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Association between Apolipoprotein E polymorphism and myocardial infarction risk: A systematic review and meta-analysis

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ABSTRACT

Published data regarding the association between *Apolipoprotein E* (*ApoE*) genetic variation and myocardial infarction (MI) risk were not always consistent. Therefore, the current meta-analysis was conducted to derive a more precise estimation of the association between ApoE polymorphism and MI risk. PubMed and Web of Science were searched to identify relevant studies. Summary odds ratio (ORs) and 95% confidence intervals (CIs) were calculated using random-effect or fixed-effect models based on the heterogeneity of included studies. All the tests were performed using Stata 11.0. A total of 22 eligible studies were identified in this meta-analysis. The results show that *ApoE* ε2 and ε4 alleles were associated with MI risk. The study suggests that there is close association between *ApoE* polymorphism and MI risk. It shows that *ApoE* ε2 allele is a protective factor of MI, while ε4 allele is a risk factor of MI, especially in Caucasian and Asian population. Nevertheless, well-designed, unbiased and larger sample size studies are required to confirm the results.

1. Introduction

Myocardial infarction (MI) is a complex syndrome affected by multiple predisposing genetic and environmental factors [1]. The association between *ApoE* polymorphisms and MI has drawn a lot of attention. ApoE is a multifunctional protein which plays a critical role in the metabolism of triglycerides and cholesterol [2,3], and the corresponding gene is considered as a excellent candidate to investigate the etiology of MI [4]. The gene is located at 19q13.2 and possesses three common alleles (ε2, ε3, ε4) and forms six genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4) [5]. As the previous studies, the *ApoE* polymorphisms were found to affect ApoE transcription and the levels of cholesterol and triglyceride [6,7], which was the main underlying risk factor of MI. However, the results of the earlier studies were inconsistent. Therefore, a system review and meta-analysis by collecting and sorting the previously published studies was conducted.

2. Materials and methods

2.1. Identification and eligibility of relevant studies

The online medical databases PubMed and Web of Science were used, using the search term "ApoE/Apolipoprotein E", "polymorphism/genetic variation" and "myocardial infarction/MI". The last retrieval was conducted in January 2015. The literatures were limited to papers in English. In addition, studies were identified by manual search of the references listed in the retrieved studies. The inclusion criteria were listed as follows: (1) case–control studies with either a population-based or a hospital-based design; (2) studies evaluated association between the *ApoE* polymorphisms and cancer risk; (3) present sufficient data to calculate an odds ratio (OR) with 95% confidence interval (CI); (4) not republished data. Moreover, the studies without raw data or those that were case-only studies, case reports, editorials and review articles (including meta-analyses) were eliminated.

2.2. Data extraction

The following detail information were extracted from each study enrolled in this study by two investigators (YLW and LZ) independently: the first author's last name, year of publication, country of subjects, ethnicity, the source of controls, genotyping method, matching numbers of genotyped cases and controls and

Abbreviations: ApoE, Apolipoprotein E; MI, myocardial infarction; OR, odds ratio; CIs, confidence intervals; HWE, Hardy–Weinberg equilibrium

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P for Hardy–Weinberg equilibrium (HWE). Furthermore, the disagreements were discussed among all authors and resolved with consensus.

2.3. Statistical analysis

The association of the *ApoE* polymorphism and risk of myocardial infarction was estimated by calculating the pooled ORs and 95%CI. The pooled ORs were estimated for seven genetic models (ε2/ε2 vs. ε3/ε3, ε2/ε3 vs. ε3/ε3, ε2/ε4 vs. ε3/ε3, ε3/ε4 vs. ε3/ε3, ε4/ε4 vs. ε3/ε3, ε2 allele vs. ε3 allele and ε4 allele vs. ε3 allele). Stratified analyses were performed by ethnicity ('other ethnicity' group was defined as those ethnicities that contained only one study). Heterogeneity across the studies was evaluated by using the Chi-square test based *Q*-statistic test [8], and it was considered significant when $P_{\text{heterogeneity}}(P_h) < 0.05$. The data were combined using random-effects (the DerSimonian and Laird method) in the presence of heterogeneity ($P < 0.05$ or $I^2 > 50\%$) and fixed-effects (the Mantel–Haenszel method) models were used in absence of heterogeneity ($P > 0.05$ or $I^2 < 50\%$) [9]. Furthermore, the sensitivity analysis was used to assess the stability of results, and publication bias was analyzed by Begg's funnel plot and Egger's regression test

