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An updated meta-analysis: *Apolipoprotein E* genotypes and risk of primary open-angle glaucoma

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Purpose: To study the association of apolipoprotein E (*APOE*) polymorphisms and primary open-angle glaucoma (POAG).
Methods: After a systematic literature search, all relevant studies evaluating the association between *APOE* polymorphisms and POAG were included. All statistical tests were calculated with Stata 11.0.
Results: Twelve independent studies on the *APOE* gene (1,971 cases, 1,756 controls) and POAG were included. A significant association between the *APOE* gene and POAG was found in the genetic model of *ε4/ε4* versus *ε3/ε3* (odds ratio [OR] = 2.09, 95% confidence interval [CI] = 1.12–3.88, p = 0.02). However, no association was detected in the models of *ε2/ε2* versus *ε3/ε3*, *ε2/ε3* versus *ε3/ε3*, *ε2/ε4* versus *ε3/ε3*, *ε3/ε4* versus *ε3/ε3*, allele *ε2* versus allele *ε3*, and allele *ε4* versus allele *ε3*. Subgroup analyses showed that a statistically significant association between the *APOE* gene and the risk of POAG existed in the genetic model of *ε4/ε4* versus *ε3/ε3* in Asians (OR = 3.55, 95% CI = 1.06–11.87, p = 0.04). No association was identified between the *APOE* gene and the risk of POAG in Caucasians.
Conclusions: The present meta-analysis indicated that the *ε4/ε4* genotype is associated with increased risk of POAG in Asians.

Glaucoma, a degenerative group of diseases characterized by visual field loss and optic nerve degenerating changes, is the second major cause of blindness in the world [1]. As a major type of primary glaucoma in most populations, primary open-angle glaucoma (POAG) is defined by an open anterior chamber angle and elevated intraocular pressure (IOP), without other comorbidities [2-4]. However, this disease progresses slowly with concealed symptoms, which are barely detectable until evident and irreversible loss in visual field emerges. Although the pathogenesis of POAG is not fully understood, many previous studies have noted that multiple genes, as well as environmental factors, play vital roles in the development of POAG [5-10]. Thus far, many genetic loci have been predicted to associate with POAG, and among them, only three genes (*GLC1A* [myocilin, *MYOC,* OMIM 601652], *GLC1E* [optineurin, *OPTN;* OMIM 602432], and *GLC1G* [WD repeat domain 36, *WDR36;* OMIM 609669]) have been confirmed [11-15].

Recently, studies have supported the existence of a strong association between Alzheimer disease (AD) and POAG [16,17]. It has also been suggested that loss of retinal ganglion cells and optic nerve degeneration occur in patients with AD [18,19]. The genotype of the *apolipoprotein E* (*APOE;*OMIM 107741) gene is one of the major genetic risk factors for AD. Therefore, a new research field has developed to study the associations between POAG and AD by focusing on the *APOE* gene and its variants. As a player in lipid metabolism, apolipoprotein E (ApoE) plays a vital role in the transportation of cholesterol and triglyceride [20-22]. The human *APOE* gene is located on chromosome 19q13.2, with three common alleles (*ε2, ε3*, and *ε4*) encoding 3 protein isoforms (E2, E3, and E4). As the most common isoform, E3 contains cysteine and arginine at amino acid positions 112 and 158, respectively. In contrast, E2 and E4 contain only cysteine and arginine residues in these positions, respectively. Since each individual inherits one allele from each parent, six possible combinations of genotypes can be generated by three alleles: *ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4,* and *ε4/ε4* [23]. Possible association between the *APOE* gene and POAG has been investigated in several studies; however, the results were conflicting. To clarify this question, a systematic meta-analysis was performed to ascertain the associations between *APOE* polymorphisms and the risk of POAG.

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METHODS

Literature search strategy: The data were obtained from PubMed, Web of Science, Embase, and China National Knowledge Infrastructure (CNKI). The following index terms were used in the search strategy to include all possible studies: (*APOE* OR *apolipoprotein E*) AND (primary open-angle glaucoma OR POAG OR high tension glaucoma OR HTG OR normal tension glaucoma OR NTG).

Inclusion criteria and data extraction: The inclusion criteria for the selected articles were as follows: (1) case–control study, (2) reports on the association between *APOE* polymorphisms and POAG, (3) studies with full text articles, and (4) the number of *APOE* genotypes/alleles in the case and control groups was calculated. Genotype *ε3/ε3* was assigned as the reference group in our study. Thus, seven genetic models were analyzed (*ε2/ε2* versus *ε3/ε3*, *ε2/ε3 versus ε3/ε3*, *ε2/ε4* versus *ε3/ε3*, *ε3/ε4* versus *ε3/ε3*, *ε4/ε4* versus *ε3/ε3*, allele *ε2* versus allele *ε3*, and allele *ε4* versus allele *ε3*). The articles were reviewed independently by two investigators (Rongfeng Liao and Minjie Ye), who also extracted and evaluated the quality of the data. A third reviewer (Xiping Xu) participated in the investigation and evaluation if there were any disagreements. For each study, the extracted information includes the first author's name, ethnicity (country), publication year, and the number of each allele and genotype in the cases and controls. (See Table 1.)

