.93)	18/87	11/84	1.65
Zhang (2014)		1.41 (0.72, 2.74)	21/167	18/194	2.02
Yan (2015)		1.65 (1.31, 2.07)	239/1,064	140/935	3.33
Overall ($l^2 = 58.5\%$, p = 0.000)		2.19 (1.90, 2.52)		1,039/11,121	
Note: weights are from random ef	fects analysis				

Fig. 2. a-d Forest plots of the relationships between ApoE gene polymorphisms and IS risk in the genetic comparisons of the $\varepsilon 4$ allele vs. the $\varepsilon 3$ allele (**a**); the $\varepsilon 2$ allele vs. the $\varepsilon 3$ allele (**b**); $\varepsilon 4$ carriers vs. $\varepsilon 3\varepsilon 3$ carriers (**c**); and $\varepsilon 2$ carriers vs. $\varepsilon 3\varepsilon 3$ carriers (**d**). (For figure 2b-d see next pages.)

Study D	OR (95% CI)	Events, experimental	Events, control	% weight
Guo (1997)	0.66 (0.27, 1.60)	7/80	23/181	1.66
/an (1997)	1.10 (0.48, 2.52)	9/82	21/209	1.80
Zhoù (1997) — — — — — — — — — — — — — — — — — — —	2.71 (0.63, 11.69		3/45	0.84
Cao (1999)	0.27 (0.06, 1.26)	2/104	11/164	0.79
.iu (1999)	0.88 (0.31, 2.50)	6/68	11/111	1.37
Peng (1999)	0.78 (0.38, 1.61)	14/156	19/169	2.05
Ding (2000)	2.15 (0.54, 8.60)	7/97	3/86	0.92
Vang (2000)	0.75 (0.27, 2.11)	7/92	9/91	1.38
(u (2000)	- 0.94 (0.22, 4.09)	5/99	3/56	0.83
i (2001)	0.87 (0.35, 2.16)	9/106	12/125	1.63
(hang (2001)	0.66 (0.28, 1.58)	15/184	9/76	1.70
hen (2002)	- 1.62 (0.64, 4.07)	8/63	14/170	1.59
(2002)	- 2.10 (0.95, 4.64)	28/179	9/111	1.89
(2002)	1.07 (0.45, 2.55)	8/77	19/194	1.70
u (2002)		13/207	21/229	2.07
	0.66 (0.32, 1.36)			1.08
(2003)	1.66 (0.48, 5.73)	6/56 5/62	5/74 4/105	0.95
Vang (2003)	2.24 (0.58, 8.66)	5/62	4/105 3/54	0.95
	2.38 (0.58, 9.73)	7/57		
i (2004)	1.32 (0.57, 3.02)	11/104	14/170	1.79
(iao (2004)	0.77 (0.51, 1.15)	47/694	56/646	3.05
in (2004)	0.65 (0.35, 1.20)	29/474	18/198	2.37
in (2004)	0.87 (0.47, 1.59)	21/391	23/374	2.39
le (2004)	0.86 (0.38, 1.96)	9/89	22/191	1.82
ao (2006)	0.89 (0.41, 1.93)	13/187	15/194	1.94
i (2006)	1.92 (0.62, 5.93)	7/80	6/126	1.23
1a (2006)	1.41 (0.57, 3.50)	18/177	7/94	1.62
(hang (2006)	2.45 (1.08, 5.55)	19/204	9/224	1.82
Ven (2006)	1.19 (0.63, 2.25)	17/117	31/248	2.30
hou (2006)	1.22 (0.57, 2.63)	17/137	13/125	1.95
aum (2006) — 📥 —	1.12 (0.77, 1.62)	59/440	70/575	3.15
Deng (2007)	1.24 (0.73, 2.12)	21/194	53/596	2.62
v (2007)	- 2.11 (0.96, 4.63)	12/52	22/177	1.90
/an (2007)	- 1.54 (0.54, 4.33)	8/64	8/94	1.38
ai (2007)	0.71 (0.38, 1.31)	29/437	18/198	2.37
iun (2008)	1.68 (0.76, 3.73)	15/133	12/171	1.88
(ie (2008)	0.57 (0.26, 1.27)	13/148	14/97	1.86
lie (2009)	0.91 (0.32, 2.59)	7/70	9/83	1.37
Vang (2009)	0.95 (0.75, 1.20)	190/623	223/706	3.56
hou (2009) 🛛 🚽 📥 🚽 🚽	0.18 (0.08, 0.39)	9/119	43/139	1.94
ang (2010) — 🔶 — 🔶 —	1.00 (0.62, 1.63)	48/434	30/272	2.78
uan (2010)	- 1.26 (0.37, 4.28)	6/89	5/92	1.10
i (2012) — •	1.12 (0.74, 1.71)	51/426	48/444	3.00
iu (2012)	0.34 (0.17, 0.65)	15/195	29/146	2.22
v (2012)	1.55 (0.80, 3.02)	15/94	32/294	2.23
Vang (2012) 🚽 🔒	0.21 (0.04, 1.01)	2/82	9/85	0.76
iu (2013)	1.39 (0.80, 2.43)	29/303	25/354	2.54
ng (2013)	1.37 (0.68, 2.76)	24/293	13/213	2.13
iu (2013)	— 1.23 (0.34, 4.47)	5/61	5/74	1.02
Vang (2013)	2.07 (1.14, 3.77)	30/168	21/221	2.42
hao (2013) — 🔺	1.11 (0.57, 2.17)	28/334	14/184	2.21
luang (2014)	1.89 (0.41, 8.73)	4/73	3/101	0.78
un (2014)	0.86 (0.39, 1.92)	13/82	16/89	1.86
(2014)	1.13 (0.54, 2.36)	15/161	16/192	2.02
ían (2015)	0.41 (0.32, 0.53)	96/921	225/1,020	3.49
Overall (l ² = 57.5%, p = 0.000)	1.01 (0.86, 1.17)	1,114/10,456		
Jote: weights are from random effects analysis	1.01 (0.00, 1.17)	.,,	.,,	
	Γ			
0.05 1	15			

2

Main Results of the Allele Comparisons

We found a significant association between the ε 4 allele and ICH risk compared with the ε 3 allele (OR 2.08, 95% CI 1.57–2.75, p < 0.001), although moderate heterogeneity between studies was observed (I² = 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 ε 4 allele and the ICH risk. For the subgroup analysis based on HWE status, an increased risk of ICH was noted for the ε 4 allele compared to the ε 3 allele (OR 2.18, 95% CI 1.64–2.89, p < 0.001), although moderate heterogeneity was observed between

