

Original Article

Association between Apolipoprotein C-III Gene Polymorphisms and Coronary Heart Disease: A Meta-analysis

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ABSTRACT: Polymorphisms in the apolipoprotein C-III (APOC3) gene have been reported to be associated with coronary heart disease (CHD), but the data so far have been conflicting. To derive a more precise estimation of these associations, we performed a meta-analysis to investigate the three main polymorphisms (SstI, T-455C, C-482T) of APOC3 in all published studies. Databases including PubMed, Web of Science, Wanfang, SinoMed and CNKI were systematically searched. The association was assessed using odds ratios (ORs) with 95% confidence intervals (CIs). The statistical analysis was performed using Review Manager 5.3.3 and Stata 12.0. A total of 31 studies have been identified. The pooled odds ratio (OR) for the association between the APOC3 gene polymorphisms and CHD and its corresponding 95% confidence interval (95% CI) were evaluated by random or fixed effect models. A statistical association between APOC3 SstI polymorphism and CHD susceptibility was observed under an allelic contrast model ($P = 0.003$, OR = 1.14, 95% CI = 1.05-1.24), dominant genetic model ($P = 0.01$, OR = 1.14, 95% CI = 1.03-1.26), and recessive genetic model ($P = 0.02$, OR = 1.35, 95% CI = 1.06-1.71), respectively. A significant association between the APOC3 T-455C polymorphism and CHD was also detected under an allelic contrast ($P < 0.0001$, OR = 1.19, 95% CI = 1.10-1.29), dominant genetic model ($P = 0.0003$, OR = 1.24, 95% CI = 1.11-1.39) and recessive genetic model ($P = 0.04$, OR = 1.30, 95% CI = 1.01-1.67). No significant association between the APOC3 C-482T polymorphism and CHD was found under an allelic model ($P = 0.94$, OR = 1.00, 95% CI = 0.93-1.08), dominant genetic model ($P = 0.20$, OR = 1.07, 95% CI = 0.97-1.18) or recessive genetic model ($P = 0.13$, OR = 0.90, 95% CI = 0.79-1.03). This meta-analysis revealed that the APOC3 SstI and T-455C polymorphisms significantly increase CHD susceptibility. No significant association was observed between the APOC3 C-482T polymorphism and CHD susceptibility.

Key words: APOC3; Coronary heart disease; Polymorphism; Meta-analysis

Coronary heart disease (CHD) is one of the leading causes of death globally. Apolipoproteins are lipid-binding proteins involved in lipid transport. Thus, the abnormal structure and synthesis of apolipoproteins affects lipid metabolism and leads to CHD. Apolipoprotein C-III (APOC3) is an 8.8kd glycoprotein comprised of 79 amino acid residues. It is synthesized in the liver and is the major protein constituent of the plasma very low density

lipoproteins (VLDLs) and chylomicrons (CMs). Transgenic animal models show that APOC3 directly impacts the level of plasma triglycerides (TGs); if the APOC3 gene is overexpressed, the levels of plasma APOC3 will be elevated, thus inhibiting the clearance of TGs and leading to high triglyceride levels [1]. In vitro studies have shown that APOC3 inhibits the activity of lipoprotein lipase (LPL), delays the clearance of TG-rich

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lipoproteins and leads to the elevation of plasma TGs [2]. High TG levels are known to increase the risk of atherosclerosis and may also increase the susceptibility to cardiovascular disease [3, 4]. Five polymorphisms have been found in the APOC3 gene promoter. The most extensively studied are the SstI, T-455C and C-482T polymorphisms and a C→G substitution at nucleotide 3238 (rs5128) in the 3' untranslated region of SstI, which generates two alleles: S1 and S2. Two promoter polymorphisms, T-455C and C-482T, have also been studied more extensively because they are located on the insulin-responsive element (IRE). Insulin exerts its action

by down-regulating APOC3 gene expression transcriptionally. The presence of mutant sequences may reduce the inhibitory effects of the hormone [5]. The relationship between APOC3 gene polymorphisms and genetic susceptibility to CHD has attracted significant clinical and epidemiological research interest in recent years, but the reported results have been inconsistent. We therefore conducted a meta-analysis of the existing published studies on this topic to evaluate the strength of the association between the three main APOC3 polymorphisms (SstI, T-455C, C-482T) and CHD.