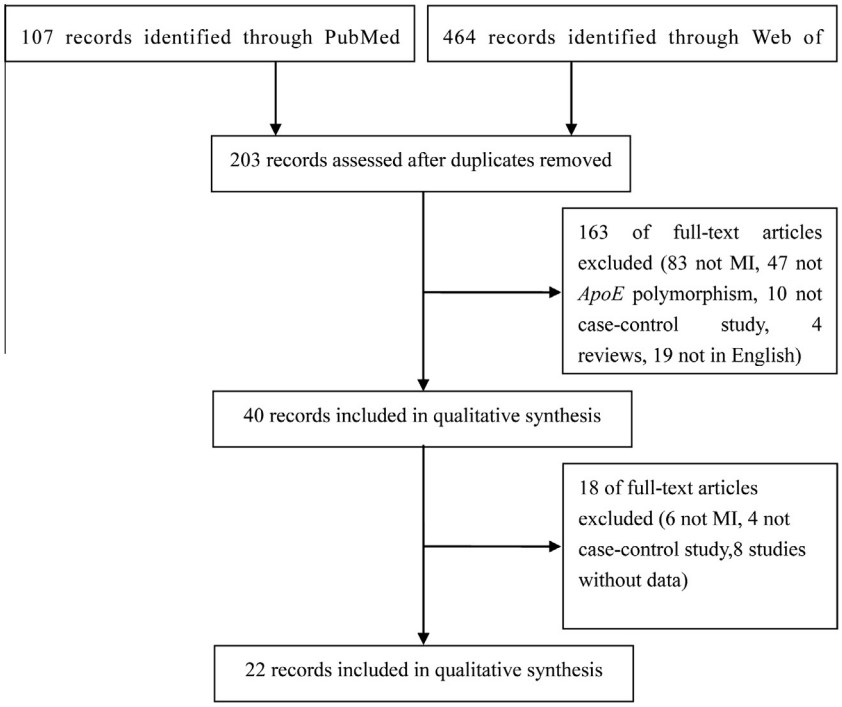

Fig. 1. Flow diagram of the study selection process.

Table 1
The characteristics of the enrolled studies in this meta-analysis.

First author	Year	Country	Ethnicity	Source of control	Genotyping method	Sample size (cases/controls)	HWE
Tanguturi	2013	India	Asian	PB	PCR-RFLP	202/210	0.097
Anand	2009	Mixed	Mixed	Mixed	IlluminaGoldenGate technology	4017/4017	0.091
Al-Bustan	2009	Kuwaiti	Asian	HB	PCR-RFLP	88/122	<0.050
Koch	2008	Germany	Caucasian	PB	TaqMan	3657/1211	0.558
Ranjith	2004	Indian	African	PB	PCR-RFLP	195/300	<0.050
Keavney	2004	UK	Caucasian	PB	PCR-RFLP	4685/3460	–
Keavney	2003	UK	Caucasian	PB	PCR-RFLP	4484/5757	0.463
Mamotte	2003	Australia	Caucasian	PB	PCR-RFLP	359/639	0.732
Wang	2001	Xinjiang	Asian	PB	PCR-RFLP	54/71	0.479
Raslova	2001	Bratislava	Caucasian	PB	PCR-RFLP	71/71	0.183
Batalla	2000	Asturias	Caucasian	PB	PCR-RFLP	220/200	0.776
Joven	1998	Spanish	Caucasian	PB	PCR-RFLP	250/250	0.109
Luc	1994	Belfast	Caucasian	PB	NA	183/176	0.405
Luc	1994	Lille	Caucasian	PB	NA	64/150	0.932
Luc	1994	Strasbourg	Caucasian	PB	NA	187/172	0.35
Luc	1994	Toulouse	Caucasian	PB	NA	140/182	0.698
Lenzen	1986	NA	Caucasian	PB	NA	570/624	0.081
Kolovou	2002	Greek	Caucasian	PB	PCR-RFLP	124/240	0.552
Kumar	2003	North India	Asian	PB	PCR-RFLP	35/45	<0.050
Baum	2006	Hong Kong	Asian	HB	PCR-RFLP	234/336	0.659
Nakai	1998	Japan	Asian	PB	PCR-RFLP	254/422	0.175
Hergenc	1995	Turkish	Caucasian	PB	PCR-RFLP	50/60	0.117
Utermann	1984	Germany	Caucasian	PB	NA	523/1031	<0.050