Statistical analysis: The statistical analyses were performed by using Stata 11.0 (StataCorp, College Station, TX). The association between *APOE* polymorphisms and risk of POAG was expressed as odds ratio (OR) and 95% confidence interval (CI). The effects of heterogeneity were quantified with the I^2 statistic, which detected variations among publications due to heterogeneity rather than chance. All ORs were calculated with the fixed effects model (the Mantel-Haenszel method) or the random effects model (the DerSimonian-Laird method) according to the heterogeneity [24,25]. When there was no heterogeneity among studies, a fixed effects model was applied; otherwise, a random effects model was applied. Subgroup analyses were performed based on ethnicity and POAG subtype. Since genotype distributions of the control group might be important in the studies, a chi-square test was applied to determine if the genotype distributions of the control group reported conformed to Hardy–Weinberg equilibrium (HWE; $p \leq 0.05$ was representative of statistical significance). Finally, the funnel plots and Egger's regression test were used to evaluate publication bias visually.

RESULTS

Characteristics of studies: In Figure 1, the study inclusion process in this meta-analysis is described. Twelve studies (1,971 cases, 1,756 controls) were included [26-37]. Among them, five studies were performed in Asians (1,064 cases and 813 controls) and seven in Caucasians (907 cases and 943 controls). Three studies on Asians and two studies on Caucasians examined the relationships between the *APOE* gene and high tension POAG (HTG), while three additional studies evaluated the association between the *APOE* gene and normal tension glaucoma (NTG). The HWE test was performed on the genotype distribution of the controls in all included studies, all of which showed $p>0.05$ in HWE, except four studies (two [26,31] showed $p<0.05$; two [34,37] lacked data). Detailed characteristics of each included study are presented in Table 1.

Meta-analysis results: The association between *APOE* gene polymorphisms and the risk of POAG was statistically significant in the genetic model of *ε4/ε4 versus ε3/ε3* (OR = 2.09, 95% CI = 1.12–3.88, p = 0.02; Figure 2). However, compared with the *ε3/ε3* genotype, no significant associations were observed in *ε2/ε2* (OR = 1.03, 95% CI = 0.40–2.69, p = 0.95; Figure 3A), *ε2/ε3* (OR = 0.87, 95% CI = 0.62–1.24, p = 0.44; Figure 3B), *ε2/ε4* (OR = 1.03, 95% CI = 0.67–1.57, p = 0.90; Figure 3C), and *ε3/ε4* (OR = 1.01, 95% CI = 0.72–1.41, p = 0.97; Figure 3D). There was no significant association between *APOE* gene polymorphisms and the risk of POAG in the allele *ε2 versus* allele *ε3* (OR = 0.99, 95% CI = 0.83–1.18, p = 0.91; Figure 4A) and the allele *ε4 versus* allele *ε3* (OR = 1.07, 95% CI = 0.81–1.42, p = 0.65; Figure 4B). The meta-analysis results of the association between the *APOE* gene and the risk of POAG are illustrated in Table 2.

Furthermore, subgroup analyses were conducted on ethnicity and subtypes of POAG (HTG, NTG). The association between the *APOE* gene and the risk of POAG was statistically significant in Asians in the genetic model of *ε4/ε4 versus ε3/ε3* (OR = 3.55, 95% CI = 1.06–11.87, p = 0.04; Figure 5) but not in Caucasians (OR = 1.65, 95% CI = 0.79–3.45, p = 0.19; Figure 5). No results showed a significant association between the *APOE* gene and POAG in other genetic models in Asians and Caucasians. Similarly, we did not find any correlation between *APOE* and HTG or NTG. The results of the subgroup analyses are illustrated in Table 2.

Potential publication bias: Funnel plots and Egger's test were applied to assess potential publication bias for *APOE*. The genetic models of *ε2/ε3* versus *ε3/ε3* (p = 0.293; Figure 6A), *ε2/ε4* versus *ε3/ε3* (p = 0.780; Figure 6B), *ε4/ε4* versus *ε3/ε3* (p = 0.560; Figure 6C), allele *ε2* versus allele *ε3* (p = 0.267; Figure 6D), and allele *ε4* versus allele *ε3* (p = 0.255; Figure

Table 1. Characteristics of studies included in this meta-analysis.

First author	Year	Ethnicity (country)	SS(case/control)	Genotypes distribution (case/control)									HWE
				ε2/ε2	*ε2/ε3*	*ε2/ε4*	*ε3/ε3*	*ε3/ε4*	*ε4/ε4*	*ε2*	*ε3*	*ε4*	*P*-value (control)
Huiping Yuan [26]	2007	Asian(China)	36/57	0/0	0/6	6/12	12/31	15/8	3/0	6/18	39/76	27/20	<0.001
Li Yun Jia [27]	2009	Asian(China)	176/200	2/1	25/29	5/4	112/136	29/28	3/2	34/35	280/329	38/36	0.964
Ching Yan Lam [28]	2006	Asian(China)	400/300	0/0	74/42	5/8	280/203	40/47	1/0	79/50	674/495	47/55	0.124
Fumihiko Mabuchi [29]	2005	Asian(Japan)	310/179	0/0	14/18	2/0	259/123	35/38	0/0	16/18	567/302	37/38	0.188
Yijun Hu [30]	2007	Asian(China)	142/77	1/0	11/11	4/0	95/52	28/14	3/0	17/11	229/129	38/14	0.576
A Jünemann [31]	2003	Caucasian (Germany)	96/32	0/0	18/3	1/6	51/14	26/9	0/0	19/9	146/40	27/15	0.027
E. Saglar [32]	2009	Caucasian(Turkey)	75/119	0/0	12/9	1/1	53/88	8/19	1/2	13/10	126/204	11/24	0.929
Madeleine Zetterberg [33]	2007	Caucasian(Estonia)	242/187	1/2	42/34	6/4	145/110	44/35	4/2	50/42	376/289	58/43	0.976
Al-Dabbagh [34]	2009	Caucasian(Saudi-Arabia)	60/130	0/0	0/0	0/0	50/119	7/11	3/0	0/0	107/249	13/11	NA
James C. Vickers [35]	2002	Caucasian (Tasmania)	142/51	6/2	8/9	7/2	78/30	42/6	1/2	27/15	208/75	51/12	0.328
S Lake [36]	2004	Caucasian (America)	155/349	1/3	16/37	10/13	91/208	31/81	6/7	28/56	229/534	53/108	0.472
Thomas Ressiniotis [37]	2004	Caucasian (England)	137/75	−/−	−/−	−/−	−/−	−/−	−/−	35/16	199/114	40/20	NA