Table 1. Characteristics of studies reporting the distribution of three APOC3 polymorphisms (SstI,-455T/C,-482C/T) in CHD cases and controls

Study [Reference]	Year	Eligible subjects		Allele frequency (case)			Method	Population	Criteria	Gender (male), %		Age (years)	
		case	control	S2	T	C				Case	Control	Case	Control
Aalto-Setälä [12]	1987	39	61	0.115	-	-	PCR-RFLP	Finnish	CHD	100	50.8	38-68	18-52
Bai [13]	1995	90	68	0.328	-	-	PCR-RFLP	Japanese	CHD	77.8	57.4	63±12	58±12
Berkinbayev [14]a	2014	161	112	0.242	-	-	PCR	Kazakhstan(Kazakh)	MI	100	100	46.4±1.9	40.7±2.1
Berkinbayev [14]b	2014	80	95	0.285	-	-	PCR	Kazakhstan(Uyghur)	CHD	100	100	47.3±0.92	41.2±1.02
Bi [15]	2005	312	317	-	-	0.452	PCR-RFLP	Chinese(Han)	CAD	67	60.3	60.2±13.3	58.9±14.3
Che [16]	2012	78	78	-	-	0.647	PCR-RFLP	Chinese	CAD	57.7	52.6	45.3±4.7	44.3±7.6
Chen [17]	2006	310	499	-	0.477	0.455	PCR-RFLP	Chinese(Han)	CHD	70.6	62.7	60.56±11.14	58.87±9.11
Chhabra [18]	2004	158	151	0.342	-	-	PCR	India	CAD	88	92	53.25±10.25	52.45±10.85
Dallongeville [19]	2006	442	475	-	-	0.263	PCR	French	CHD	100	100	35-64	35-64
Dan [20]	1995	43	60	0.221	-	-	PCR-RFLP	Chinese	CHD	N/A	N/A	57.6-6.9	55.4-4.3
Ding [21]	2012	229	254	-	0.548	-	PCR	Chinese(Han)	ACS	55.9	53.9	59.1±9.4	59.3±9.6
Han [22]	2011	275	289	-	-	0.481	PCR-RFLP	Chinese(Han)	CHD	56.4	56.4	59.2±9.8	61.6±10.7
Izar [23]	2003	112	112	0.136	-	-	PCR	Brazil	CAD	58	59	M<45, W<55	N/A
Kee [24]	1999	614	761	0.093	-	-	PCR	Europe	MI	100	100	25-64	N/A
Li [25]	2006	47	104	0.274	-	-	PCR-RFLP	Chinese(Han)	CAD, MI	72.3	60.6	62.5±12.1	60.0±8.0
Liu [26]	2004	385	373	0.116	-	-	PCR-RFLP	Caucasian	MI	100	100	60±9	59±9
Liu [27]	2005	483	502	0.301	0.534	0.449	PCR-RFLP	Chinese(Han)	CHD	59	63.1	54.2±6.3	58.2±6.2
Liu [28]	2005	267	491	0.301	-	-	PCR-RFLP	Chinese(Han)	CHD	70.4	63.7	60.3±8.9	58.8±9.2
Martinelli [29]	2007	669	244	-	-	-	PCR	Italy	CAD, MI	81.3	75	60.7±9.3	58.7±12.7
Muendlein [30]	2008	332	225	-	-	0.297	PCR	Caucasian	CAD	79.5	54.7	62.5±10.3	61.5±10.2
Olivieri [31]	2002	549	251	-	0.416	-	PCR	Northern Italy	CAD	81.8	66.9	60.4±9.4	57.6±12.6
Ordovas [32]	1991	202	145	0.125	-	-	PCR-RFLP	Northern Italy	CAD	N/A	N/A	47.2±8.8	49.6±6.9
Paulweber [33]	1988	106	118	0.104	-	-	PCR-RFLP	Austrian	CAD, MI	100	100	47.3±5.7	49.7±5.4
Rigoli [34]	1995	62	62	0.169	-	-	PCR-RFLP	Southern Italy	CHD	69.4	67.7	58.2±7.1	57.6±7.7
Sediri [35]	2011	326	361	0.103	0.411	-	PCR	Tunisia	MI	100	100	53.8±8.6	51.1±9.5
Tarek [36]	2013	156	154	0.292	-	-	PCR-RFLP	Egyptian	CAD	100	100	51.5±7.9	50.7±9.4
Tarek [37]	2011	200	100	0.145	-	-	PCR	Egyptian	MI	67	64	50.7±9.5	52.9±11.3
Tobin [38]	2004	547	505	-	0.355	0.255	PCR-RFLP	UK	MI	68	62	61.9±9.2	58.6±10.7
Weng [39]	2000	50	50	0.16	-	-	PCR	Chinese(Han)	CAD, MI	76	74	57±6.8	55±8.7
Wu [40]	2000	131	229	0.233	-	-	PCR	Chinese	CAD	69.5	56.8	59.1±10.9	51±15.3
Yang [41]	2008	85	87	-	-	0.412	PCR-RFLP	Chinese	CHD	54.1	52.9	52.79±7.15	50.63±7.50
Yi [42]	2006	195	181	-	-	0.541	PCR-RFLP	Chinese (Han)	CAD	56.4	56.4	69.48±9.21	58.63±14.79
Yu [43]	2011	286	325	-	0.42	0.517	TaqMan	Chinese (Han)	CHD	74.8	52.9	56.30±11.57	55.79±12.40