NA: not available; PB: population based; HB: hospital based; PCR-RFLP: restriction fragment length polymorphism; HWE: Hardy–Weinberg equilibrium. –: the data of the study are not enough.

[10]. Additionally, HWE was used to assess the genotype frequencies of the polymorphism by the chi-square test. All statistical tests were performed with STATA 11.0 and all the *P* values were two-sided.

3. Results

3.1. Characteristics of studies

Based on the search strategy, 571 potentially eligible studies were identified in the initial search. Among these, 22 studies were enrolled in this meta-analysis based on the inclusion criteria [11–32] (Fig. 1). The study by Luc et al. [30] investigated in four countries and was divided into four studies. The main characteristics of the enrolled 22 studies are summarized in Table 1.

3.2. Quantitative synthesis

In the pooled analysis, significant association was observed between *ApoE* polymorphism and risk of myocardial infarction. The main results were presented in Table 2, and the result of ε2/ε3 vs. ε3/ε3 was also shown in Fig. 2.

Additionally, the subgroup analysis by ethnicity was also conducted, and significant associations with myocardial infarction were observed in Caucasian (Fig.3) and Asian population. The main results were presented in Table 2.

3.3. Sensitivity analysis

To assess the stability of the results and assess the source of the heterogeneity, the sensitivity analysis was performed by omitting individual eligible study to reflect the influence of the individual data on the summary ORs. The pooled ORs were not altered for all comparison models. Among all the enrolled studies, four studies did not follow HWE, the corresponding summary ORs were not materially altered with or without these studies. Therefore, the results of current study were statistically robust. The result of ε2/ε2 vs. ε3/ε3 was shown in Fig. 4.

3.4. Heterogeneity analysis

There was significant between-study heterogeneity in ε2/ε2 vs. ε3/ε3 ($P = 0.001$, $I^2 = 63.4$), ε2/ε3 vs. ε3/ε3 ($P = 0.005$, $I^2 = 48.3$), ε3/ε4 vs. ε3/ε3 ($P = 0.000$, $I^2 = 58.0$), ε2 allele vs. ε3 allele ($P = 0.000$, $I^2 = 64.3$) and ε4 allele vs. ε3 allele ($P = 0.000$, $I^2 = 65.5$). In contract, no significant heterogeneity was observed in other two genetic models (ε2/ε4 vs. ε3/ε3: $P = 0.750$, $I^2 = 0.0$; ε4/ε4 vs. ε3/ε3: $P = 0.194$, $I^2 = 20.6$). In order to detect the sources of heterogeneity, the sensitivity analysis was performed based on HWE and ethnicity. However, the heterogeneity was not materially altered. As a consequence, we conducted a Galbraith plot to graphically assess the source of heterogeneity. The results indicated that a total of eight studies contributed to the heterogeneity. Two studies were the main sources for ε2/ε2 vs. ε3/ε3 [20,32] (Fig. 5), three studies for ε2/ε3 vs. ε3/ε3 [15,21,27], four studies for ε3/ε4 vs. ε3/ε3 [16,19,27,32], four studies for ε2 allele vs. ε3 allele [15,21,27,32] and five studies for ε4 allele vs. ε3 allele [11,16,19,27,32], and after removal of these outlier studies, the heterogeneity was effectively removed (ε2/ε2 vs. ε3/ε3: $P = 0.640$, $I^2 = 0.0$; ε2/ε3 vs. ε3/ε3: $P = 0.828$, $I^2 = 0.0$; ε3/ε4 vs. ε3/ε3: $P = 0.800$, $I^2 = 0.0$; ε2 allele vs. ε3 allele: $P = 0.651$, $I^2 = 0.0$; ε4 allele vs. ε3 allele: $P = 0.566$, $I^2 = 0.0$). Meanwhile, the corresponding pooled ORs were not materially altered in all comparisons. As a consequence, the results of heterogeneity analysis indicated that our results were statistically robust and credible.