SS: sample size. −/−: Ressiniotis et al. only provided the frequencies of APOE alleles, the frequencies of APOE genotypes could not be calculated. HWE: Hardy–Weinberg equilibrium; NA: not available.

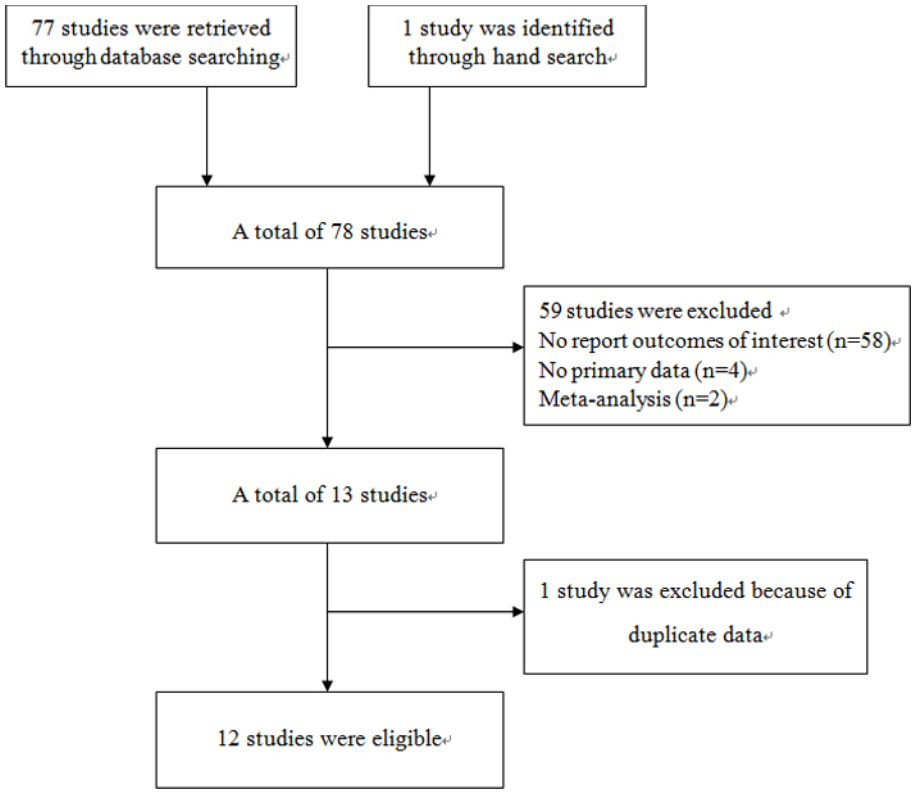

Figure 1. Flow diagram of the study selection process.

