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REVIEW

The relationship between apolipoprotein E ε2/ε3/ε4 polymorphisms and hypertension: a meta-analysis of six studies comprising 1812 cases and 1762 controls

Wenquan Niu[1,2,3,4,7], Yue Qi[5,7], Yuesheng Qian[6], Pingjin Gao[1,2,4] and Dingliang Zhu[1,2,3]

We performed a meta-analysis in an effort to systematically explore the association between apolipoprotein E (ApoE) ε2/ε3/ε4 polymorphisms and hypertension. We searched for case–control studies in English-language publications performed with human subjects using MEDLINE and included appropriate studies that had been published as of 6 May 2009. Fixed-effects models were used to pool data when between-study heterogeneity was absent, and random-effects models were used otherwise. Data and study quality were assessed in duplicate. Publication bias was assessed by calculating the fail-safe number. From six heterogeneous studies that included a total of 1812 patients with hypertension and 1762 controls, we found that the ApoE ε4 allele was significantly associated with hypertension using a random-effects model (odds ratio (OR)=1.79; 95% confidence interval (CI): 1.04 to 1.19; *P*=0.04). With regard to ApoE genotypes, we observed that the association with hypertension was more prominent when ApoE4/4 was compared with E3/3, with a nearly twofold increased risk identified for the ApoE4/4 genotype using a random-effects model (OR=1.97; 95% CI: 1.11 to 3.52; *P*=0.02). Furthermore, after restricting our analysis to Asian populations, the contrasts between the risk of hypertension among individuals possessing ApoE ε4 *vs.* ε3 and ApoE4/4 *vs.* ApoE3/3 were positively reinforced, with ORs of 1.97 (95% CI, 0.93 to 4.15; *P*=0.08) and 2.27 (95% CI, 1.03 to 4.98; *P*=0.04), respectively. The fail-safe number supported these significant associations at a significance level of 0.05. Taken together, our meta-analysis expands the data available regarding genetic risk factors for hypertension by illustrating that the presence of the ApoE ε4 allele is associated with an increased risk of developing hypertension and that it appears to be recessive. Of note, this effect was more pronounced in Asians.
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INTRODUCTION

Hypertension is a complex and heritable disorder. As collectively estimated from animal models, human twin studies and family studies, 30–50% of blood pressure variation is determined by heritable factors.[1–3] Single-nucleotide polymorphisms are considered the major source of genomic variation responsible for the phenotypic differences between individuals.[4] Mounting evidence indicates that patients with hypertension tend to have a high prevalence of associated dyslipidemias, such as elevated total cholesterol and triglyceride levels and reduced low-density lipoprotein cholesterol levels.[5,6] However, the genetic factors underlying these lipoprotein abnormalities remain to be established.

Among the potential candidate genes that may serve as modulators for circulating lipoproteins, several common genetic variants of apolipoprotein E (ApoE), such as ApoE ε2, ε3 and ε4 rank high on the list of single-nucleotide polymorphisms to study.[7–9] ApoE alleles do appear to have a role in hypertension. Several case–control studies have investigated the association between ApoE ε2/ε3/ε4 polymorphisms and hypertension, although these studies had low statistical power and their results were often not reproducible. To systematically address this issue, we performed a meta-analysis of all available case–control studies reported in the English language to explore the association between ApoE ε2/ε3/ε4 polymorphisms and hypertension among 1812 hypertension patients and 1762 healthy controls.

LITERATURE SEARCH

The PubMed search engine (http://ncbi.nlm.nih.gov/entrez/query) was used to search for electronic publications that were published as of 6 May 2009. The keywords used for the search were 'hypertension'

[1]State Key Laboratory of Medical Genomics, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [3]Sino-French Research Center for Life Science and Genomics, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [4]Shanghai Key Laboratory of Vascular Biology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [5]Department of Epidemiology, Capital Medical University Affiliated Beijing Anzhen Hospital, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Anzhenli, Beijing, China and [6]Department of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China
[7]These authors contributed equally to this work.
Correspondence: Dr D Zhu, State Key Laboratory of Medical Genomics, Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Ruijin Second Road 197, Shanghai 200025, China.
E-mail: zhudingliang@sibs.ac.cn
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and 'Apolipoprotein E or ApoE' combined with 'gene or variants or polymorphism or alleles', all of which were MeSH terms (Medical Subject Headings in the US National Library of Medicine). The 'related articles' option in MEDLINE, as well as reference lists of all retrieved studies, were checked to search for other relevant publications that were not initially identified. If there were multiple publications from the same study group, the most complete and recent results were used. Search results were limited to articles published in English and studies performed in human. We did not restrict on the basis of the country in which the study was performed. To avoid selection bias, no study was rejected because of poor quality scores.