itudy D		OR (95% CI)	Events, experimental	Events, control	% weight
Guo (1997)		2.55 (1.04, 6.28)	13/41	12/78	1.84
an (1997)		3.57 (1.53, 8.32)	16/41	14/92	1.94
hou (1997)		→ 4.75 (0.82, 27.50)	6/18	2/21	0.82
ao (1999)		1.45 (0.44, 4.76)	6/53	6/74	1.39
u (1999)			15/37	8/49	1.67
		3.49 (1.28, 9.52)			1.92
eng (1999)		2.67 (1.13, 6.32)	21/76	9/72	
ng (2000)		3.08 (1.02, 9.34)	15/52	5/43	1.50
ang (2000)		0.94 (0.30, 2.98)	7/43	7/41	1.45
(2000)		3.51 (1.07, 11.51)	22/58	4/27	1.39
(2001)		- 4.50 (1.52, 13.32)	17/54	5/54	1.54
iang (2001)		→ 5.17 (1.47, 18.19)	36/101	3/31	1.30
en (2002)		— 5.10 (1.83, 14.20)	12/32	8/76	1.63
a (2002)	· · · · · · · · · · · · · · · · · · ·	2.82 (1.12, 7.08)	26/84	7/51	1.81
iu (2002)	_	3.13 (1.40, 7.00)	18/41	18/90	2.03
(2003)		2.16 (0.92, 5.08)	18/103	9/101	1.93
(2003)		- 4.33 (1.32, 14.18)	13/31	5/35	1.39
ang (2003)	è	2.65 (1.07, 6.53)	16/36	13/56	1.84
iou (2003)		→ 5.65 (1.81, 17.69)	21/34	6/27	1.46
(2004)		- 5.67 (2.28, 14.07)	22/55	8/76	1.83
ao (2004)		1.09 (0.72, 1.65)	58/332	49/301	2.83
ao (2004) n (2004)		0.41 (0.21, 0.81)	19/199	20/98	2.03
				24/180	2.60
(2004)	•	2.35 (1.39, 3.99)	55/207		
(2004)		3.18 (1.24, 8.13)	13/48	9/86	1.78
io (2006)	•	2.31 (0.84, 6.39)	13/88	6/86	1.64
(2006)		3.87 (1.58, 9.51)	19/45	10/63	1.85
a (2006)		- 4.11 (1.48, 11.45)	33/94	5/43	1.63
iang (2006)		1.91 (0.88, 4.16)	19/102	12/112	2.08
en (2006)		1.76 (0.78, 4.00)	13/54	16/105	2.00
iou (2006)		0.40 (0.13, 1.24)	5/57	11/57	1.47
um (2006)	b	1.18 (0.72, 1.94)	36/191	40/243	2.66
eng (2007)	ii	1.14 (0.59, 2.21)	14/84	41/274	2.31
(2007)	- · · · · · · · · · · · · · · · · · · ·	→ 6.32 (2.36, 16.95)	14/26	12/77	1.69
an (2007)		→ 4.94 (1.54, 15.84)	13/33	5/43	1.42
i (2007)		1.61 (0.91, 2.85)	67/229	20/98	2.51
in (2008)		4.38 (1.70, 11.26)	19/63	7/78	1.77
e (2008)			30/79	1/37	0.65
		→ 22.04 (2.87, 169.22)	9/33	2/34	0.03
e (2009)		→ 6.00 (1.19, 30.35)			
ang (2009)		3.09 (2.01, 4.74)	98/222	42/206	2.80
iou (2009)		→ 7.17 (2.01, 25.59)	23/69	3/46	1.28
ng (2010)	i	1.04 (0.59, 1.85)	38/195	23/122	2.50
an (2010)		→ 5.57 (2.01, 15.42)	24/52	6/45	1.64
(2012)	-+ • ¦	1.32 (0.81, 2.18)	44/193	35/192	2.66
ı (2012)		— 3.82 (1.07, 13.65)	18/95	3/52	1.28
(2012)		3.91 (1.79, 8.52)	18/47	17/124	2.07
ang (2012)	_ !	0.85 (0.35, 2.06)	15/49	14/41	1.87
(2013)		1.16 (0.64, 2.10)	25/138	27/168	2.45
g (2013)		0.92 (0.48, 1.75)	25/139	21/109	2.35
(2013)		→ 6.53 (1.90, 22.45)	16/35	4/35	1.33
ang (2013)		2.36 (1.25, 4.46)	33/84	23/107	2.37
		2.30 (1.23, 4.40)			
ao (2013)	•	2.39 (1.10, 5.21)	37/173	9/88	2.07
iang (2014)		→ 7.64 (3.11, 18.77)	32/50	10/53	1.85
n (2014)		2.87 (0.97, 8.52)	14/40	6/38	1.53
iang (2014)		1.43 (0.69, 2.95)	20/76	18/90	2.18
n (2015)		2.34 (1.68, 3.27)	144/495	62/416	2.98
verall ($I^2 = 63.2\%$, p = 0.000)		2.41 (2.00, 2.89)	1,393/5,106	762/5,041	100.00
ote: weights are from random effe	cts analysis				
0.05	1	15			

Downloaded from http://www.karger.com/ced/article-pdf/41/3-4/119/2353988/000442678.pdf by guest on 20 April 2024

studies (I² = 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 (I² = 82.3%, P_Q = 0.018).

Furthermore, compared with the ε 3 allele, the ε 2 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).

tudy D	OR (95% CI)	Events, experimental	Events, control	% weight
Guo (1997)	0.79 (0.26, 2.37)	5/33	15/81	1.14
'an (1997)	1.31 (0.51, 3.37)	8/33	19/97	1.13
(1997)	2.38 (0.34, 16.36)	3/15	2/21	0.21
Cao (1999)	0.26 (0.06, 1.24)	2/49	11/79	1.25
iu (1999)	1.04 (0.31, 3.47)	5/27	9/50	0.79
Peng (1999)	0.88 (0.39, 1.96)	13/68	17/80	1.95
Ding (2000)	2.05 (0.35, 11.90)	4/41	2/40	0.28
Vang (2000)	0.81 (0.25, 2.65)	6/42	7/41	0.94
iu (2000)	0.81 (0.23, 2.83)	4/40	3/26	0.54
i (2001)			10/59	1.09
	1.19 (0.44, 3.23)	9/46		
(hang (2001)	0.48 (0.17, 1.39)	9/74	8/36	1.46
hen (2002)	1.13 (0.33, 3.90)	4/24	12/80	0.71
(ia (2002)	— 1.99 (0.81, 4.92)	21/79	8/52	1.09
(hu (2002)	1.46 (0.53, 4.02)	7/30	15/87	0.91
u (2003)	0.57 (0.24, 1.35)	9/94	17/109	2.20
iu (2003)	1.67 (0.42, 6.56)	5/23	5/35	0.48
Vang (2003)	1.43 (0.22, 9.26)	2/22	3/46	0.27
(2003)	1.62 (0.28, 9.23)	3/16	3/24	0.30
i (2004)	1.20 (0.43, 3.34)	7/40	12/80	1.02
(2004)	0.86 (0.55, 1.34)	44/318	47/299	6.44
in (2004)	0.87 (0.37, 2.01)	18/198	9/87	1.75
in (2004)	0.86 (0.43, 1.74)	16/168	19/175	2.60
le (2004)	0.68 (0.21, 2.22)	4/39	13/90	1.09
Gao (2006)	0.91 (0.40, 2.10)	12/87	14/94	1.79
i (2006)			4/57	0.37
	1.53 (0.32, 7.34)	3/29		
	1.35 (0.47, 3.85)	13/74	6/44	0.96
(hang (2006)	— 1.81 (0.62, 5.29)	9/92	6/106	0.78
Ven (2006)	0.92 (0.41, 2.04)	11/52	26/115	1.97
(hou (2006)	1.05 (0.43, 2.56)	13/65	11/57	1.45
aum (2006)	0.97 (0.63, 1.50)	46/201	62/265	6.36
Deng (2007)	1.48 (0.82, 2.67)	20/90	45/278	2.64
v (2007)	0.77 (0.16, 3.85)	2/14	14/79	0.56
/lan (2007)	1.90 (0.58, 6.18)	7/27	7/45	0.60
ai (2007)	0.96 (0.41, 2.24)	18/180	9/87	1.68
un (2008)	— 1.94 (0.77, 4.86)	12/56	10/81	0.99
ie (2008)	0.60 (0.23, 1.60)	9/58	11/47	1.58
lie (2009)	1.00 (0.31, 3.27)	6/30	8/40	0.85
Vang (2009)	1.01 (0.72, 1.42)	114/238	149/313	10.34
(hou (2009)	0.21 (0.07, 0.61)	5/51	22/65	2.69
ang (2010)		40/197	25/124	3.77
	1.01 (0.58, 1.77)			
uan (2010)	1.86 (0.38, 8.96)	4/32	3/42	0.35
i (2012)	0.92 (0.58, 1.48)	42/191	48/205	5.57
iu (2012)	0.38 (0.17, 0.82)	13/90	22/71	3.25
v (2012)	1.07 (0.46, 2.50)	9/38	31/138	1.58
Vang (2012) 🚽 🔺	0.10 (0.01, 0.84)	1/35	8/35	1.20
iu (2013)	1.47 (0.79, 2.74)	26/139	22/163	2.54
ng (2013)	- 1.83 (0.77, 4.38)	19/133	8/96	1.23
iu (2013) — — — — — — — — — — — — — — — — — — —	1.63 (0.30, 8.92)	3/22	3/34	0.31
Vang (2013)	- 2.09 (0.97, 4.47)	19/70	15/99	1.40
hao (2013)	0.84 (0.34, 2.05)	13/149	9/88	1.59
luang (2014)	→ 3.58 (0.55, 23.29)	3/21	2/45	0.17
un (2014)	0.98 (0.34, 2.85)	8/34	10/42	1.06
(hang (2014)	1.20 (0.54, 2.69)	14/70	15/87	1.65
'an (2015)	0.75 (0.54, 2.69)	52/403	70/424	9.16
Dverall ($l^2 = 0.0\%$, p = 0.488)	0.75 (0.51, 1.10) 0.98 (0.88, 1.09)	52/405 774/4,487	961/5,240	
νοταιι (ι- – 0.0%, μ = 0.400)	0.96 (0.66, 1.09)	114/4,401	501/5,240	100.00
0.05 1	15			

Main Results of the Genotype Comparisons

A significant difference in ICH risk was detected between ϵ 4 carriers and ϵ 3 ϵ 3 genotype carriers (OR 2.41, 95% CI 1.68–3.47, p < 0.001) was noted based on a REM (I² = 70.9%, P_Q <0.000). For the subgroup analyses based on SOC (population-based or non-population-based), significant associations were found between ϵ 4 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 ϵ 4 carriers compared with the ϵ 3 ϵ 3 genotype carriers in the HWE subgroup (OR 2.50, 95% CI 1.69–3.71, p < 0.001), although moderate