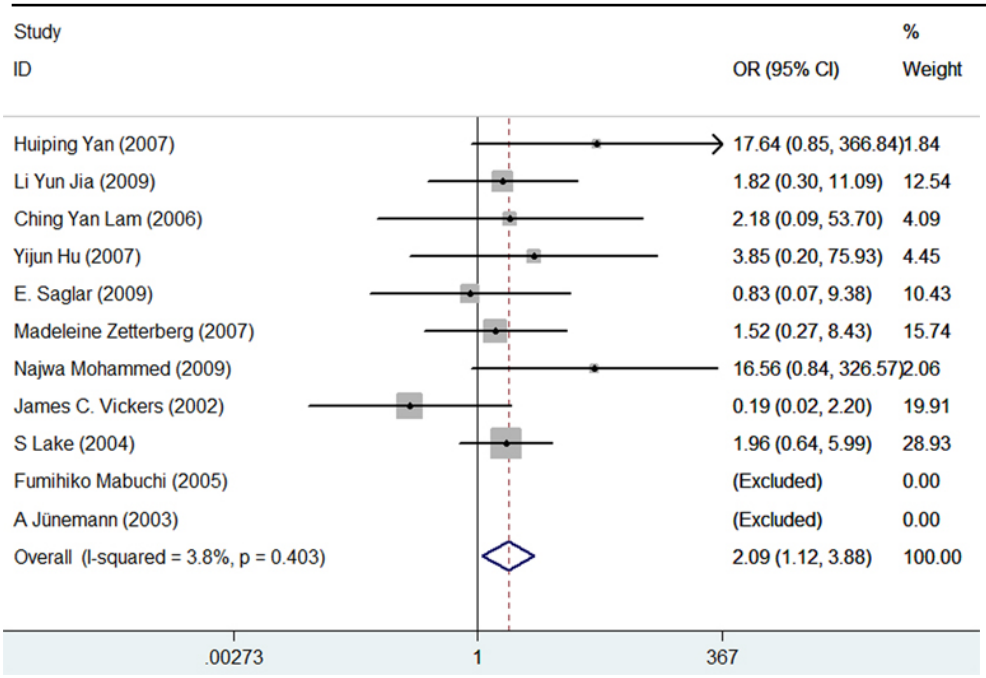

Figure 2. Forest plot for the genetic model of ε4/ε4 vs. ε3/ε3. Every study was represented by a square whose size was proportional to the weight of the study. Diamond indicated summary odds ratios (OR) with its corresponding the pseudo 95% confidence limits (95% CI).

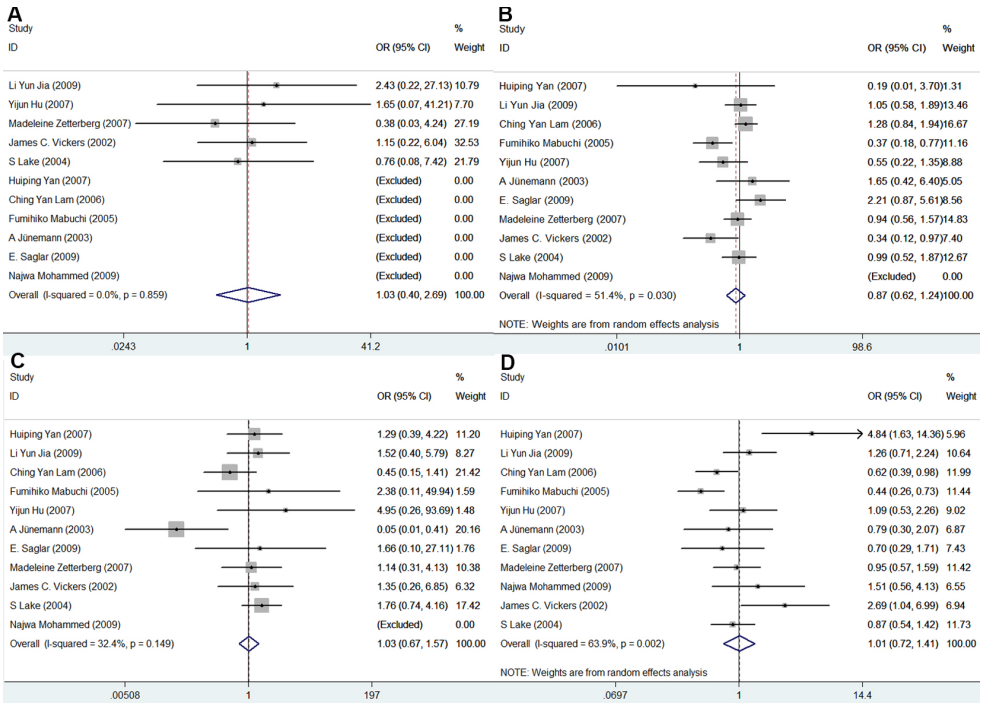

Figure 3. Forest plots of the association of AOPE polymorphisms with primary open-angle glaucoma. Every study was represented by a square whose size was proportional to the weight of the study. Diamond indicated summary odds ratios (OR) with its corresponding the pseudo 95% confidence limits (95% CI). **A**: Forest plot for APOE polymorphisms and POAG risk in the genetic model of ε2/ε2 vs. ε3/ε3. **B**: Forest plot for APOE polymorphisms and POAG risk in the genetic model of ε2/ε3 vs. ε3/ε3. **C**: Forest plot for APOE polymorphisms and POAG risk in the genetic model of ε2/ε4 vs. ε3/ε3. **D**: Forest plot for APOE polymorphisms and POAG risk in the genetic model of ε3/ε4 vs. ε3/ε3.