INCLUSION/EXCLUSION CRITERIA

Case–control studies were included in this meta-analysis, regardless of sample size, if they made an effort to explore the association between ApoE ε2/ε3/ε4 polymorphisms and hypertension among unrelated subjects, if genotyping was performed using validated methods and if they provided sufficient information on genotype or allele frequencies to allow an estimation of relative risk and its corresponding confidence interval (CI). All odds ratios (ORs) were calculated using healthy normotensive subjects as the reference group. Hypertension was defined as systolic blood pressure exceeding 140 mm Hg, diastolic blood pressure (DBP) exceeding 90 mm Hg or treatment with an antihypertensive medication. Studies evaluating secondary hypertension or other types of monogenic hypertension were excluded.

DATA EXTRACTION

Two authors (W Niu and Y Qi) independently extracted the following information from each study: first author's last name, year of publication, ethnicity of the population studied, study design, number of subjects in each category, baseline information of the study population and the number of individuals in both the case and control groups with each different genotype tested. Information on Hardy–Weinberg equilibrium among the controls was collected or calculated if the genotype data were available. Following data extraction, discrepancies were adjudicated by discussion between the authors and a consensus was reached. All quantitative variables were expressed as mean ± s.d. Standard error (s.e.) was converted to s.d. using the formula s.d.=s.e.$\times n^{1/2}$, where n is equal to the number of subjects studied.

QUALITY SCORE ASSESSMENT

The study quality was assessed using a quality assessment score developed for genetic association studies by Thakkinstian *et al.*[10] Total scores ranged from 0 (worst) to 12 (best). The criteria used for the quality assessment of the genetic association between ApoE ε2/ε3/ε4 polymorphisms and hypertension is described in the Appendix Table.

STATISTICAL ANALYSIS

The meta-analysis was conducted using Review Manager software (version 5.0.19) (http://www.cc-ims.net/revman/download). Hardy–Weinberg equilibrium was assessed using the χ^2-test (SAS version 9.1.3, SAS Institute, Cary, NC, USA) in controls for studies without a track record. Comparisons between the ApoE ε2 or ε4 alleles *vs.* the ApoE ε3 allele among cases and controls were expressed in the form of ORs and 95% CIs. As for the genotype comparisons, ApoE2/4 was excluded from the analysis because of the opposite net effect between ApoE ε2 and ε4 alleles.[11] The genotype effects were estimated using the model-free approach, in which no assumptions about genetic models are required.

The presence of between-study heterogeneity was calculated using the χ^2-based Cochran's Q-statistic with statistical significance set at a level of 0.10, because this statistic has been proven to have poor power if there are few studies included in the analysis.[12,13] In addition, the I^2 statistic was documented for the percentage of observed between-study variability that was due to heterogeneity rather than chance. This statistic yields result ranging from 0 to 100% (I^2=0–25%, no heterogeneity; I^2=25–50%, moderate heterogeneity; I^2=50–75%, large heterogeneity; I^2=75–100%, extreme heterogeneity).[13] A fixed-effects model using the Mantel–Haenszel method was used in the absence of between-study heterogeneity, and a random-effects model using the DerSimonian–Laird method was used in all other cases. Theoretically, random-effects models are more conservative and have wider CIs than fixed-effects ones.

To examine specific subsets in these studies, separate analyses were undertaken. This was achieved by performing a sensitivity analysis, in which an individual study was removed each time to assess the influence of each study. Likewise, a cumulative analysis was performed according to the ascending date of publication to identify the influence of the first published study on the subsequent publications and the evolution of the combined estimates over time.[14]

Publication bias was assessed by the fail-safe number (N_{fs}) of each meta-analysis. If the N_{fs} for one polymorphism was smaller than the number of observed studies for that polymorphism, this was interpreted as meaning that the meta-analysis result of that particular genetic variant might have a significant publication bias. In this study, the N_{fs} significance was established at $P=0.05\times(N_{fs0.05}=(\sum Z/1.64)^2-k)$, where k is equal to the number of articles included in each meta-analysis.