128

2

Table 2. T	ne main results of	studies associated	with IS	included	idies associated with IS included in this meta-analysis	lysis					
Study	Studies	e4 vs. e3			e2 vs. e3			£4 carrier vs. £3£3 carrier	carrier		ε2 carrier vs. ε3ε3
subgroup	(size/control)	OD (DE0% CI)	6	12 02	12 0/ OB (050/ CI)	-	T2 0/	12 0/ OB (050/ CT)	-	12 0/	

I², %

OR (95% CI)

I², %

 \mathbf{P}_{Q}

OR (95% CI)

%

I²,

 \mathbf{P}_{Q}

OR (95% CI)

%

I²,

 \mathbf{P}_{Q}

OR (95% CI)

e3 carrier $\mathbf{P}_{\mathbf{Q}}$ 0.0

0.488

0.99 (0.89-1.11)

63.2

0.000

 $2.41(2.00-2.89)^{*}$

57.5

0.000

1.01(0.86 - 1.17)

58.5

0.000

 $2.19(1.90-2.52)^{*}$

54 (6, 190/6, 248)

0.0 31.0

0.1090.879

0.89 (0.72-1.11)

72.2

0.000

2.08 (1.53-2.84)*

2.61 (2.08-3.28)*

0.0 79.5

0.751

1.12 (0.98-1.28) 0.85 (0.63-1.14)

60.5

55.4

0.000 0.001

2.42 (1.99-2.93)* 1.87 (1.53-2.29)*

37 (3,052/3,449)

17 (3,138/2,799)

0.000

56.7

0.000

1.10 (0.94-1.27)

2.5

0.4240.522

1.01 (0.89-1.14)

64.1 61.2

0.000

2.54 (2.07-3.11)* 1.73 (1.06-2.84)*

41.080.0

0.002

0.000

0.92 (0.52-1.64)

38.9

59.0

0.000 0.146

2.29 (1.96-2.68)* 1.58 (1.14-2.20)*

48 (5,124/5,172) 6 (1,066/1,076)

1.02 (0.89-1.18)

0.000

0.93 (0.71-1.22)

0.0

Table 2. Π	Study subgroup	IS HWE	Yes No	SOC PB	Non-PB	Subtype ACI	LI
	E Polymo erent Sub				Ris	k of	

0.503	0.459	controls c
0.99(0.88 - 1.11)	1.02(0.90 - 1.15)	-PB = hospital-based
63.6	64.3	ols; non
0.000 63.6	0.000	sed contr
$2.45(2.02 - 2.96)^{*}$	2.51 (2.05–3.08)*	* 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 o trols; PCR-based = PCR based genotypic method; high quality = NOS score >7.
57.3	41.6	terogeneit
0.000	0.002	stic for he
0.99(0.85 - 1.16)	1.03(0.90-1.19)	I ² = value of I ² stati score >7.
59.4	58.9	geneity; ⁄ = NOS
0.000	0.000	for hetero gh quality
$2.20(1.90-2.55)^{*}$	2.27 (1.94–2.65)*	* p < 0.05. $P_Q = A$ p value of the Cochrane's Q test for heterogeneity; I^2 = value ontrols; PCR-based = PCR based genotypic method; high quality = NOS score >7.
PCR-based 52 (5,840/5,948)	High quality 47 (5,008/5,132)	. P _Q = A p value of 1 -based = PCR based
PCR-based	High quality	* p < 0.05 controls; PCR

ols or mixed

0.0

0.7

0.0 0.0

0.792 0.977

0.95 (0.72-1.25) 1.15 (0.80-1.64)

53.2

0.012

19.7

0.280

1.77 (1.29–2.42)*

2.47 (1.66-3.67)*

0.0

0.5450.795

0.98 (0.77-1.23) 1.06 (0.78-1.43)

55.3 29.1

0.008

2.26 (1.60-3.20)* 1.61 (1.23-2.12)*

13 (880/1,131)

7 (285/372)

0.206

0.0

heterogeneity between studies was observed ($I^2 = 69.8\%$, $P_{O} = 0.000$). 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 ($I^2 = 72.2\%$, $P_O = 0.058$).

The pooled OR for £2 carriers compared to £3£3 genotype carriers was 1.01 (95% CI 0.84-1.22, p = 0.887), although mild heterogeneity was observed between studies $(I^2 = 25.7\%, P_0 = 0.153)$. 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 (ɛ4 allele vs. ɛ3 allele, p = 0.24; $\varepsilon 2$ allele vs. $\varepsilon 3$ allele, p = 0.18; $\varepsilon 4$ carrier vs. $\varepsilon 3\varepsilon 3$ carrier, p = 0.17; $\varepsilon 2$ carrier vs. $\varepsilon 3\varepsilon 3$ 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 E4 carriers compared with ε3ε3 genotype carriers (OR 2.04, 95% CI 1.21-3.45, p = 0.008), but no association was detected among £2 carriers compared with ɛ3ɛ3 genotype carriers (OR 0.72, 95% CI 0.40-1.31, p = 0.282). Similarly, we found a significant association of the ɛ4 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 ɛ2 allele with SAH risk compared with the ɛ3 allele (OR 0.80, 95% CI 0.48-1.32, p = 0.377).

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

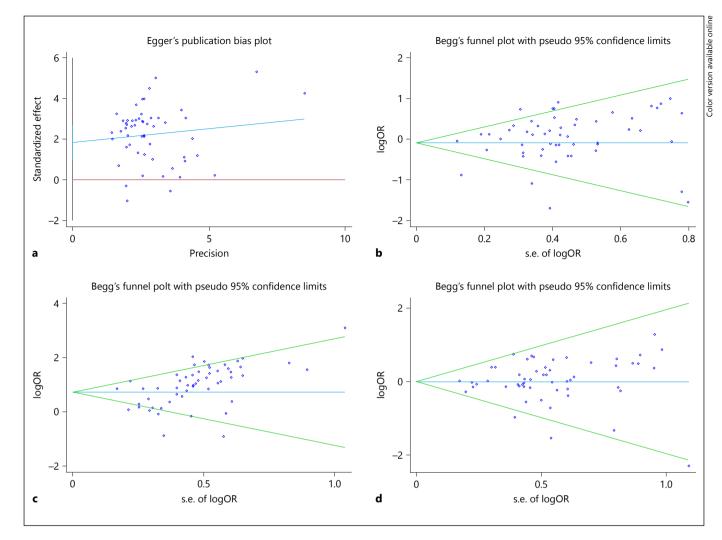


Fig. 3. a–**d** Begg's funnel plots of the relationships between ApoE gene polymorphisms and IS risk in the genetic comparisons of the ε 4 allele vs. the ε 3 allele (**a**); the ε 2 allele vs. the ε 3 allele (**b**); ε 4 carriers vs. ε 3 ε 3 carriers (**c**); and ε 2 carriers vs. ε 3 ε 3 carriers (**d**).

Discussion

130

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 ε 4 allele with IS risk compared with the ε 3 allele, and ε 4 carriers showed a significantly higher risk of developing IS than ε 3 ε 3 genotype carriers. In contrast, the evidence did not support an association of the ε 2 allele or ε 2 carriers with

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	06/06	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	×	8/3	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	ia 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	×	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	×	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	×	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	×	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	3 133/127	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 con	itrols; HB = hosp	vital-based o	controls.												
PB	PB = Population-based controls; HB = hospital-based controls.	ıtrols; HB = hosp	vital-based	controls.												

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

ApoE Polymorphisms and the Risk of Different Subtypes of Stroke Downloaded from http://www.karger.com/ced/article-pdf/41/3-4/119/2353988/000442678.pdf by guest on 20 April 2024