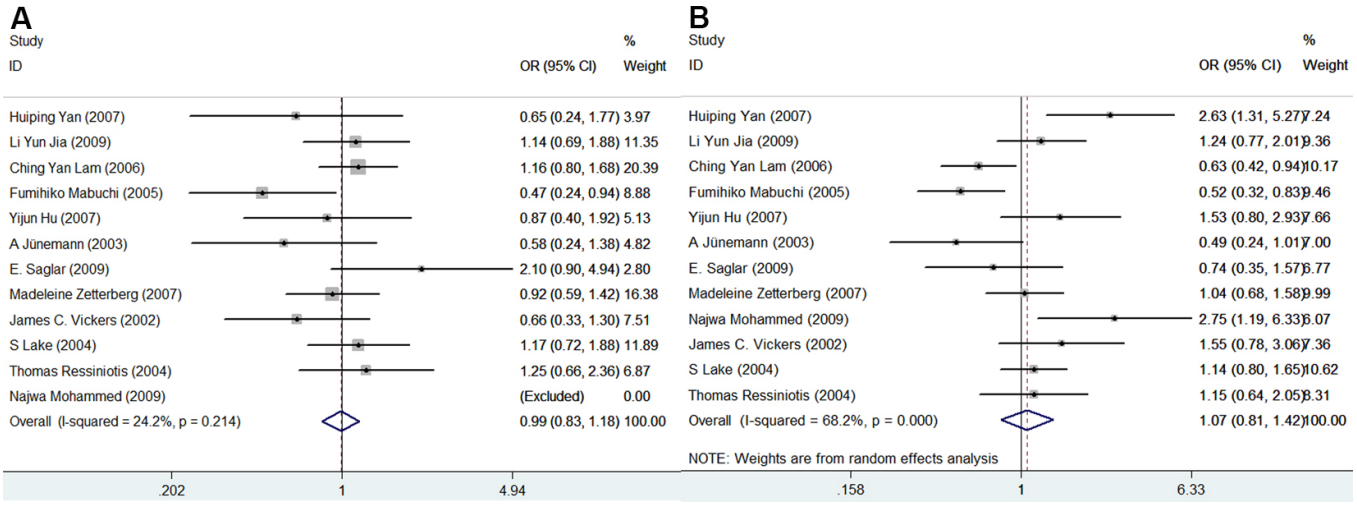

Figure 4. Forest plots for APOE polymorphisms and primary open-angle glaucoma risk in the genetic models of ε2 allele vs. ε3 allele and ε4 allele vs. ε3 allele. Every study was represented by a square whose size was proportional to the weight of the study. Diamond indicated summary odds ratios (OR) with its corresponding the pseudo 95% confidence limits (95% CI). **A**: Forest plot for APOE polymorphisms and POAG risk in the genetic model of ε2 allele vs. ε3 allele. **B**: Forest plot for APOE polymorphisms and POAG risk in the genetic model of ε4 allele vs. ε3 allele.

Table 2. Results of meta-analysis for *APOE* gene polymorphism and risk for primary open-angle glaucoma.

Category	ε2/ε2 versus ε3/ε3 OR (95%CI) P value (Model*)	ε2/ε3 versus ε3/ε3 OR (95%CI) P value (Model*)	ε2/ε4 versus ε3/ε3 OR (95%CI) P value (Model*)	ε3/ε4 versus ε3/ε3 OR (95%CI) P value (Model*)	ε4/ε4 versus ε3/ε3 OR (95%CI) P value (Model*)	ε2allele versus ε3 allele OR (95%CI) P value (Model*)	ε4 allele versus ε3 allele OR (95%CI) P value (Model*)	Reference
POAG:	1.03(0.40–2.69) 0.95F	0.87(0.62–1.24) 0.44R	1.03(0.67–1.57) 0.90F	1.01(0.72–1.41) 0.97R	2.09(1.12–3.88) **0.02**F	0.99(0.83–1.18) 0.91F	1.07(0.81–1.42) 0.65R	26–37
				Subgroup:				
Asian	2.10(0.30–14.63) 0.45F	0.74(0.42–1.29) 0.29R	1.09(0.58–2.05) 0.79F	1.00(0.54–1.87) 0.99R	3.55(1.06–11.87) **0.04**F	0.96(0.75–1.23) 0.77F	1.06(0.61–1.82) 0.84R	26–30
Caucasian	0.79(0.26–2.44) 0.68F	1.00(0.72–1.39) 0.99F	0.87(0.30–2.57) 0.80R	1.02(0.77–1.34) 0.90F	1.65(0.79–3.45) 0.19F	1.02(0.80–1.30) 0.90F	1.10(0.89–1.35) 0.37F	31–37
HTG	1.14(0.28–4.59) 0.85F	0.91(0.52–1.57) 0.73R	0.69(0.20–2.36) 0.55R	0.93(0.69–1.25) 0.63F	1.19(0.39–3.61) 0.76F	0.87(0.56–1.36) 0.53R	0.96(0.66–1.41) 0.84R	27, 28, 30, 31, 35
NTG	1.53(0.42–5.59) 0.52F	0.80(0.48–1.33) 0.38F	1.86(0.87–4.01) 0.11F	1.37(0.67–2.81) 0.40R	1.66(0.65–4.26) 0.29F	1.06(0.73–1.55) 0.77F	1.30(0.97–1.76) 0.08F	30, 35, 36

*If the results of the studies were heterogeneous, the random effects model was used for meta-analysis; otherwise, the fixed-effects model was used. F means fixed-effects model; R means random effects model. POAG: primary open-angle glaucoma. HTG: high tension glaucoma. NTG: normal tension glaucoma.