MATERIALS AND METHODS

Literature Search

All studies that reported the association between the APOC3 gene polymorphisms and CHD were identified by comprehensive computer-based searches of PubMed (from 1980 to June 2014), the Web of Science, Wanfang, the China Biological Medicine Database (SinoMed) and the China National Knowledge Infrastructure (CNKI). These computer searches were limited to English and Chinese language articles published before June 2014, and did not include reviews and editorials. The following keywords were used for the search: “apolipoprotein C-III” OR “APOC3” AND “polymorphism” OR “mutation” OR “genotype” OR “variant” AND “coronary heart disease” OR “CHD” OR “coronary artery disease” OR “CAD” OR “myocardial infarction” OR “MI” OR “Acute coronary syndrome” OR “ACS”.

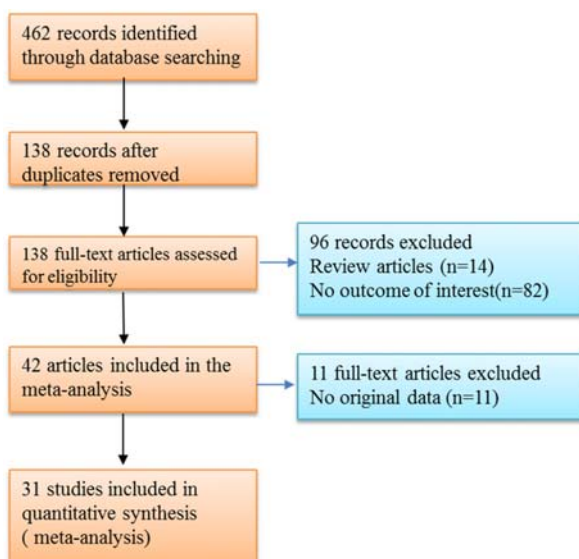


Figure 1. Flow diagram of the study identification.

Inclusion Criteria

The diagnosis of CHD was determined based on examination results including coronary arteriography, clinical symptoms, echocardiography, the treadmill exercise test, electrocardiogram results, and myocardial perfusion imaging in Emission Computed Tomography. The inclusion criteria were as follows: (1) studies were limited to three main (SstI, T-455C, C-482T) polymorphisms of the APOC3 gene and CHD, (2) all studied were independent case-control studies using either

a hospital-based or a population-based design, (3) studies were selected using the literature research methods, (4) the existing literature provided us with a comprehensive statistical index and sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). Studies were excluded from analysis when (1) it was not possible to extract data from the published results, (2) the reported appropriate outcomes were excluded, or (3) they contained republished data.