STUDY CHARACTERISTICS

There were 151 published papers identified in the initial literature search. The second screening identified nine original papers, in which the principal hypothesis examined the involvement of ApoE ε2/ε3/ε4 polymorphisms in hypertension. One study was excluded for investigating another polymorphism in the ApoE promoter region,[15] and two for lack of necessary information regarding the cases' and controls' genotypes.[16,17] Thus, a total of six studies[18–23] that included a total of 1812 patients with hypertension and 1762 healthy controls were ultimately analyzed. The quality score of these studies ranged from 1 to 9 out of a maximal score of 12. The detailed characteristics of each study are summarized in Table 1.

For all studies, the genotype distributions of the ApoE ε2/ε3/ε4 polymorphisms satisfied Hardy–Weinberg equilibrium among the controls at a significance level of 0.05. The percentage of males included in the studies ranged from 38.7 to 87.0%. Except for one study without a clear definition of hypertension[19] and one including patients not taking any medications,[22] all studies included patients receiving antihypertensive medications. The frequencies of the ApoE ε4 allele ranged widely, from 2.38 to 13.79%, and the range of frequencies was even more striking for the ApoE ε2 allele (3.25 to 33.26%).

META-ANALYSIS RESULTS

Compared with the ApoE ε3 allele, the individual estimates of the ORs examining the association between a given allele and hypertension exhibited significant heterogeneity for the ε4 allele (I^2=89%, $P<0.00001$), but not for the ε2 allele (I^2=36%, P=0.17). Figures 1 and 2 show the associations between hypertension and the ε2 and ε4 alleles (as compared with the ε3 allele) for all studies, respectively. Except for the initial study that identified a significant association between the presence of the ApoE ε2 allele (*vs.* the ε3 allele) and hypertension (OR=1.76; 95% CI, 1.16 to 2.68), other studies failed to show this trend with ORs leftward approaching the unity. The

Table 1 The detailed information for all the studies included in this meta-analysis

Study	Subjects	Status	Quality score	Age*(years)	Case characteristics	Control characteristics	ε2 allele frequency (%)		ε3 allele frequency (%)		ε4 allele frequency (%)	
							HTs	NTs	HTs	NTs	HTs	NTs
Imazu *et al.*[18]	Japanese-American	Hypertension	7	Total: 40–79	n=315; male/female: 122/193; SBP⩾160 mm Hg or DBP⩾95 mm Hg or use of antihypertensive medications; without diabetes history or diagnosed diabetes.	n=617; male/female: 252/365; without diabetes history or diagnosed diabetes.	6.98	4.05	81.91	83.71	9.52	10.62
Yilmaz *et al.*[19]	Turkish	Mild-to-moderate hypertension	1	Cases: 47.96±15.94, controls: 46.72±10.11	n=88; patients with mild-to-moderate hypertension.	n=63	3.97	5.50	88.06	92.00	7.95	2.38
Li *et al.*[20]	Chinese	Essential hypertension	9	Cases: 63.81±11.19, controls: 57.93±12.95	n=94; male/female: 51/43; with a documented history; SBP>140 mm Hg or DBP>90 mm Hg or use of antihypertensive medications.	n=102; male/female: 57/45; matched with patients for age and BMI; with no systemic diseases.	6.38	8.82	80.85	83.82	12.77	7.35
Bhavani *et al.*[21]	Indian	Essential hypertension	9	Cases: 51.0±8.70, controls: 45.6±7.49	n=185; male/female: 161/24; hospital-based; with a history of hypertension or use of antihypertensive agents or SBP>140 mm Hg or DBP>90 mm Hg.	n=200; male/female: 104/96; randomly selected; with no systemic diseases.	2.70	3.25	85.14	90.75	12.16	5.75
Niu *et al.*[22]	Chinese	Essential hypertension	9	Cases: onset age <65, controls: age-matched	n=269; male/female: 153/116; age<65 years; SBP>140 mm Hg or DBP>90 mm Hg; without drug medications.	n=236; male/female: 131/105; matched for area, gender and age; without familial hypertension history and systemic diseases.	28.25	33.26	51.67	61.02	20.07	5.72
Fuzikawa *et al.*[23]	Brazilian	Prevalent hypertension	9	Total: 60–95	n=862; SBP>140 mm Hg or DBP>90 mm Hg or use of antihypertensive medications.	n=544	6.38	6.71	80.39	79.50	13.23	13.79

Abbreviations: DBP, diastolic blood pressure; HTs, hypertensives, NTs, normotensives; SBP, systolic blood pressure. *Age was expressed as the range or the mean ± s.d.