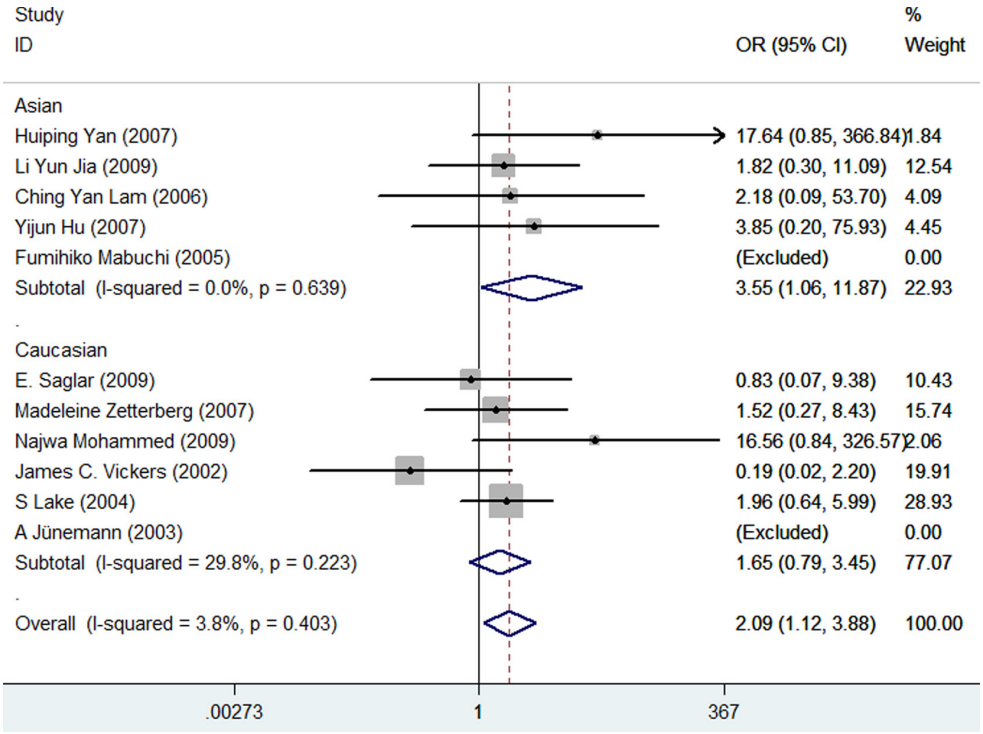

Figure 5. Subgroup analysis stratified by ethnicity in the genetic model of ε4/ε4 vs. ε3/ε3. Every study was represented by a square whose size was proportional to the weight of the study. Diamond indicated summary odds ratios (OR) with its corresponding the pseudo 95% confidence limits (95% CI).

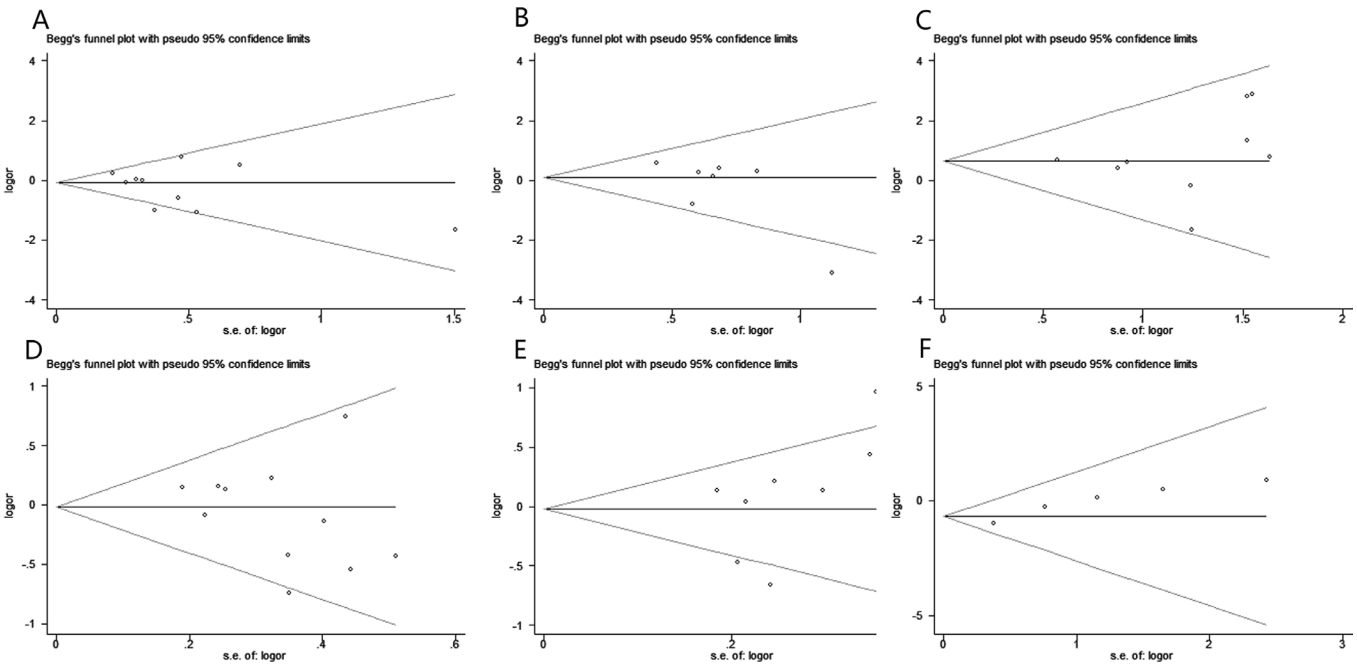

Figure 6. Begg's funnel plots of publication bias analyses. The horizontal line in the figure means the overall estimated log-transformed odds ratio (OR) and the two diagonal lines represent the pseudo 95% confidence limits of the effect estimate(95% CI). **A**: Funnel plot for the genetic model of ε2/ε3 vs. ε3/ε3. **B**: Funnel plot for the genetic model of ε2/ε4 vs. ε3/ε3. **C**: Funnel plot for the genetic model of ε4/ε4 vs. ε3/ε3. **D**: Funnel plot for the genetic model of ε2 allele vs. ε3 allele. **E**: Funnel plot for the genetic model of ε4 allele vs. ε3 allele. **F**: Funnel plot for the genetic model of ε2/ε2 vs. ε3/ε3.