Data Extraction

Two authors (JZ Zhang and CF Dai) independently extracted data from the studies. Disagreement was resolved by consensus. If these two authors could not reach a consensus, the result was reviewed by a third author (X Xie). The extracted data consisted of the following items: the first author's name, the publication year, the total number of cases and controls, the allele frequency (cases), the methods, the population (ethnicity), the selection criteria, the percentage of the male sex, and the age (in years).

Quality assessment

To determine the methodological quality of each study, we used the Newcastle-Ottawa scale (NOS), which uses a “star” rating system to judge the quality of observational studies [6]. The NOS ranges between zero stars (worst) and nine stars (best). Studies with a score equal to or greater than seven were considered to be of high quality. Two investigators (GT Yin and MM Zhang) independently assessed the quality of the included studies, and the results were reviewed by a third investigator (YT Ma). Disagreement was resolved by discussion.

Statistical analysis

The associations between the SstI, T-455C and C-482T polymorphisms of the APOC3 gene and CHD were compared by using the odds ratio (OR) corresponding to 95% confidence interval (CI) by using Review Manager 5.33 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen). Heterogeneity between the studies was assessed using the I^2 statistic; $P < 0.10$ and $I^2 > 50\%$ indicated evidence of heterogeneity [7,8]. If heterogeneity existed among the studies, the random effects model was used to estimate the pooled OR (DerSimonian and Laird method) [9]. Otherwise, the fixed effects model was adopted (Mantel–Haenszel method) [10]. For the APOC3 gene polymorphisms, we investigated associations between the genetic variants and CHD risk in allelic contrast, recessive and dominant genetic models. The Z test was used to determine the pooled OR, and

significance was set at $P < 0.05$. The Hardy–Weinberg equilibrium (HWE) for each nucleotide polymorphism was assessed for the controls in each study using X^2 test at a significant level of $P < 0.05$. The potential publication bias was investigated using a funnel plot.

Egger’s test ($P < 0.05$) was also considered to be representative of statistically significant publication bias [11], which was conducted with the Stata 12.0 software.