Study ID		Events, Events, % OR (95% CI) experimental control weig	ght
Peng (1999)		1.37 (0.62, 3.03) 15/152 12/162 5.5	57
Cheng (2001)		1.66 (0.61, 4.49) 17/99 6/54 4.4	44
Li (2001)		→ 15.52 (6.06, 39.75) 25/51 7/120 4.7	72
Wu (2002)		2.66 (1.51, 4.68) 81/420 16/194 7.1	12
Wang (2003)		1.58 (0.70, 3.58) 13/73 14/116 5.4	41
Zhou (2003)		2.38 (0.72, 7.83) 7/32 6/57 3.5	58
Lu (2003)	s	1.07 (0.36, 3.18) 5/93 11/219 4.0	
Xiao (2004)	_	1.00 (0.67, 1.50) 49/564 56/646 8.3	32
Xu (2006)		1.81 (1.20, 2.74) 105/745 33/398 8.2	24
Li (2006)			52
Sun (2008)		2.14 (0.62, 7.37) 4/37 9/168 3.4	41
Lin (2009)		3.46 (1.49, 8.03) 23/140 8/149 5.2	28
Chen (2009)		1.51 (0.95, 2.41) 42/401 37/516 7.8	88
Yang (2010) -		0.96 (0.35, 2.62) 5/50 28/270 4.4	40
Yuan (2010)		1.21 (0.40, 3.67) 6/60 8/95 3.9	
Lv (2012)		- 3.78 (1.65, 8.66) 26/148 8/150 5.3	
Zhang (2012)		3.03 (1.77, 5.18) 54/334 20/334 7.3	
Huang (2012)			48
Overall ($I^2 = 61.9\%$, p = 0.000)	$\langle \rangle$	2.08 (1.57, 2.75) 516/3,632 300/3,927 10	0.00
NOTE: weights are from random			
effects analysis a 0.05	! 1	15	
I	1	Events, Events, %	eight
a 0.05 Study	1	Events, Events, % OR (95% Cl) experimental control wei	eight
a 0.05 Study ID	1	Events, Events, % OR (95% CI) experimental control wei 1.70 (0.90, 3.22) 28/165 18/168 5	
a 0.05 Study ID Peng (1999)	1	Events, OR (95% CI) Events, experimental Events, control % 1.70 (0.90, 3.22) 28/165 18/168 5 1.27 (0.45, 3.56) 13/95 6/54 2	5.28
a 0.05 Study ID Peng (1999) Cheng (2001)	1	Events, OR (95% CI) Events, experimental Events, control % 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1.	5.28 2.35 1.39
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001)	1	Events, OR (95% Cl) Events, experimental Events, control % 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1.	5.28 2.35 1.39
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003)		Events, OR (95% Cl) Events, experimental Events, control % 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0.	5.28 2.35 1.39 10.9
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002)		Events, oR (95% Cl) Events, experimental Events, control % 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0. + 4.08 (0.94, 17.68) 6/31 3/54 0.	5.28 2.35 1.39 10.9 ⁻).99
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003)		Events, experimental Events, control Events, wei 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0. 4.08 (0.94, 17.68) 6/31 3/54 0. 0.79 (0.32, 1.92) 7/95 21/229 4.	5.28 2.35 1.39 10.9 0.99 0.63 1.07
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003)		OR (95% Cl) Events, experimental Events, control % weil 1.70 (0.90, 3.22) 28/165 18/168 5 1.27 (0.45, 3.56) 13/95 6/54 2 3.26 (1.24, 8.54) 9/35 12/125 1 0.61 (0.35, 1.06) 30/369 26/204 1 2.97 (0.84, 10.58) 7/67 4/106 0 4.08 (0.94, 17.68) 6/31 3/54 0 0.79 (0.32, 1.92) 7/95 21/229 4 1.27 (0.87, 1.86) 62/577 56/646 1	5.28 2.35 1.39 10.9 0.99 0.63 1.07 16.8
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Xiao (2004) Xu (2006)		OR (95% Cl) Events, experimental Events, control % wei 1.70 (0.90, 3.22) 28/165 18/168 5 1.27 (0.45, 3.56) 13/95 6/54 2 3.26 (1.24, 8.54) 9/35 12/125 1 0.61 (0.35, 1.06) 30/369 26/204 1 2.97 (0.84, 10.58) 7/67 4/106 0 4.08 (0.94, 17.68) 6/31 3/54 0 0.79 (0.32, 1.92) 7/95 21/229 4 1.27 (0.87, 1.86) 62/577 56/646 1 1.12 (0.73, 1.73) 67/707 34/399 1	5.28 2.35 1.39 10.9).99).63 1.07 16.8
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Xiao (2004)		OR (95% CI) Events, experimental Events, control % wei wei 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0. 4.08 (0.94, 17.68) 6/31 3/54 0. 0.79 (0.32, 1.92) 7/95 21/229 4. 1.27 (0.87, 1.86) 62/577 56/646 1. 1.12 (0.73, 1.73) 67/707 34/399 1. 2.11 (0.70, 6.30) 8/84 6/126 1.	5.28 2.35 1.39 10.9).99).63 1.07 16.8
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Zhou (2003) Lu (2003) Xiao (2004) Xiao (2006) Li (2006)		OR (95% CI) Events, experimental Events, control % wei 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0. 4.08 (0.94, 17.68) 6/31 3/54 0. 0.79 (0.32, 1.92) 7/95 21/229 4. 1.27 (0.87, 1.86) 62/577 56/646 1. 1.12 (0.73, 1.73) 67/707 34/399 1. 2.11 (0.70, 6.30) 8/84 6/126 1. 1.20 (0.32, 4.51) 3/36 12/171 1.	5.28 2.35 1.39 10.9).99).63 1.07 16.8 14.07 1.55 1.36
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003) Xiao (2004) Xu (2006) Li (2006) Li (2006) Sun (2008) Lin (2009)		OR (95% Cl) Events, experimental Events, control % weil 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0. 4.08 (0.94, 17.68) 6/31 3/54 0. 0.79 (0.32, 1.92) 7/95 21/229 4. 1.27 (0.87, 1.86) 62/577 56/646 1. 1.12 (0.73, 1.73) 67/707 34/399 1. 2.11 (0.70, 6.30) 8/84 6/126 1. 1.20 (0.32, 4.51) 3/36 12/171 1. 0.88 (0.34, 2.25) 8/125 11/152 3.	5.28 2.35 1.39 10.9).63 1.07 16.8 14.0 1.55 1.36 3.31
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003) Xiao (2004) Xu (2006) Li (2006) Li (2008) Lin (2009) Chen (2009)		DR (95% Cl) Events, experimental Events, control Weil 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0. 0.79 (0.32, 1.92) 7/95 21/229 4. 1.27 (0.87, 1.86) 62/577 56/646 1. 1.12 (0.73, 1.73) 67/707 34/399 1. 2.11 (0.70, 6.30) 8/84 6/126 1. 0.88 (0.34, 2.25) 8/125 11/152 3. 1.03 (0.65, 1.65) 34/393 44/523 1.	5.28 2.35 1.39 10.91 0.99 0.63 1.07 16.8 14.02 1.55 1.36 3.31
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003) Xiao (2004) Xu (2006) Li (2006) Li (2006) Sun (2008) Lin (2009) Chen (2009) Yang (2010)		OR (95% CI) Events, experimental Events, control % weil 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0. 0.79 (0.32, 1.92) 7/95 21/229 4. 1.27 (0.87, 1.86) 62/577 56/646 1. 1.27 (0.87, 1.86) 62/577 56/646 1. 1.12 (0.73, 1.73) 67/707 34/399 1. 2.11 (0.70, 6.30) 8/84 6/126 1. 1.20 (0.32, 4.51) 3/36 12/171 1. 0.88 (0.34, 2.25) 8/125 11/152 3. 1.03 (0.65, 1.65) 34/393 44/523 1. 1.79 (0.82, 3.92) 10/55 30/272 2	5.28 2.35 1.39 10.9').99).63 1.07 16.8' 1.40 1.55 1.36 3.31 12.29
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003) Xiao (2004) Xu (2006) Li (2006) Li (2009) Chen (2009) Yang (2010) Yuan (2010)		DR (95% CI) Events, experimental Events, control Weil 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 1. 2.97 (0.84, 10.58) 7/67 4/106 0. 4.08 (0.94, 17.68) 6/31 3/54 0. 0.79 (0.32, 1.92) 7/95 21/229 4. 1.27 (0.87, 1.86) 62/577 56/646 1. 1.12 (0.73, 1.73) 67/707 34/399 1. 2.11 (0.70, 6.30) 8/84 6/126 1. 1.20 (0.32, 4.51) 3/36 12/171 1. 0.88 (0.34, 2.25) 8/125 11/152 3. 1.03 (0.65, 1.65) 34/393 44/523 1. 1.79 (0.82, 3.92) 10/55 30/272 2. 1.29 (0.33. 5.01) 4/58 5/92 1	5.28 2.35 1.39 10.97 0.63 4.07 16.8° 1.4.03 1.55 1.36 3.31 12.29 2.94 1.28
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003) Xiao (2004) Xu (2006) Li (2006) Li (2006) Sun (2008) Lin (2009) Chen (2009) Chen (2009) Yang (2010) Yuan (2010) Lv (2012)		OR (95% CI) Events, experimental Events, control Wei 1.70 (0.90, 3.22) 28/165 18/168 5 1.27 (0.45, 3.56) 13/95 6/54 2 3.26 (1.24, 8.54) 9/35 12/125 1 0.61 (0.35, 1.06) 30/369 26/204 10 2.97 (0.84, 10.58) 7/67 4/106 0 4.08 (0.94, 17.68) 6/31 3/54 0 0.79 (0.32, 1.92) 7/95 21/229 4 1.27 (0.87, 1.86) 62/577 56/646 10 1.12 (0.73, 1.73) 67/707 34/399 14 2.11 (0.70, 6.30) 8/84 6/126 15 1.20 (0.32, 4.51) 3/36 12/171 15 0.88 (0.34, 2.25) 8/125 11/152 33 1.03 (0.65, 1.65) 34/393 44/523 14 1.79 (0.82, 3.92) 10/55 30/272 2 1.29 (0.33, 5.01) 4/58 5/92 1	5.28 2.35 1.39 10.97 0.63 1.07 16.8 1.4.03 1.55 1.36 1.36 1.229 2.94 1.28 3.08
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003) Xiao (2004) Xi (2006) Li (2006) Li (2006) Sun (2008) Lin (2009) Chen (2009) Chen (2009) Yang (2010) Yuan (2010) Lv (2012) Zhang (2012)		OR (95% CI) Events, experimental Events, control % wei 1.70 (0.90, 3.22) 28/165 18/168 5 1.27 (0.45, 3.56) 13/95 6/54 2 3.26 (1.24, 8.54) 9/35 12/125 1 0.61 (0.35, 1.06) 30/369 26/204 1 2.97 (0.84, 10.58) 7/67 4/106 0 4.08 (0.94, 17.68) 6/31 3/54 0 0.79 (0.32, 1.92) 7/95 21/229 4 1.27 (0.87, 1.86) 62/577 56/646 1 1.12 (0.73, 1.73) 67/707 34/399 1 2.11 (0.70, 6.30) 8/84 6/126 1 1.20 (0.32, 4.51) 3/36 12/171 1 0.88 (0.34, 2.25) 8/125 11/152 3 1.03 (0.65, 1.65) 34/393 44/523 1 1.29 (0.33, 5.01) 4/58 5/92 1 0.93 (0.36, 2.43) 8/130 10/152 3	5.28 2.35 1.39 10.97 0.99 0.63 1.07 16.8 1.4.03 1.55 1.36 3.31 12.29 2.94 1.28 3.08 3.08
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003) Xiao (2004) Xu (2006) Li (2006) Li (2006) Li (2006) Sun (2008) Lin (2009) Chen (2009) Chen (2009) Yang (2010) Yuan (2010) Lv (2012) Zhang (2012) Huang (2012) —		OR (95% CI) Events, experimental Events, control % wei 1.70 (0.90, 3.22) 28/165 18/168 5. 1.27 (0.45, 3.56) 13/95 6/54 2. 3.26 (1.24, 8.54) 9/35 12/125 1. 0.61 (0.35, 1.06) 30/369 26/204 10 2.97 (0.84, 10.58) 7/67 4/106 0. 4.08 (0.94, 17.68) 6/31 3/54 0. 0.79 (0.32, 1.92) 7/95 21/229 4. 1.27 (0.87, 1.86) 62/577 56/646 10 1.12 (0.73, 1.73) 67/707 34/399 12 2.11 (0.70, 6.30) 8/84 6/126 13 1.20 (0.32, 4.51) 3/36 12/171 14 0.88 (0.34, 2.25) 8/125 11/152 33 1.03 (0.65, 1.65) 34/393 44/523 14 1.29 (0.33, 5.01) 4/58 5/92 1 0.93 (0.36, 2.43) 8/130 10/152 33 1.12 (0.64, 1.98) 26/306 26/340	5.28 2.35 1.39 10.97 0.99 0.63 14.07 16.8 14.03 1.55 1.36 1.36 1.22 2.94 1.28 3.03 3.03 0.62
a 0.05 Study ID Peng (1999) Cheng (2001) Li (2001) Wu (2002) Wang (2003) Zhou (2003) Lu (2003) Lu (2003) Xiao (2004) Xi (2006) Li (2006) Li (2006) Sun (2008) Lin (2009) Chen (2009) Chen (2009) Yang (2010) Yuan (2010) Lv (2012) Zhang (2012)		OR (95% CI) Events, experimental Events, control % wei 1.70 (0.90, 3.22) 28/165 18/168 5 1.27 (0.45, 3.56) 13/95 6/54 2 3.26 (1.24, 8.54) 9/35 12/125 1 0.61 (0.35, 1.06) 30/369 26/204 1 2.97 (0.84, 10.58) 7/67 4/106 0 4.08 (0.94, 17.68) 6/31 3/54 0 0.79 (0.32, 1.92) 7/95 21/229 4 1.27 (0.87, 1.86) 62/577 56/646 1 1.12 (0.73, 1.73) 67/707 34/399 1 2.11 (0.70, 6.30) 8/84 6/126 1 1.20 (0.32, 4.51) 3/36 12/171 1 0.88 (0.34, 2.25) 8/125 11/152 3 1.03 (0.65, 1.65) 34/393 44/523 1 1.29 (0.33, 5.01) 4/58 5/92 1 0.93 (0.36, 2.43) 8/130 10/152 3	2.35 1.39 10.97 0.99 0.63 1.07 16.81 14.03 1.55 1.36 3.31 12.29 2.94 1.28 3.08 3.03 3.03 0.62