Table 2
Stratified analyses of the *ApoE* polymorphism and MI risk.

Variables	n[a]	ε2/ε2 vs. ε3/ε3			ε2/ε3 vs. ε3/ε3			ε2/ε4 vs. ε3/ε3			ε3/ε4 vs. ε3/ε3			ε4/ε4 vs. ε3/ε3			ε2 allele vs. ε3 allele			ε4 allele vs. ε3 allele		
		OR(95%CI)	P^b	I^2	OR(95%CI)	P^b	I^2	OR(95%CI)	P^b	I^2	OR(95%CI)	P^b	I^2	OR(95%CI)	P^b	I^2	OR(95%CI)	P^b	I^2	OR(95%CI)	P^b	I^2
Total	23	0.56 (0.31,1.02)[c]	0.001	63.4	**0.79 (0.70,0.91)**[c]	0.005	48.3	0.96 (0.81,1.14)	0.750	0.0	**1.20 (1.08,1.34)**[c]	0.000	58.0	**1.39 (1.19,1.64)**	0.194	20.6	**0.74 (0.65,0.85)**[c]	0.000	64.3	**1.22 (1.11,1.35)**[c]	0.000	65.5
Ethnicity																						
Caucasian	15	0.64 (0.27,1.51)[c]	0.000	76.5	**0.83 (0.72,0.96)**[c]	0.026	46.1	1.05 (0.99,1.12)	0.390	5.6	1.12 (1.00,1.26)[c]	0.007	54.0	**1.26 (1.05,1.52)**	0.914	0.0	**0.77 (0.65,0.91)**[c]	0.000	70.6	**1.11 (1.01,1.21)**[c]	0.041	42.6
Asian	6	0.52 (0.18,1.49)	0.866	0.0	0.68 (0.34,1.37)[c]	0.022	61.9	1.16 (0.57,2.35)	0.864	0.0	**1.52 (1.19,1.93)**	0.333	12.8	**5.67 (2.68,12.02)**	0.553	0.0	**0.58 (0.43,0.79)**	0.071	50.7	**1.92 (1.26,2.92)**[c]	0.004	70.9
Other	2	**0.40 (0.20,0.83)**	0.704	0.0	**0.79 (0.68,0.93)**	0.629	0.0	0.94 (0.77,1.14)	0.555	0.0	1.72 (0.69,4.27)[c]	0.001	91.3	1.34 (0.91,1.98)	0.186	42.7	**0.77 (0.67,0.89)**	0.388	0.0	1.42 (0.85,2.38)[c]	0.022	81.0

Statistically significant results were in bold.
[a] Number of comparisons.
[b] *P* value of *Q*-test for heterogeneity test.
[c] Random-effect model was applied when *P* value for heterogeneity <0.05; otherwise, fixed-effect model was applied.

3.5. Publication bias

To evaluate the publication bias of enrolled studies, the Begg's funnel plot and Egger's test were performed. The shapes of funnel plots did not show any obvious asymmetry in all genetic models. Therefore, the Egger's test was performed to provide statistical evidence of funnel plot symmetry, and the results confirmed the absence of publication bias (Table 3).