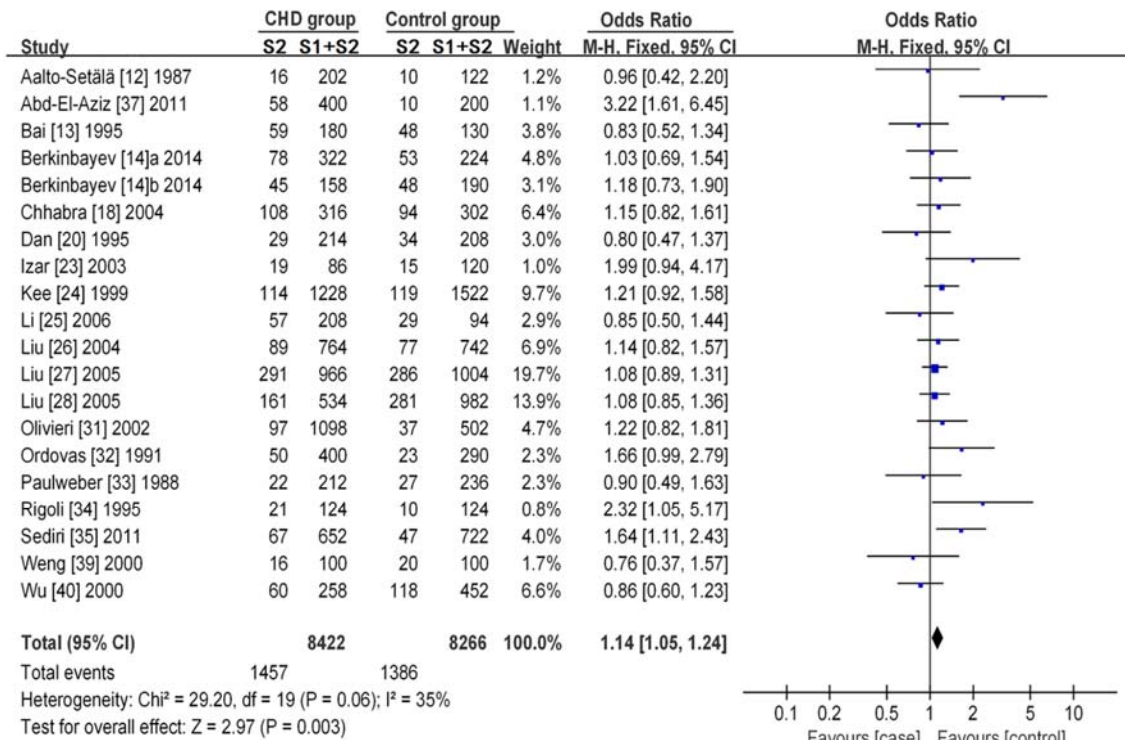


Figure 2. Forest plot of the association between the APOC3 SstI polymorphism and CHD under the allelic contrast model (S2 vs. S1). The horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and the 95% CI.

RESULTS

Study Characteristics

A total of 31 studies [12–43] were included in the final meta-analysis, based on the above inclusion criteria. These studies consisted of 19 studies for SstI, 7 for T-455C and 11 for C-482T, for a total of 8311, 5653 and 6828 samples for the 3 polymorphisms, respectively. All included studies were approved by the various Ethics Committees of their institutions. Figure 1 shows the process of literature retrieval. Table 1 shows the main

characteristics of the studies. In all studies, the genotype frequencies in the control population were consistent with the HWE. The NOS results showed that the methodological quality was generally good.

Main Results, Heterogeneity and Sensitivity Analysis

No significant heterogeneity was observed for the APOC3 SstI polymorphism and its relationship to CHD under the allelic contrast model ($I^2 = 35\%$, $P = 0.06$), dominant genetic model ($I^2 = 40\%$, $P = 0.04$) and the recessive genetic model ($I^2 = 0\%$, $P = 0.70$). Therefore, the Mantel-

Haenszel fixed effects model was applied.

A statistical association between the APOC3 SstII polymorphism and CHD susceptibility was observed under an allelic contrast model ($P = 0.003$, OR = 1.14, 95% CI = 1.05-1.24), the dominant genetic model ($P = 0.01$, OR = 1.14, 95% CI = 1.03-1.26), and the recessive genetic model ($P = 0.02$, OR = 1.35, 95% CI = 1.06-1.71). We used the forest plot of the allelic contrast model as an example (Figure 2), as the dominant and recessive gene models do not fully show the results.

For the APOC T-455C polymorphism and risk of CHD, no significant heterogeneity was found under the allelic contrast model ($I^2 = 46%$, $P = 0.09$) or dominant genetic model ($I^2 = 0%$, $P = 0.53$), so we used the Mantel-

Haenszel fixed effects model. Heterogeneity was found under the recessive genetic model ($I^2 = 65%$, $P = 0.008$). The random-effects model (DerSimonian and Laird) was also applied. A significant statistical association was observed between the APOC T-455C polymorphism and CHD under the allelic contrast model (C vs. T, $P < 0.0001$, OR = 1.19, 95% CI = 1.10-1.29) (Figure 3), the dominant genetic model (CT+CC vs. TT, $P = 0.0003$, OR = 1.24, 95% CI = 1.11-1.39) and the recessive genetic model (CC vs. CT+TT, $P = 0.04$, OR = 1.30, 95% CI = 1.01-1.67).