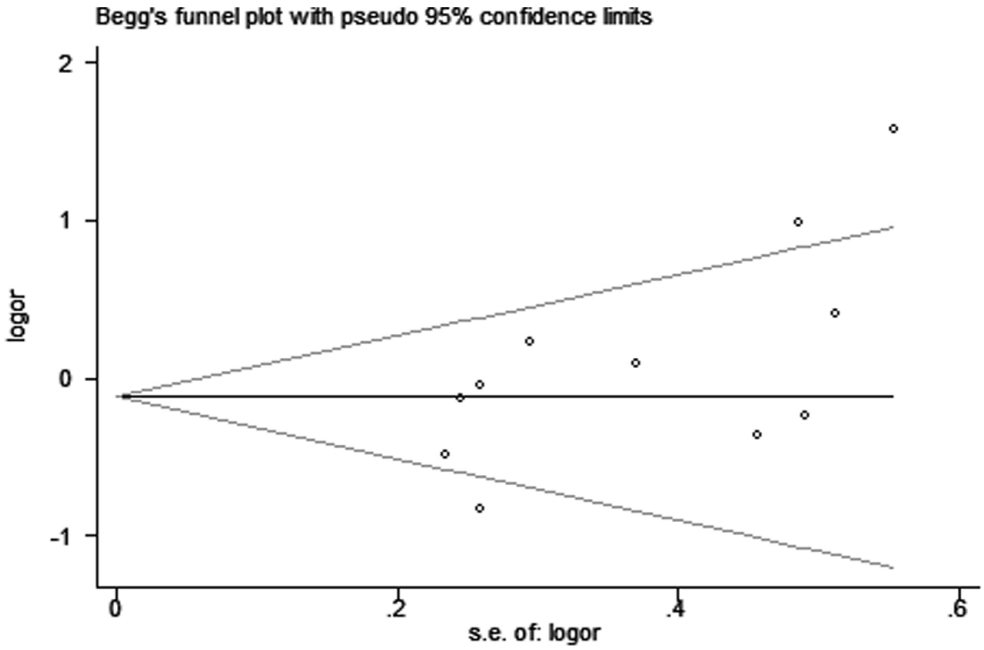

Figure 7. Begg's Funnel plot for the meta-analysis of the genetic model of ε3/ε4 vs. ε3/ε3. The horizontal line in the figure means the overall estimated log-transformed odds ratio (OR) and the two diagonal lines represent the pseudo 95% confidence limits of the effect estimate(95% CI).

6E) revealed no publication bias among the studies. However, publication bias was observed in the genetic models of *ε2/ε2* versus *ε3/ε3* (p = 0.008; Figure 6F), as well as *ε3/ε4* versus *ε3/ε3* (p = 0.034; Figure 7).

DISCUSSION

Genetic factors are major factors in the development of POAG. Previously, several studies investigated the association between *APOE* gene polymorphisms and POAG, but the results were controversial. Recently, two meta-analysis studies were performed, and both indicated no association between the *APOE* gene and the POAG risk. Song et al. [38] conducted a meta-analysis based on nine case-control studies to evaluate the association between the *APOE* gene *ε2/ε3/ε4* polymorphism and the risk of POAG. However, some issues must be addressed: (1) The study included two "eligible studies" that were published that may have used the same case series [28,39]. (2) The eligible studies of the meta-analysis included a study that evaluated the association between the *APOE* gene and patients who had POAG and AD [40]. However, since the *APOE ε4* allele is regarded as a major risk for AD, the frequencies of the *APOE* genotypes may be affected by AD in patients who also have POAG. These issues may imply that the results of this meta-analysis were not completely accurate. Wang et al. [41] performed a similar meta-analysis that had the same eligible studies as our study, but they evaluated only the genetic models of the allele *ε2 versus* allele *ε3*, allele *ε4 versus* allele *ε3*, *e2* carriers versus allele *ε3*, and *e4* carriers versus allele *ε3*, and ignored the functions of the genotypes of the *APOE* gene. Thus, we performed an updated meta-analysis to better ascertain the role of *APOE* gene polymorphisms in POAG pathogenesis.

Apolipoprotein E (ApoE) is one of the major apolipoproteins in the central nervous system. Compared with ApoE2 and ApoE3, neurons have a lower cholesterol uptake rate and a less efficient cholesterol efflux when lipids are bound to ApoE4. Expression of ApoE3, but not ApoE4, protects neurons against excitotoxin-induced neuronal damage and age-dependent neurodegeneration [42]. Individuals with *APOE ε4* have severe amyloid plaque, neurofibrillary tangle pathology, and increased mitochondrial damage compared to individuals with other *APOE* polymorphisms [43]. Previous studies have shown that the *ε4* allele has been linked to central nervous diseases, such as Parkinson disease, Alzheimer disease, and amyotrophic lateral sclerosis [44-46]. In fact, POAG can be considered a neurodegenerative disease as well [47]. In the retina, retinal ganglion cells and optic nerve axons are vulnerable to degeneration. ApoE proteins are synthesized by Müller cells, absorbed by retinal ganglion cells, and transported to the optic nerve, which may play an important role in retinal ganglion cell metabolism and neuronal survival [48]. Copin et al. reported that the *APOE* promoter gene polymorphism affected visual field loss and optic nerve damage [49]. Therefore, the pathogenic mechanisms of POAG may also be linked to the *ε4* allele.