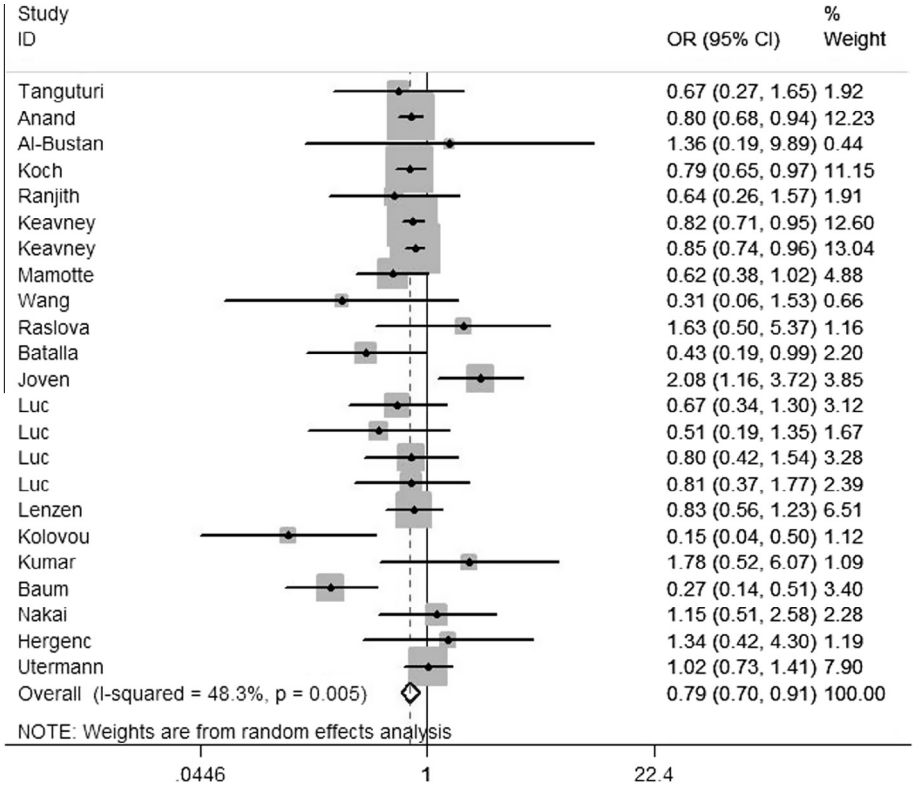

Fig. 2. Forest plot for *ApoE* polymorphism and MI risk in the genetic model of ε2/ε3 vs. ε3/ε3.

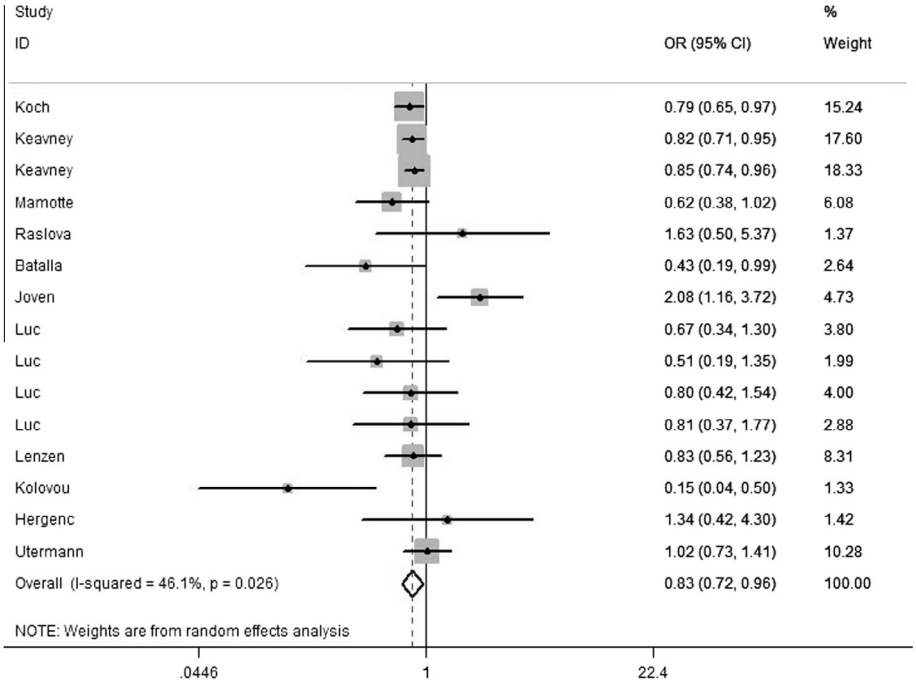

Fig. 3. Forest plot for *ApoE* polymorphism and MI risk among the Caucasian population in the genetic model of ε2/ε3 vs. ε3/ε3.