association between the ε4 allele (*vs.* the ε3 allele) and hypertension remained significant for all other studies except for the initial study[18] and another study[23] conducted in Brazilians. The findings were especially significant in a study conducted in Chinese individuals (OR=4.14, 95% CI, 2.63 to 6.52).[22]

The summary OR obtained using a fixed-effects model showed that ApoE ε2 allele carriers were 1.05 times more likely to develop hypertension than were individuals that did not possess that allele, although this effect failed to reach significance (95% CI, 0.88 to 1.25, P=0.59) (Figure 1). However, ApoE ε4 allele carriers had a 79% higher risk of hypertension compared with their ApoE ε3 allele-carrying counterparts, as identified by the pooled OR computed from the random-effects model (OR=1.79; 95% CI, 1.04 to 3.09; P=0.04) (Figure 2).

The overall ORs for the genotype associations between ApoE ε2/ε3/ε4 polymorphisms and hypertension were calculated as follows. Results from two Asian studies[20,21] could not be summarized because they did not include individuals with the ApoE2/2 genotype in either the case or control group. Except for the case of the ApoE3/4 allele (I^2=84%, $P<0.00001$), no significant inter-study heterogeneity was observed for any genotypes (I^2=0–17%, $P\geqslant0.30$). After assigning genotype E3/3 as a reference group, a significant association between genotype and hypertension was noticed exclusively for the E4/4 genotype (overall OR=1.97; 95% CI, 1.11 to 3.52; P=0.02) using a fixed-effects model (I^2=0%, P=0.43) (Figure 3). Therefore, except for the initial study that illustrated that the E4/4 genotype had a protective effect, others showed an increased risk of hypertension among E4/4 genotype carriers, although only one study reached statistical significance.[21] In light of the nonsignificant association observed between the ApoE3/4 genotype and hypertension (OR=1.09; 95% CI, 0.91 to 1.31; P=0.36) (data not shown), it appears that the ApoE ε4 allele is recessive.

SENSITIVITY ANALYSES

To investigate the influence of individual data sets on the pooled ORs, we deleted a single study involved in the meta-analysis each time. As shown in Table 2, no individual study had an undue influence on the summary ORs for comparing ε2 *vs.* ε3 or E2/2 and E2/3 *vs.* E3/3 with regard to the association of each allele and hypertension. However, with regard to the comparison of the ε4 allele *vs.* the ε3 allele and the risk of hypertension, the results of the analysis were quite different when the initial[18] and final study[23] were excluded from the analysis. When each of these studies was excluded, the ORs obtained were 2.13 (95% CI, 1.05 to 4.33) and 2.12 (95% CI, 1.07 to 4.20), respectively, with both reaching statistical significance. A study conducted in Indians[21] showed that the pooled ORs for examining the association between hypertension and the E3/4 and E4/4 genotypes (*vs.* the E3/3 genotype) were robust, but attenuated the pooled action. In addition, a study performed in Chinese individuals[22] had a striking influence on the pooled OR examining the association between the E3/4 allele *vs.* the E3/3 allele and hypertension (OR=0.94; 95% CI, 0.78 to 1.15) (Table 4).

Among the six included studies, except for the one performed in Turkish individuals[19] and another performed in Brazilians,[23] the other studies were performed among Asian individuals, including one study that was performed in Japanese-Americans.[18] After restricting our analysis to individuals of the Asian race,[18,20,22,24] we found that the associations between hypertension and the ε4 *vs.* ε3 allele (OR=1.97; 95% CI, 0.93 to 4.15; P=0.08) as well as the E4/4 allele *vs.* E3/3 allele (OR=2.27; 95% CI, 1.03 to 4.98; P=0.04) were stronger. They were found to be even stronger after the study conducted in