Fig. 4. a–d Forest plot of the relationships between ApoE gene polymorphisms and ICH risk in the genetic comparisons of the $\varepsilon 4$ allele vs. the $\varepsilon 3$ allele (**a**); the $\varepsilon 2$ allele vs. the $\varepsilon 3$ allele (**b**).

Study ID	Events, Eve OR (95% CI) experimental co	ents, % htrol weight
Peng (1999)	1.80 (0.74, 4.40) 14/63 10/7	3 5.71
Cheng (2001)	1.21 (0.32, 4.55) 8/41 4/24	
Li (2001)	→ 24.50 (6.54, 91.74) 15/21 5/54	4.05
Wu (2002) —	2.82 (1.45, 5.46) 67/195 13/8	
Wang (2003)	• <u>1.80 (0.71, 4.61)</u> 12/34 13/5	
Zhou (2003)	1.94 (0.47, 8.05) 5/14 6/27	
Lu (2003)	1.05 (0.30, 3.61) 4/43 9/10	1 4.34
Xiao (2004)	- 1.19 (0.77, 1.84) 50/266 49/3	
Xu (2006) —	2.03 (1.28, 3.22) 95/347 29/1	
Li (2006) —	2.84 (1.13, 7.14) 15/43 10/6	
Sun (2008)	→ 22.46 (8.26, 61.09) 31/45 7/78	
Lin (2009)	2.86 (1.15, 7.14) 18/66 8/69	
Chen (2009)		
Yang (2010)		
Yuan (2010)	1.08 (0.28, 4.24) 4/28 6/45	
Lv (2012)	3.10 (1.26, 7.63) 20/70 8/70	
Zhang (2012)	<u> </u>	
Huang (2012)	3.98 (1.23, 12.87) 14/65 4/62	
Overall (l ² = 70.9%, p = 0.000)	2.41 (1.68, 3.47) 459/1,724 255/	
Study ID	Events, Ev OR (95% CI) experimental co	ents, % ntrol weigh
Peng (1999)	2.17 (1.05, 4.47) 27/76 16/	
Cheng (2001)	• 1.36 (0.37, 5.01) 9/42 4/2	
Li (2001)	1.53 (0.57, 5.67) 5/42 4/2 1.63 (0.29, 9.29) 2/8 10/	
Wu (2002)	0.43 (0.22, 0.85) 18/146 23/	
Wang (2003)	3.26 (0.71, 14.91) 5/27 3/4	
Zhou (2003)	2.33 (0.39, 13.85) 3/12 3/2	
Lu (2003)		109 3.95
Xiao (2004) — • –		299 17.03
Xu (2006)		185 13.73
Li (2006)	2.84 (0.74, 10.90) 6/34 4/5	
Sun (2008)	2.84 (0.74, 10.90) 6/34 4/3 	
Lin (2009)	0.81 (0.29, 2.24) 7/55 11/	
Chen (2009)		72 5.04 243 13.56
Yang (2010)		1243 13.30 124 4.78
	1.34 (0.72, 3.26) 14/30 23/ 1.08 (0.17, 6.96) 2/26 3/4	
Yuan (2010)		72 3.58
Yuan (2010) Lv (2012)		
Yuan (2010) Lv (2012) Zhang (2012)	1.15 (0.59, 2.25) 19/129 21/	161 7.36
Yuan (2010) Lv (2012)		1617.36848.45

Fig. 4. a–d Forest plot of the relationships between ApoE gene polymorphisms and ICH risk in the genetic comparisons of $\varepsilon 4$ carriers vs. $\varepsilon 3\varepsilon 3$ carriers (c); and $\varepsilon 2$ carriers vs. $\varepsilon 3\varepsilon 3$ carriers (d).