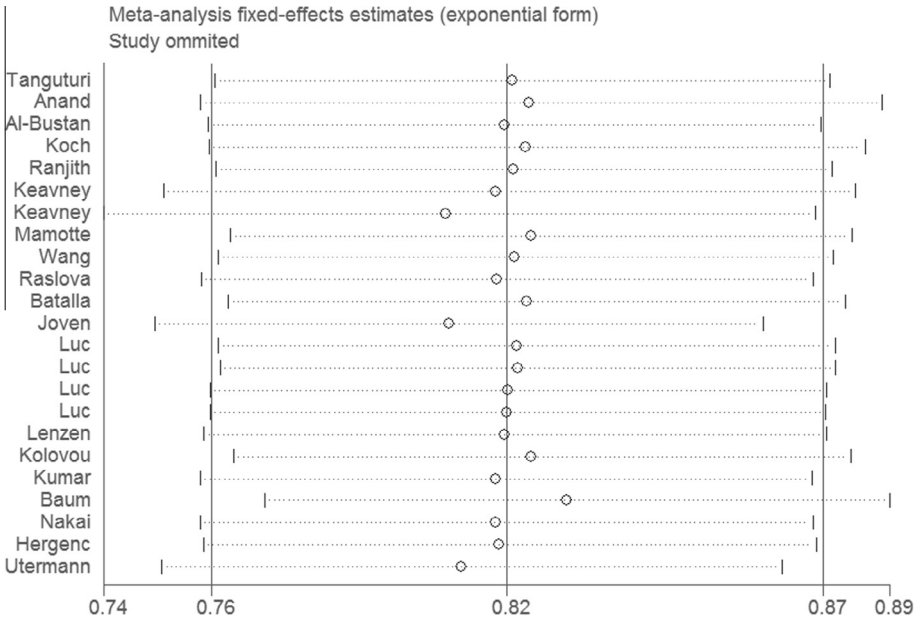

Fig. 4. The sensitivity analysis in the genetic model of ε2/ε2 vs. ε3/ε3. The omitted study is indicated by the first author's last name.

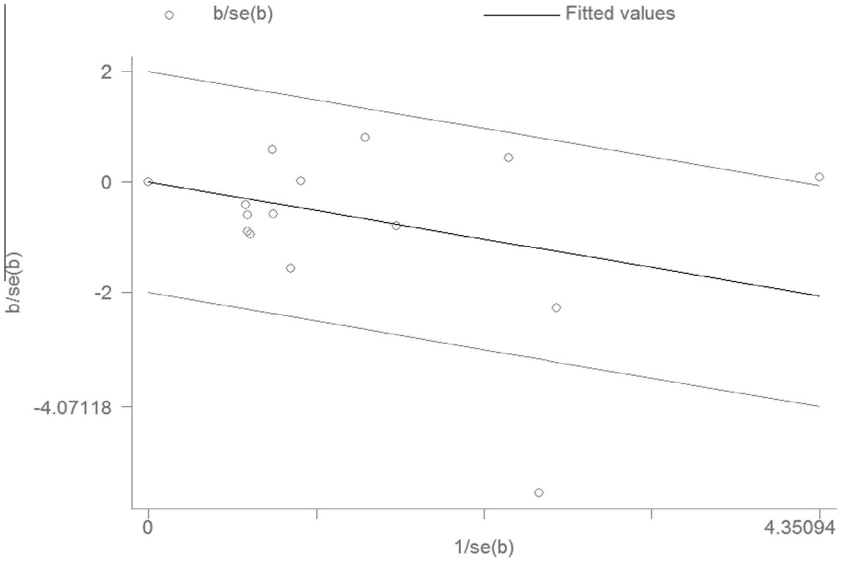

Fig. 5. Galbraith plot for ApoE gene polymorphism and MI risk in the genetic model of ε2/ε2 vs. ε3/ε3.

Table 3
Egger's test for *ApoE*polymorphism.