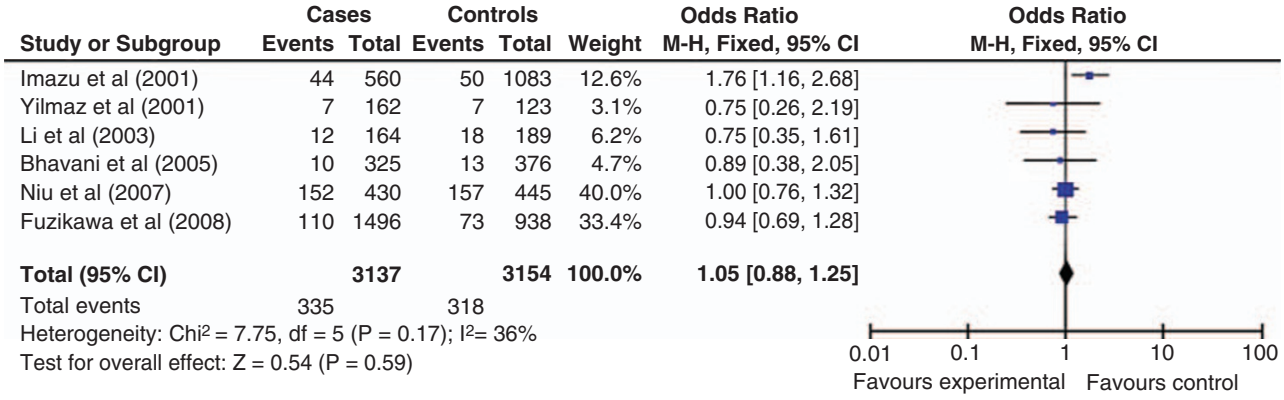

Figure 1 The association between hypertension and the ApoE ε2 allele *vs.* the ε3 allele, obtained from a fixed-effects model.

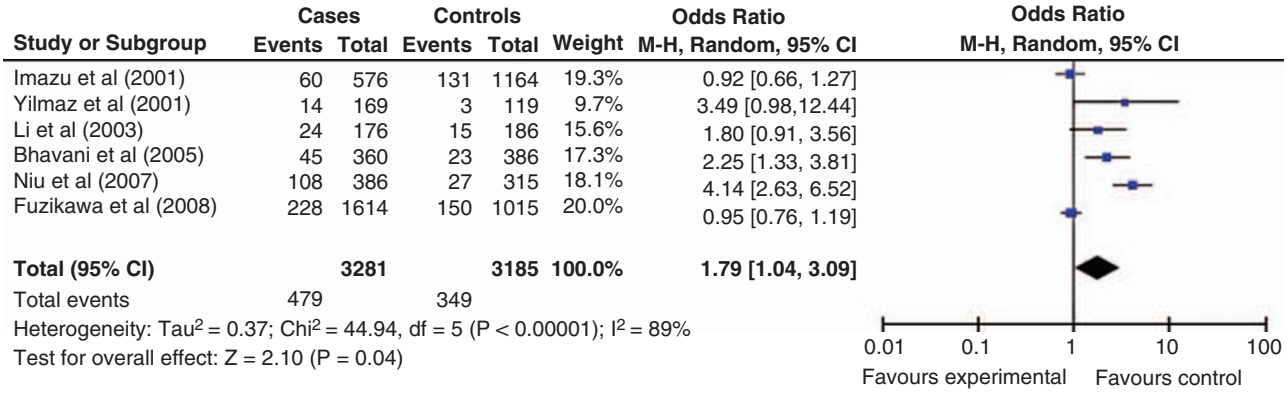

Figure 2 The association between hypertension and the ApoE ε4 allele *vs.* the ε3 allele, obtained from a random-effects model.

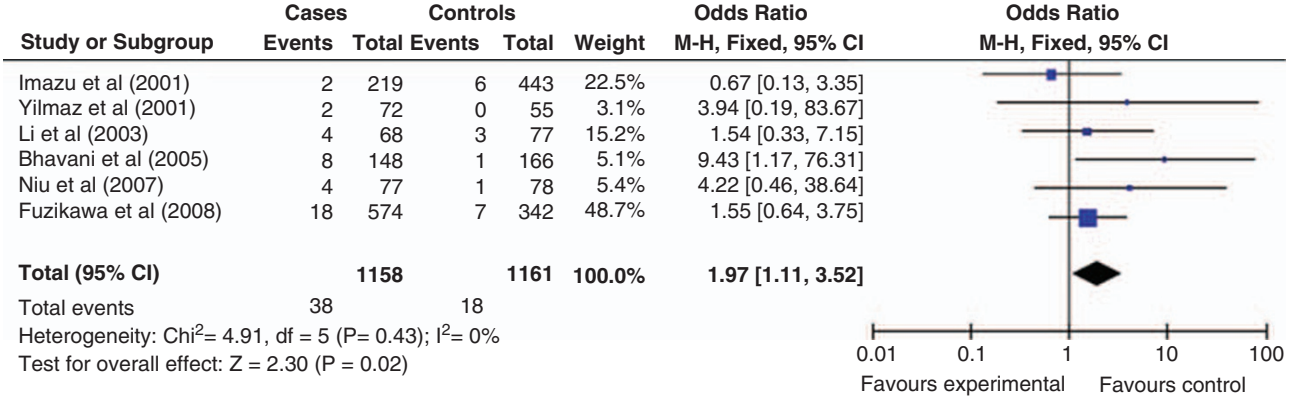

Figure 3 The association between hypertension and the ApoE4/4 genotype *vs.* the E3/3 genotype, obtained from a fixed-effects model.