Our study showed that the risk of development of POAG in *ε4/ε4* genotype carriers was 2.09 fold higher than

in individuals with the *ε3/ε3* genotype. However, there was no significant association between *APOE* gene polymorphisms and the risk of POAG in the allele *ε4 versus* allele *ε3*. Therefore, the *ε4/ε4* genotype of *APOE* is a possible genetic predisposition factor for POAG. To further investigate the association between the allele *ε4* and POAG risk, the following settings were used. Similar to other studies, we defined individuals who have the *ε2/ε2* and *ε2/ε3* genotypes as carriers of the *ε2* allele, and individuals with the *ε3/ε4* and *ε4/ε4* genotypes as carriers of the *ε4* allele; we chose the carriers of the *ε3/ε3* genotype as the reference group [50]. Although there was no direct evidence of any association between *APOE* gene polymorphisms and the risk of POAG in the carriers of *ε2* allele *versus ε3/ε3* (OR = 0.95, 95% CI = 0.76–1.17, p = 0.61) and the carriers of *ε4* allele *versus ε3/ε3* (OR = 1.07, 95% CI = 0.76–1.52, p = 0.69). Moreover, we investigated the association between the *APOE* gene and risk of POAG/NTG/HTG in the genetic model of *ε4* carrier versus non-*ε4* carrier. The results illustrated that there was no association between *APOE* gene polymorphisms and the risk of POAG in the genetic model of *ε4* carrier versus non-*ε4* carrier (OR = 1.05, 95% CI = 0.75–1.48, p = 0.77). Similarly, we did not find any correlation between *APOE* and HTG or NTG in the genetic model of *ε4* carrier versus non-*ε4* carrier (OR = 0.99, 95% CI = 0.62–1.61, p = 0.98; OR = 1.29, 95% CI = 0.92–1.81, p = 0.14, respectively).

Why was the risk for POAG associated with the *ε4/ε4* genotype but not with the *ε4* allele? There were several possible explanations for this discrepancy: (1) Compared with *ε2/ε4* and *ε3/ε4,* the *ε4/ε4* alleles encode only ApoE4. The homozygote *ε4* carriers do not have protection from ApoE2 and ApoE3 proteins. As a result, these carriers are susceptible to glaucoma. (2) Subjects with homozygote *ε4* may be more susceptible to POAG than those with only one *ε4* allele, which is supported by the study by Corder et al., who claimed that the effects of the *ε4* allele dose are associated with increased risk for AD [45]. Similarly, Schmechel et al. also noted that patients with two *ε4* alleles exhibited a distinct neuropathological phenotype compared with other patients [51].

The present meta-analysis suggested that the genotype *ε4/ε4* of *APOE* increases the risk of POAG in Asians but not in Caucasians, which may be related to differences in lifestyle, environmental factors, nutrition, and genetic factors. No significant differences were observed between the *APOE* gene and the risk of HTG and NTG, probably because of the small size of the samples and limited trials.

In our study, we detected heterogeneities in meta-analyses of *ε2/ε3 versus ε3/ε3, ε3/ε4 versus ε3/ε3,* and *ε4* allele *versus ε3* allele. The heterogeneities could be due to the sample sizes, diversity in study designs, inclusion criteria, and genotyping methods. Since the subjects came from different populations that perhaps have genetic heterogeneity, subgroup analyses were conducted on ethnicity. The results revealed no heterogeneity in the majority of the genetic models, except the models of *ε2/ε3* versus *ε3/ε3*, *ε3/ε4* versus *ε3/ε3*, and *ε4* allele *versus ε3* allele among Asians and the model of *ε2/ε3* versus *ε3/ε3* among Caucasians. The overall analysis involved two subtypes of POAG (NTG and HTG), which have possible differences in etiopathogenesis and genetic risks, and they could be another factor that causes heterogeneities.

Some limitations of our study should be considered. First, our meta-analysis included only studies with accessible full-text articles, in English or Chinese. Therefore, missing some otherwise eligible studies that were reported in other languages could lead to inevitable publication bias in the results. Second, due to the lack of detailed data in the primary articles, subgroup analysis was not conducted according to factors such as age and gender. Third, Asian and Caucasian populations possess a low frequency of the APOE *ε4* allele, especially the homozygote *ε4* [52,53]. In several included studies, neither the case nor control groups involved *ε2/ε2* or *ε4/ε4* genotypes. These studies were excluded when we performed analyses in the genetic models of *ε2/ε2 versus ε3/ε3* and *ε4/ε4 versus ε3/ε3*, which reduced the overall sample size. Our results indicated that the *ε4/ε4* genotype is associated with increased risk for POAG in Asians. With a small number of cases/controls carried homozygote *ε4*, more research that supports our results is needed. Last, the included studies lack data about potential gene–gene interactions. Since the roles of several genes in the pathogenesis of POAG have been established, further investigations should be performed in this direction.

In summary, the present meta-analysis suggested that *ε4/ε4* is associated with increased risk of POAG in Asian populations but not in Caucasian populations. Further studies are required to further clarify the associations between *APOE* polymorphisms and genetic predisposition for POAG.

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