an
eta-
ñ
cluded in this meta-an
л.
led
luc
inc
∖H i
ιI⁄
with
ed
ciat
esults of studies associated with IAH included in this meta-ar
ies
tud
ofs
ts of
ain result
ı re
he main r
he 1
F.
4
able 4. ${ m T}$
Ĕ

ualysis

Study	Studies (size/	e4 vs. e3			e2 vs. e3		ŵ	e4 carrier vs. e3e3 carrier	carrier	ε2 carrier vs. ε3ε3 carrier	e3e3 carri	er
subgroup	control)	OR (95% CI)	$P_{\rm Q}$	I ² , %	$P_Q = I^2, \% = OR (95\% \ CI) \\ P_Q = I^2, \% = OR (95\% \ CI) $	$P_Q I^2$,	% C)R (95% CI)	P _Q I ² , 9	OR (95% CI)	P_{Q}	I ² , %
ICH HWE	18 (2,018/2,143)	18 (2,018/2,143) 2.08 (1.57–2.75)*		61.9	$0.000 61.9 1.13 \\ (0.96 - 1.33) 0.067 35.7 2.41 \\ (1.68 - 3.47)^* 0.000 70.9 1.01 \\ (0.84 - 1.22) 0.153 25.7 2.5.7 2$	0.067 35	.7 2	.41 (1.68–3.47)*	0.000 70.9	1.01 (0.84–1.2	(2) 0.153	25.7
Yes	16(1,627/1,701)	16 (1,627/1,701) 2.18 (1.64–2.89)*	0.006	53.3	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	0.177 24	1.5 2	.50 (1.69-3.71)*	0.000 69.8	1.11 (0.89-1.3	(2) 0.266	16.4
No	2 (391/442)	1.63 (0.56–4.74)	0.018	82.3	82.3 0.99 (0.72-1.37) 0.016 82.8 1.92 (0.60-6.10) 0.058 72.2	0.016 82	8 1	.92 (0.60–6.10)	0.058 72.2	0.74 (0.50–1.11) 0.139	1) 0.139	54.4
PB	16 (1,748/1,873)	16 (1,748/1,873) 2.07 (1.52-2.82)*	0.000	63.4	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	0.053 39	.5 2	.38 (1.59–3.56)*	0.000 72.6	0.94(0.77 - 1.1)	5) 0.261	16.8
Non-PB	2 (270/270)	$2.15(1.00-4.65)^{*}$	0.104 6	62.1	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	0.336 0	0.0	.81 (1.36–5.80)*	0.179 44.7	1.55 (0.95–2.5	(2) 0.207	37.1
High quality	r 16 (1,748/1,873)	High quality 16 (1,748/1,873) 2.07 (1.52–2.82)*	0.000	63.4	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	0.053 39	.5 2	.38 (1.59–3.56)*	0.000 72.6	0.94(0.77 - 1.1)	5) 0.261	16.8
* p < 0.05. P pital-based con	* $p < 0.05$. $P_Q = A p$ value of the Cochrane's Q te pital-based controls or mixed controls; high quality	* $p < 0.05$. $P_Q = A p$ value of the Cochrane's Q test for heterogeneity; $I^2 = value$ of I^2 statistic for heterogeneity; PB = population-based controls; non-PB = hos-al-based controls or mixed controls; high quality = NOS score >7.	st for heterogene = NOS score >7.	srogen ore >7.	eity; I ² = value of	I ² statistic	tor h	eterogeneity; PB :	= populati	on-based control	s; non-Pl	

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 E4 allele with ICH risk compared with the ɛ3 allele, and ɛ4 carriers showed a significantly higher risk of developing ICH than ɛ3ɛ3 genotype carriers. Conversely, the evidence did not support an association of £2 allele or £2 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 ɛ4 carriers and ɛ3ɛ3 genotype carriers or between the $\varepsilon 4$ allele and the $\varepsilon 3$ 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 ϵ 4 carriers, but not ϵ 2 carriers, compared with ϵ 3 ϵ 3 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

Downloaded from http://www.karger.com/ced/article-pdf/41/3-4/119/2353988/000442678.pdf by guest on 20 April 2024

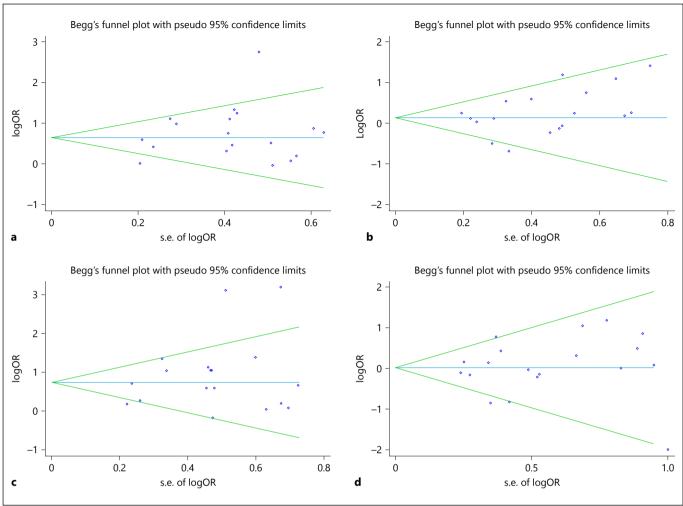


Fig. 5. a-d Begg's funnel plots of the relationships between ApoE gene polymorphisms and ICH risk in the genetic comparisons of the $\varepsilon 4$ allele vs. the $\varepsilon 3$ allele (**a**); the $\varepsilon 2$ allele vs. the $\varepsilon 3$ allele (**b**); $\varepsilon 4$ carriers vs. $\varepsilon 3\varepsilon 3$ carriers (**c**); and $\varepsilon 2$ carriers vs. $\varepsilon 3\varepsilon 3$ 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 ɛ4 allele may predict an increased risk for different subtypes of stroke, including IS, ICH and SAH, as £4 carriers showed a significantly ele-

ApoE Polymorphisms and the Risk of Different Subtypes of Stroke

vated risk of developing different subtypes of stroke. However, neither the ɛ2 allele nor ɛ2 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.

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

References

- Lozano R, Naghavi M, Foreman K, et al: Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2095– 2128.
- 2 Murray CJ, Vos T, Lozano R, et al: Disabilityadjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2197–2223.
- 3 Lisabeth LD, Diez Roux AV, Escobar JD, Smith MA, Morgenstern LB: Neighborhood environment and risk of ischemic stroke: the brain attack surveillance in Corpus Christi (BASIC) project. Am J Epidemiol 2007;165: 279–287.
- 4 Honjo K, Iso H, Nakaya T, Hanibuchi T, Ikeda A, Inoue M, Sawada N, Tsugane S; Japan Public Health Center-Based Prospective Study Group: Impact of neighborhood socioeconomic conditions on the risk of stroke in Japan. J Epidemiol 2015;25:254–260.
- ⁵ Traylor M, Farrall M, Holliday EG: Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. Lancet Neurol 2012;11:951–962.
- 6 Chou SH, Shulman JM, Keenan BT, Secor EA, Buchman AS, Schneider J, Bennett DA, De Jager PL: Genetic susceptibility for ischemic infarction and arteriolosclerosis based on neuropathologic evaluations. Cerebrovasc Dis 2013;36:181–188.
- 7 Casas JP, Hingorani AD, Bautista LE, Sharma P: Meta-analysis of genetic studies in ischemic stroke: thirty-two genes involving approximately 18,000 cases and 58,000 controls. Arch Neurol 2004;61:1652–1661.
- 8 Peck G, Smeeth L, Whittaker J, Casas JP, Hingorani A, Sharma P: The genetics of primary haemorrhagic stroke, subarachnoid haemorrhage and ruptured intracranial aneurysms in adults. PLoS One 2008;3:e3691.
- 9 Sudlow C, Martínez González NA, Kim J, Clark C: Does apolipoprotein E genotype influence the risk of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage? Systematic review and meta-analyses of 31 studies among 5961 cases and 17,965 controls. Stroke 2006;37:364–370.
- 10 Mahley RW: Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 1988;240:622–630.
- 11 Mahley RW, Rall SC Jr: Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet 2000;1:507–537.
- 12 Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC: Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol 2002; 155:487–495.
- 13 Greenow K, Pearce NJ, Ramji DP: The key role of apolipoprotein E in atherosclerosis. J Mol Med (Berl) 2005;83:329–342.