Japanese-Americans[18] was removed, with respective ORs of 2.67 (95% CI, 1.61 to 4.43; *P*=0.0001) and 3.67 (95% CI, 1.32 to 10.19; *P*=0.01) (data not shown).

CUMULATIVE ANALYSES

To identify the influence of the initial study on the subsequent publications, we performed a cumulative meta-analysis (Table 2). The summary ORs examining the association of ε2 *vs.* ε3 and hypertension were statistically significant in only the first two studies,[18,19] whereas those examining the association of ε4 *vs.* ε3 and hypertension changed significantly over time, especially in the last two studies.[22,23] When genotypes were considered, the cumulative ORs did not change much over time when the associations between hypertension E2/2 and E2/3 *vs.* E3/3 were examined (Table 3). However, the cumulative ORs failed to indicate significance after the first publication until the last two studies[22,23] when the associations between hypertension and E4/4 and E3/4 *vs.* E3/3 were examined (Table 4).

Table 2 Sensitivity and cumulative analyses for the contrasts of ε2 and ε4 alleles *vs.* ε3 allele

	Sensitivity analysis		*Cumulative analysis*	
Study	*ε2 vs. ε3*	*ε4 vs. ε3*	*ε2 vs. ε3*	*ε4 vs. ε3*
Imazu *et al.*[18]	0.95 (0.78, 1.14)	2.13 (1.05, 4.33)	1.76 (1.16, 2.68)	0.92 (0.66, 1.27)
Yilmaz *et al.*[19]	1.06 (0.89, 1.26)	1.67 (0.94, 2.95)	1.56 (1.06, 2.31)	1.55 (0.43, 5.58)
Li *et al.*[20]	1.07 (0.89, 1.28)	1.80 (0.97, 3.35)	1.33 (0.94, 1.88)	1.50 (0.74, 3.04)
Bhavani *et al.*[21]	1.06 (0.88, 1.26)	1.72 (0.93, 3.19)	1.25 (0.91, 1.73)	1.68 (0.93, 3.06)
Niu *et al.*[22]	1.08 (0.86, 1.35)	1.38 (0.92, 2.07)	1.10 (0.89, 1.36)	2.12 (1.07, 4.20)
Fuzikawa *et al.*[23]	1.10 (0.89, 1.36)	2.12 (1.07, 4.20)	1.05 (0.88, 1.25)	1.79 (1.04, 3.09)

Abbreviations: CI, confidence interval; OR, odds ratio.
Data are expressed as OR (95% CI).

Table 3 Sensitivity and cumulative analyses for the contrasts of E2/2 and E2/3 genotypes *vs.* E3/3 genotype

	Sensitivity analysis		*Cumulative analysis*	
Study	*E2/2 vs. E3/3*	*E2/3 vs. E3/3*	*E2/2 vs. E3/3*	*E2/3 vs. E3/3*
Imazu *et al.*[18]	0.93 (0.43, 2.02)	0.80 (0.63, 1.02)	3.02 (0.50, 18.21)	1.50 (0.92, 2.44)
Yilmaz *et al.*[19]	1.09 (0.53, 2.23)	0.90 (0.72, 1.12)	2.91 (0.60, 14.05)	1.45 (0.92, 2.30)
Li *et al.*[20]	1.12 (0.55, 2.26)	0.92 (0.74, 1.15)	2.91 (0.60, 14.05)	1.24 (0.83, 1.85)
Bhavani *et al.*[21]	1.12 (0.55, 2.26)	0.92 (0.73, 1.15)	2.91 (0.60, 14.05)	1.13 (0.78, 1.63)
Niu *et al.*[22]	2.61 (0.62, 10.94)	0.98 (0.76, 1.26)	1.09 (0.53, 2.24)	0.93 (0.70, 1.23)
Fuzikawa *et al.*[23]	1.09 (0.53, 2.24)	0.93 (0.70, 1.23)	1.12 (0.55, 2.26)	0.91 (0.73, 1.12)

Abbreviations: CI, confidence interval; OR, odds ratio.
Data are expressed as OR (95% CI).