Egger's test	ε2/ε2 vs. ε3/ε3	ε2/ε3 vs. ε3/ε3	ε2/ε4 vs. ε3/ε3	ε3/ε4 vs. ε3/ε3	ε4/ε4 vs. ε3/ε3
t	−0.53	−0.73	0.6	1.46	0.48
p	0.607	0.474	0.554	0.159	0.638

4. Discussion

A total of 22 studies were included in this meta-analysis to investigate the association between *ApoE* polymorphisms and MI. The results of the overall studies showed that the ε2/ε3 genotype was associated with a decreased risk of MI, while the ε3/ε4 and ε4/ε4 genotypes were associated with an increased risk of MI. The current results were in accord with the previous observers, which support the ε4 allele as a risk factor of MI [16,33,34]. For the ε2 allele, it was found significantly protective against MI [12,21]. The discrepancy of the effect on MI risk between different *ApoE* genotypes might be supported by earlier studies [35,36]. It provided evidence that the ApoE E4 coding by ε4 allele exhibits enhanced transfer from HDL to TG-rich lipoproteins, promoting hepatic remnant clearance by apoE receptors and decreasing LDLR, thereby increasing cholesterol levels. On the contrary, the ApoE E2 coding by ε2 allele binds LDLR poorly, which can increase the LDLR numbers, thereby lowering cholesterol level. A previous meta-analysis showed no significant association between ε2 carriers and MI risk (ε2 carriers vs. ε3/ε3: OR = 0.90, 95%CI = 0.76–1.06, $P = 0.120$), whereas an increased MI risk with ε4 carriers (ε4 carriers vs. ε3/ε3: OR = 1.18, 95%CI = 1.05–1.33, $P = 0.003$) [37]. By comparison, our results were not completely consistent with previous meta-analysis. The discrepancy may partly result from the genetic diversity among ethnicities.

Furthermore, the subgroup analysis by ethnicity showed a decreased MI risk in ε2 carriers, while an increased MI risk in ε4 carriers compared with ε3 carriers in both Asian and Caucasian population. These results were consistent with the studies enrolled in our meta-analysis [11,12,15,19,26,30]. Furthermore, sensitivity analysis was also performed to make sure whether modification of the inclusion criteria of the meta-analysis affected the final results. The results showed that corresponding pooled ORs were not materially altered in all genetic models which indicated that the results were statistically robust.

Heterogeneity is a potentially important factor to influence the interpretation of the current results. In this meta-analysis, significant heterogeneity existed in ε2/ε2 vs. ε3/ε3, ε2/ε3 vs. ε3/ε3, ε3/ε4 vs. ε3/ε3, ε2 allele vs. ε3 allele and ε4 allele vs. ε3 allele. Common reasons of heterogeneity may attribute to the diversity in design, study quality, sample-sizes, genotyping methods, inclusion criteria and some studies without HWE. To explore the sources of heterogeneity, we first performed the sensitivity analyses based on HWE and ethnicity. However, the heterogeneity was not effectively removed. Therefore, a Galbraith plot was performed to further evaluate the source of heterogeneity. After excluding eight outlier studies, the heterogeneity was effectively removed. Moreover, the corresponding pooled ORs were not materially altered in all comparisons, which also suggested that our results were statistically robust.

Some limitations of the meta-analysis should be addressed. Firstly, the potential factors such as gender, age, smoking, drinking, living habits were not considered in this meta-analysis. Secondly, between-study heterogeneity should be paid attention, which may affect the results. Thirdly, only studies in English were enrolled in this meta-analysis, which may lose some studies in other languages consistent with inclusion criteria. Regardless of such limitations, this meta-analysis still had some advantages. Firstly, all enrolled studies were consistent with inclusion criteria well. Secondly, no publication bias was observed indicating that the whole pooled results might be unbiased.

In conclusion, the current meta-analysis of 22 studies indicated that *ApoE* ε2 allele was a protective factor of MI, while ε4 allele was a dangerous factor of MI, especially in Asian and Caucasian population. However, the results should be further conformed in well-designed, unbiased, powered studies.

Author contributions

YLW conceived and designed the project. LMS, LZ and HTX acquired the data. ZD and LQ analyzed and interpreted the data. YLW and MLW wrote the paper.

Conflict of interest

The authors declare that they have no competing interests.

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None.

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