- 14 McCarron MO, Nicoll JA: Apolipoprotein E genotype and cerebral amyloid angiopathyrelated hemorrhage. Ann N Y Acad Sci 2000; 903:176–179.
- 15 Niu W, Qi Y, Qian Y, Gao P, Zhu D: The relationship between apolipoprotein E epsilon2/epsilon3/epsilon4 polymorphisms and hypertension: a meta-analysis of six studies comprising 1812 cases and 1762 controls. Hypertens Res 2009;32:1060–1066.
- 16 Zhang R, Wang X, Tang Z, Liu J, Yang S, Zhang Y, Wei Y, Luo W, Wang J, Li J, Chen B, Zhang K: Apolipoprotein E gene polymorphism and the risk of intracerebral hemorrhage: a meta-analysis of epidemiologic studies. Lipids Health Dis 2014;13:47.
- 17 Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–269, W64.
- 18 Anthopoulos PG, Hamodrakas SJ, Bagos PG: Apolipoprotein E polymorphisms and type 2 diabetes: a meta-analysis of 30 studies including 5423 cases and 8197 controls. Mol Genet Metab 2010;100:283–291.
- 19 Guo Y, Guo JJ, Nao JF, Wang FW: The relations between polymorphisms of apolipoprotein E gene and atherosclerotic cerebral infarction. Chin J Neurol 1997;30:236–239.
- 20 Yan SK, Zhou X, Li XL, Yu DL, Ha DW: Study on the relationship between polymorphism of apolipoprotein E gene and atherosclerotic cerebral infarction. Chin J Med Genet 1997;14: 318–320.
- 21 Zhou K, Yu SZ, Wang GJ: The relationship between apolipoprotein E gene polymorphism and vascular demention and cerebral infarction. Chin J Geriatr 1997;16: 368–369.
- 22 Cao W, Chen F, Teng L, Wang S, Fu S, Zhang G: [The relationship between apolipoprotein E gene polymorphism and coronary heart disease and arteriosclerotic cerebral infarction]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 1999; 16:249–251.
- 23 Liu WG, Li ZH: The relationship between polymorphisms of apolipoprotein E gene and atherosclerotic cerebral infarction in middleaged and young adults. J Clin Neurol 1999;12: 134–136.
- 24 Peng DQ, Zhao SP: Comparison of apolipoprotein E genotype distribution in two types of stroke. Chin J Arteriosclerosis 1999;7:34– 36.
- 25 Ding J, Zhu WB, Fan W, Han QQ, Zhang JG, He L: Study on the correlation of apolipoprotein E gene polymorphism and cerebral infarction. Chin J Nerv Ment Dis 2000;26:371– 372.
- 26 Wang TG, He ZY, Li YQ, Liu FP, Huang SS, Zhou TH: The relationship between apolipoprotein E gene polymorphism and atherosclerotic cerebral infarction. Hereditas 2000;22: 4–6.

- 27 Yu X, Shao XG, Tan L, Luo B: Apolipoprotein E polymorphism and cerebral infarction. Acta Acad Med Qingdao Univ 2000;36:265– 267.
- 28 Li YW, He X, Zhang LX, Li F, Zhang DZ: The relationship between polymorphisms of apolipoprotein E gene and cerebrovascular disorder. Prev Treat Cardio Cereb Vasc Dis 2001; 1:17–19.
- 29 Zhang X, Hao HJ, Yuan JM, Wang XT: Early recurrent cerebral infarction and polymorphism of apolipoprotein E gene. Zhejiang Clin Med J 2001;3:467–468.
- 30 Shen LH, Ke KF, Li ZH, Pan Y: Research on apolipoprotein E gene polymorphism in patients with atherosclerotic cerebral infarction. Jiao Tong Yi Xue 2002;16:504–505.
- 31 Xia Y, Li HL, Wang JL: Association between apolipoprotein E polymorphism and lipid metabolism in patients with cerebral infarction. Chin J Pathophysiol 2002;18:826–829.
- 32 Zhu L, Cui TP: The relationship between apolipoprotein E gene polymorphism and cerebral infarction. Chin J Thromb Hemost 2002; 8:14–15.
- 33 Lu HY: Relationship Between Apolipoprotein E Gene Polymorphism and Cerebral Vascular Disease and Vascular Dementia. Tianjin Medical University Postgraduate Paper, 2003.
- 34 Su J, Tan L, Chang GF: Study on the correlation between apolipoprotein E gene polymorphism and vascular dementia. Chin J Nerv Ment Dis 2003;29:457–460.
- 35 Wang XT, Huang HJ, Yu K, Shen ZJ, Tan YX, Hu XX: Apolipoprotein E gene polymorphism in people with cerebrovascular disease in south of Zhejiang province. Nerv Dis Ment Hygiene 2003;3:17–19.
- 36 Zhou J: The Clinical Study of Serum Lipid, Serum Lipoprotein Electrophoretagram and Apolipoprotein E Polymorphisms in Patients with Stroke. First Military Medical University Postgraduate Paper, 2003.
- 37 Li ZH, Shen LH, Ke KF: Genetic polymorphism of apolipoprotein E in patients with family aggregation or non-family aggregation of cerebral infarction. Chin J Clin Rehabil 2004;8:7064–7066.
- 38 Xiao ZJ, Zhao SP, Nie S, Tan LM, Jiang B, Wu J: The relationship between ApoE gene polymorphism and cerebral infarction. Zhonghua Liu Xing Bing Xue Za Zhi 2005;26:533–536, 267.
- 39 Lin HF, Lai CL, Tai CT, Lin RT, Liu CK: Apolipoprotein E polymorphism in ischemic cerebrovascular diseases and vascular dementia patients in Taiwan. Neuroepidemiology 2004;23:129–134.
- 40 Jin ZQ, Fan YS, Ding J, Chen M, Fan W, Zhang GJ, Zhang BH, Yu SJ, Zhang YS, Ji WF, Zhang JG: Association of apolipoprotein E 4 polymorphism with cerebral infarction in Chinese Han population. Acta Pharmacol Sin 2004;25:352–356.

- 41 He J, Gui JH, Yu WZ, Chou DH: Study on the association of apolipoprotein E genotypes with cerebral infarction and myocardial infarction in the Urumqi old population. Chin J Physician 2004;2:49–51.
 42 Gao X, Yang H, ZhiPing T: Association stude
- 42 Gao X, Yang H, ZhiPing T: Association studies of genetic polymorphism, environmental factors and their interaction in ischemic stroke. Neurosci Lett 2006;398:172–177.
- 43 Li J, Gao HF, Cao YB: Association of ApoE gene polymorphism with cerebral vascular disease and the susceptibility of blood lipid levels. Chin J Coal Indust Med 2006;9:1150–1151.
- 44 Ma F, Wu W, Wang F, Zhang Y, Lu X: Association of apolipoprotein E polymorphism with lipid metabolism and ischemic stroke subtypes. Chin J Geriatr Heart Brain Vessel Dis 2006;8:513–516.
- 45 Zhang B, Zhang ZB, Liu H, He L, Jiang XF, Wang XH, Cai ZL, Zeng H, Luo ZM, Xu YM: Study of the relationship between apolipoprotein E polymorphism and cerebral infarction. Med J West China 2006;21:90–91.
- 46 Wen HM, Baum L, Cheung WS, Mok V, Lam WW, Tomlinson B, Wong KS, Ng HK: Apolipoprotein E epsilon4 allele is associated with the volume of white matter changes in patients with lacunar infarcts. Eur J Neurol 2006;13:1216–1220.
- 47 Zhou J, Yu FM, Li XX: The relationship between apolipoprotein E gene polymorphism and cerebral infarction. Chin J Cerebrovasc Dis 2006;3:263–266.
- 48 Baum L, Ng HK, Wong KS, Tomlinson B, Rainer TH, Chen X, Cheung WS, Tang J, Tam WW, Goggins W, Tong CS, Chan DK, Thomas GN, Chook P, Woo KS: Associations of apolipoprotein E exon 4 and lipoprotein lipase S447X polymorphisms with acute ischemic stroke and myocardial infarction. Clin Chem Lab Med 2006;44:274–281.
- 49 Deng K, Xiao ZJ, Zhao SP, Nie S, Huang F, Ni XD, Tan LM: The study on the apolipoprotein E gene polymorphism in patients with lacunar infarction. J Brain Nerv Dis 2007;15:425–427.
- 50 Lv J, Qu F, Wang JH, Cao GS: The relationship between apolipoprotein E gene polymorphism and cerebral infarction. Haerbin Med J 2007;27:9–11.
- 51 Man X, Yu BX, Pang ZY, Len ZP: Study of the relationship between the polymorphism of ApoE gene and cerebral infarction. Chin J Behav Med Sci 2007;16:797–798.
- 52 Lai CL, Liu CK, Lin RT, Tai CT: Association of apolipoprotein E polymorphism with ischemic stroke subtypes in Taiwan. Kaohsiung J Med Sci 2007;23:491–497.
- 53 Sun HY, He JL, Yuan LH, Yang YM, Cheng JL: Relationship of apolipoprotein E gene polymorphism with cerebral vascular disease. Med J West China 2008;20:60–63.
- 54 Xie DL, Xu H, Wang YM, Liu H: Relationship between apolipoprotein E gene polymorphism and atherosclerotic cerebral infarction. J Clin Neurol 2008;21:58–59.
- 55 Nie L: Apolipoprotein E Gene Polymorphism in Cerebrovascular Diseases of the Chinese

Bai Populations from Yunnan Province. Kunming Medical University Postgraduate Paper, 2009.