Table 4 Sensitivity and cumulative analyses for the contrasts of E4/4 and E3/4 genotypes *vs.* E3/3 genotype

	Sensitivity analysis		*Cumulative analysis*	
Study	*E4/4 vs. E3/3*	*E3/4 vs. E3/3*	*E4/4 vs. E3/3*	*E3/4 vs. E3/3*
Imazu *et al.*[18]	2.35 (1.23, 4.49)	2.74 (1.83, 4.09)	0.67 (0.13, 3.35)	0.87 (0.60, 1.26)
Yilmaz *et al.*[19]	1.91 (1.06, 3.44)	1.44 (1.11, 1.88)	1.07 (0.30, 3.86)	0.95 (0.67, 1.36)
Li *et al.*[20]	2.05 (1.10, 3.83)	1.43 (1.09, 1.88)	1.24 (0.47, 3.31)	1.07 (0.77, 1.48)
Bhavani *et al.*[21]	1.57 (0.85, 2.92)	1.05 (0.86, 1.28)	2.15 (0.95, 4.87)	1.16 (0.87, 1.55)
Niu *et al.*[22]	1.84 (1.01, 3.36)	0.94 (0.78, 1.15)	2.37 (1.11, 5.07)	1.49 (1.15, 1.93)
Fuzikawa *et al.*[23]	2.37 (1.11, 5.07)	1.49 (1.15, 1.93)	1.97 (1.11, 3.52)	1.09 (0.91, 1.31)

Abbreviations: CI, confidence interval; OR, odds ratio.
Data are expressed as OR (95% CI).

PUBLICATION BIAS

To assess publication bias, we calculated the fail-safe number (N_{fs}) at a significance level of 0.05 for each comparison. The $N_{fs0.05}$ values for the comparison of ε4 *vs.* ε3 ($N_{fs0.05}$=65), E4/4 ($N_{fs0.05}$=9) and E3/4 ($N_{fs0.05}$=45) *vs.* E3/3 were greater than the number of studies included in the meta-analysis.

DISCUSSION

To the authors' knowledge, this is the first meta-analysis investigating the association between ApoE ε2/ε3/ε4 polymorphisms and hypertension. Although some statistical bias could not be eliminated and there was a slight indication of significant between-study heterogeneity, this meta-analysis suggests that the ApoE ε4 allele appears be associated with an increased risk of hypertension and also appears to be recessive. We found that this phenomenon was more prominent among ApoE4/4 genotype carriers, with a nearly twofold increased risk of hypertension observed. Notably, this effect was even more pronounced in Asians.

The presence of ApoE polymorphisms, first described by Utermann *et al.*[25] has inspired widespread interest in the genetic associations between these single-nucleotide polymorphisms and a series of complex diseases, such as Alzheimer's disease,[24] macular degeneration,[26] stroke,[27,28] hypertension[22] and several others. In addition, several studies have provided evidence that ApoE was functional. Structural defects in ApoE might result in an impaired interaction between ApoE-containing lipoproteins and their receptors and induce the development of atherogenic dyslipidemias and premature cardiovascular disease.[29] In addition, ApoE knockout mice exhibited hypertension and endothelial dysfunction.[30] Although much has been elucidated about the genetic and biological implications of ApoE single-nucleotide polymorphisms, the exact role of specific polymorphisms within this gene remains elusive.

It has been estimated that ApoE polymorphisms may account for 2 to 11% of the total variance present in the serum or plasma cholesterol levels of apparently healthy White individuals.[31] Previously, we,[22] as well as another research group,[21] consistently found that plasma total cholesterol and low-density lipoprotein cholesterol levels tended to be higher among individuals possessing the ε4 allele as compared with their ε3-possessing counterparts. As the ε4 allele lacks a supradyl group, it is thought that under oxidative conditions, ε4 lipoproteins are more easily cleared by scavenger receptors, as compared with ε3 lipoproteins.[32] Thus, on the basis of the results of this meta-analysis, it is reasonable to hypothesize that, if ApoE is implicated in hypertension, the ε4 allele is associated with hypertension, in part, by modulating lipoprotein levels. As not all studies have linked ApoE ε2/ε3/ε4 polymorphisms to lipoprotein profiles, it remains unknown whether the association between ApoE alleles and plasma lipoprotein levels directly reflects the involvement of the ApoE protein in lipoprotein metabolism, and the mechanism underlying the development of hypertension in these individuals thus requires additional analysis.

Although the sample size of about 3600 subjects in this meta-analysis is not small, it may not be large enough to detect genes that contribute to hypertension-related phenotypes, such as hyperlipidemia, by small effects. In view of the finding that the fail-safe numbers (at a significance level of 0.05) were greater than the number of reports included that examined the association between hypertension and the ε4 allele *vs.* ε3 and the E4/4 genotype *vs.* the E3/3 genotype, it seems unlikely that the significance of these findings are due to chance. In addition, we calculated the minimal sample size required to examine the association between the presence of ε4 *vs.* ε3 and hypertension (n=2812, including 1406 cases and 1406 controls) and the presence of E4/4 *vs.* E3/3 and hypertension (n=2826, including 1413 cases and 141 controls) under the premise of 80% power (α=0.05). The present sample size of 3574 (1812 cases and 1762 controls) was smaller than the combined sample size required to have enough power to detect differences between the aforementioned groups. However, the wide CIs generated by these significant associations provide an indication of the insufficient study power of this meta-analysis. Thus, the jury must remain out on this topic until more studies confirm or refute our results.

The present meta-analysis should be interpreted within the context of its limitations. First, this meta-analysis only focused on papers published in the English language. Second, because of the case–control design of all included studies, this meta-analysis inevitably suffers from the weaknesses of this type of study, that is, the inability to prove the existence of a causality relationship. Third, owing to the relatively small number of the eligible studies, we were unable to perform subgroup analyses by ethnicity, which might confound our results, especially when genetic heterogeneity for ApoE ε2/ε3/ε4 polymorphisms among different ethnicities exists. Fourth, we could not retrieve information regarding various confounding factors, such as smoking and salt consumption, which are considered modulators of the development of hypertension, from the original publications. Last but not least, in this study, we examined only the association between ApoE ε2/ε3/ε4 polymorphisms and hypertension. We did not evaluate other polymorphisms in ApoE or other targeted genes that might be associated with hypertension, such as the low-density lipoprotein receptor gene. It is possible that the potential role of ApoE ε2/ε3/ε4 polymorphisms is diluted or masked by gene–gene or gene–environment interactions, such as polymorphisms in other genes, and hypertension triggers, such as smoking and excess salt consumption.

In conclusion, our meta-analysis expands the currently available data on hypertension by showing that the presence of the ApoE ε4 allele is associated with an increased risk of hypertension. Furthermore, we found that this trait is likely to be recessive and that the effect of the ApoE ε4 allele is more pronounced in Asians. Additional cross-sectional or longitudinal studies examining genotype–phenotype relationships and gene–gene or gene–environment interactions, as well as studies seeking to provide biological or clinical validations of our findings, are warranted to comprehensively address the present results.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

Criteria for quality assessment of genetic association of ApoE ε2/ε3/ε4 polymorphism with hypertension

Criteria	*Quality score*
Representativeness of cases	
A. Consecutive/randomly selected from case population with clearly defined random frame	2
B. Consecutive/randomly selected from case population without clearly defined random frame or with extensive inclusion criteria	1
C. Method of selection not described	0
Representativeness of controls	
D. Controls were consecutive/randomly drawn from the same area (ward/community) as cases with the same criteria	2
E. Controls were consecutive/randomly drawn from a different area than cases	1
F. Not described	0
Ascertainment of hypertension cases	
G. Clearly described objective criteria for diagnosis of hypertension	1
H. Not described	0
Ascertainment of controls	
I. Clinical examinations were performed on controls to prove that controls did not have hypertension	2
J. Article merely stated that controls were subjects who did not have hypertension; no proof provided	1
K. Not described	0
Ascertainment of genotyping examination	
L. Genotyping done under "blind" conditions	1
M. Unblended or not mentioned	0
Test for Hardy–Weinberg equilibrium	
N. Hardy–Weinberg equilibrium in control group	2
O. Hardy–Weinberg disequilibrium in control group	1
P. Hardy–Weinberg equilibrium not checked	0
Association assessment	
Q. Assessed association between genotypes and hypertension with appropriate statistic and adjusting confounders	2
R. Assessed association between genotypes and hypertension with appropriate statistic without adjusting confounders	1
S. Inappropriate statistic used	0