- 56 Wang B, Zhao H, Zhou L, Dai X, Wang D, Cao J, Niu W: Association of genetic variation in apolipoprotein E and low density lipoprotein receptor with ischemic stroke in Northern Han Chinese. J Neurol Sci 2009;276:118– 122.
- 57 Zhou ZY, Fu XN, Su QJ, Long DY, Chen ZB, Wang T: Relationship of ApoE gene polymorphism and cerebral infarction in Hainan Li nationality population. Chongqing Med J 2009;38:2822–2824.
- 58 Yang FB, Li XY, Mu JX: Study on the relationship between apolipoprotein E gene polymorphism and vascular cognitive impairment. Chin J Integr Med Cardio Cerebrovasc Dis 2010;8:1194–1196.
- 59 Yuan QH: Apolipoprotein E Gene Polymorphism in Cerebrovascular Diseases of the Chinese Naxi Populations from Yunnan Province. Kunming Medical University Postgraduate Paper, 2010.
- 60 Li XJ, Guo DY, Zeng BY: Relationship of ApoE gene polymorphism and cerebral infarction in old population. Chin J Gerentol 2012;32:3920–3921.
- 61 Liu HJ, Wang QS, Guan YM, Liu XC, Wang J, Huang HL: Relationship of ApoE gene polymorphism and cerebral infarction. Mil Med J Southeast China 2012;14:195–198.
- 62 Lv ZF, Pang GF, Hu CY, Lv Y: Comparative study on ApoE gene polymorphism between coronary disease and cerebral infarction in elderly. J Guangxi Med 2012;34: 1610–1612.
- 63 Wang YQ, Wu CJ, Yao M, Zhang YA, Zheng LL: Study on the ApoE gene polymorphism in Li population patients with cardiovascular and cerebrovascular disease. Lab Med 2012; 27:308–315.
- 64 Gu L, Su L, Chen Q, Liang B, Qin Y, Xie J, Wu G, Yan Y, Long J, Wu H, Tan J, Dou W, Chen W, Wu P, Wang J: Association between the apolipoprotein E gene polymorphism and ischemic stroke in Chinese populations: new data and meta-analysis. Exp Ther Med 2013; 5:853–859.
- 65 Jing HS: The Correlation of ApoE Gene Polymorphism and the Locality and Size of Cerebral Infarction. Luzhou Medical College Postgraduate Paper, 2013.
- 66 Liu J: Apolipoprotein E Gene Polymorphism in Cerebrovascular Diseases of the Chinese Yi Populations from Yunnan Province. Kunming Medical University Postgraduate Paper, 2013.
- 67 Wang J, Zhong CM, Tian XJ, Wang XJ, Cheng H: Relationship between gene polymorphism of apolipoprotein E and cerebral infarction in middle-aged and young adults. Chin J Clin Med 2013;20:462–464.
- 68 Zhao X: Study on the Relationship between Gene Polymorphism of Apolipoprotein E and Cerebral Infarction. Jilin Medical University Postgraduate Paper, 2013.

- 69 Huang BJ: Apolipoprotein E Gene Polymorphism in Cerebrovascular Diseases of the Chinese Wa Populations from Yunnan Province. Kunming Medical University Postgraduate Paper, 2014.
- 70 Sun J: Relationship of ApoE gene polymorphism and cerebral infarction. Chin J Gerontol 2014;34:3443–3444.
- 71 Zhang YH, Zhu L, Zheng DJ, Pan JY, Fang JZ: Relationship between apolipoprotein E gene polymorphism and cerebral infarction patients with different gender and etiological typing. Chin J Cerebrovasc Dis 2014;11:305– 310.
- 72 Yan HQ, Yuan Y, Zhang P, Huang Z, Chang L, Gui YK: Association of the ApoE gene polymorphism and dietary factors with cerebral infarction and circulating lipid concentrations. Genet Mol Res 2015;14:665–670.
- 73 Special report from the national institute of neurological disorders and stroke. classification of cerebraovascular disorders III. Sroke 1990;21:637–676.
- 74 Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd: Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke 1993;24:35–41.
- 75 Cheng QZ, Dong WL: The relationship between apolipoprotein E genotype and lobar intracerebral hemorrhage. Acta Acad Med Suzhou 2001;20:831–833.
- 76 Wu P, Sun XJ, Zhang J, Weng Q: The relationship between apolipoprotein E gene polymorphism and intracerebral hemorrhage. Chin J Gerentol 2001;22:94–95.
- 77 Xiao ZJ, Zhao SP, Nie S, Tan LM, Jiang B, Wu J: The relationship between ApoE gene polymorphism and cerebral hemorrhage. Stroke Nerv Dis 2004;12:185–187.
- 78 Xu Z: The Relationship between ApoE Gene Polymorphism and Cerebral Hemorrhage. Nantong Medical University Postgraduate Paper, 2006.
- 79 Lin YF, Zhang MH: The significance and exploration of detecting the polymorphism of ApoE gene for patients with cerebral hemorrhage by real-time fluorescence quantitative PCR. Strait Pharm J 2009;21:70–72.
- 80 Chen YC, Lee-Chen GJ, Wu YR, Hu FJ, Wu HC, Kuo HC, Chu CC, Ryu SJ, Chen ST, Chen CM: Analyses of interaction effect between apolipoprotein E polymorphism and alcohol use as well as cholesterol concentrations on spontaneous deep intracerebral hemorrhage in the Taiwan population. Clin Chim Acta 2009;408:128–132.
- 81 Lv J, Qu F: Study of the relationship of APOE gene polymorphisms and cerebral hemorrhage. CJGMCM 2012;27:1752–1754.
- 82 Zhang R, Wang X, Liu J, Yang S, Tang Z, Li S, Peng Y, Zhang H, Yang X, Zhou Y, Shao W: Apolipoprotein E gene polymorphism and the risk of intracerebral hemorrhage in the Chinese population. Genet Test Mol Biomarkers 2012;16:63–66.

- 83 Huang HL, Zhou KQ, Wang QS, Liu HJ, Liu XC, Guan YM, Wang W: ApoE gene polymorphism in patients with intracerebral hemorrhage. Chin J Geriatr Heart Brain Vessel Dis 2013;15:492–495.
- 84 Dai HH: The Influence of Apolipoprotein E Genotype on the Onset, Cerebral Vasospasm and Outcome of Aneurysmal Subarachnoid Hemorrhage. Sun Yat-sen University Postgraduate Paper, 2005.
- 85 Wu JW: The Relationship between Genotype of Candidate Susceptibility Gene and Spontaneous Aneurysmal Subarachnoid Hemorrhage. Guangzhou Medical College Postgraduate Paper, 2006.
- 86 Chaudhary R, Likidlilid A, Peerapatdit T, Tresukosol D, Srisuma S, Ratanamaneechat S, Sriratanasathavorn C: Apolipoprotein E gene polymorphism: effects on plasma lipids and risk of type 2 diabetes and coronary artery disease. Cardiovasc Diabetol 2012;11:36.

- 87 Zhang MD, Gu W, Qiao SB, Zhu EJ, Zhao QM, Lv SZ: Apolipoprotein E gene polymorphism and risk for coronary heart disease in the Chinese population: a meta-analysis of 61 studies including 6634 cases and 6393 controls. PLoS One 2014;9:e95463.
- 88 Ward A, Crean S, Mercaldi CJ, Collins JM, Boyd D, Cook MN, Arrighi HM: Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. Neuroepidemiology 2012; 38:1–17.
- 89 Liu M, Bian C, Zhang J, Wen F: Apolipoprotein E gene polymorphism and Alzheimer's disease in Chinese population: a meta-analysis. Sci Rep 2014;4:4383.
- 90 Huang X, Chen P, Kaufer DI, Tröster AI, Poole C: Apolipoprotein E and dementia in Parkinson disease: a meta-analysis. Arch Neurol 2006;63:189–193.

- 91 Raffeld MR, Biffi A, Battey TW, Ayres AM, Viswanathan A, Greenberg SM, Rosand J, Anderson CD: ApoE ε4 and lipid levels affect risk of recurrent nonlobar intracerebral hemorrhage. Neurology 2015;85:349–356.
- 92 Chatzistefanidis D, Giannopoulos S, Spengos K, Vassilopoulou S, Vemmos K, Dova L, Vartholomatos G, Kyritsis AP, Georgiou I, Markoula S: Apolipoprotein E polymorphisms and ischaemic stroke: a two-center Greek study. Eur J Neurol 2014;21:1083–1088.
- 93 Fontanella M, Rainero I, Gallone S, Rubino E, Rivoiro C, Valfrè W, Garbossa D, Nurisso C, Ducati A, Pinessi L: Lack of association between the apolipoprotein E gene and aneurysmal subarachnoid hemorrhage in an Italian population. J Neurosurg 2007;106:245–249.
- 94 Wang QY, Wang WJ, Wu L, Liu L, Han LZ: Meta-analysis of ApoE ε2/ε3/ε4 polymorphism and cerebral infarction. J Neural Transm (Vienna) 2013;120:1479–1489.

Chen/Hu