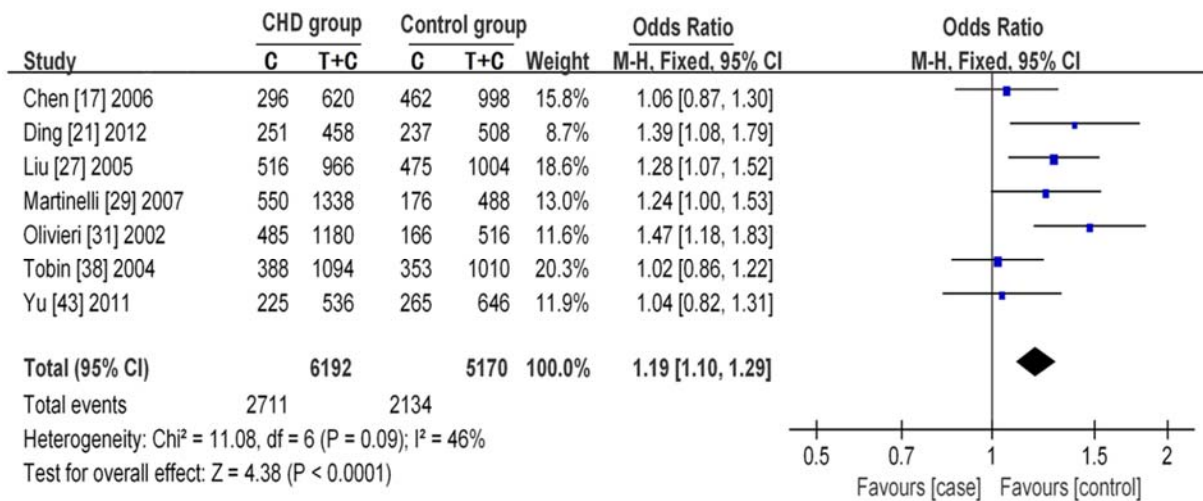


Figure 3. Forest plot of the association between the APOC3 T-455C polymorphism and CHD under the allelic contrast model (C vs. T). The horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and the 95% CI.

As for the APOC C-482T polymorphism and its relationship to CHD, no significant heterogeneity was found under the allelic contrast model ($I^2 = 0%$, $P = 0.56$), the dominant genetic model ($I^2 = 0%$, $P = 0.82$) or the recessive genetic model ($I^2 = 15%$, $P = 0.30$). For this reason, the Mantel-Haenszel fixed effects model was used. No significant statistical association was found under the allelic contrast model (T vs. C, $P = 0.94$, OR = 1.00, 95% CI = 0.93-1.08) (Figure 4), dominant genetic model (TT+TC vs. CC, $P = 0.20$, OR = 1.07, 95% CI = 0.97-1.18) or recessive genetic model (TT vs. TC+CC, $P = 0.13$, OR = 0.90, 95% CI = 0.79-1.03).

Sensitivity analysis

The contribution of each study to the pooled estimate was determined to assess the sensitivity analysis. We excluded individual studies one at a time and recalculated the pooled P or OR estimates for the remaining studies. Ding [21], Liu [27], Martinelli [29] and Olivieri [31] had undue influences on the summary ORs under the recessive genetic model for the T-455C polymorphism. Similarly, Liu [27] had undue influences on the pooled P or OR estimates for the C-482T polymorphism. However, their data did not substantially change the pooled point estimate

when converting the random-effects model to the fixed effects model in all studies. Thus, our results are fairly reliable.

Publication Bias

The publication bias of the individual studies was evaluated using a funnel plot and Egger’s test. We also took the figure alleles of the SstI, T-455C and C-482T polymorphisms of APOC3 as representative. No visual publication bias was found in the funnel plot for the SstI

(Figure 5A), T-455C (Figure 5B) or C-482T (Figure 5C) gene polymorphisms using the allelic contrast model. We further used Egger’s test to assess the whole test publication bias. No statistically significant difference was detected in the Egger’s test by using the allelic contrast model for the SstI ($T = -0.56, P = 0.697$), T-455C ($T = 0.09, P = 0.932$) or C-482T ($T = -0.29, P = 0.778$) polymorphisms in all studies. This indicated that the publication bias was low in the current meta-analysis.

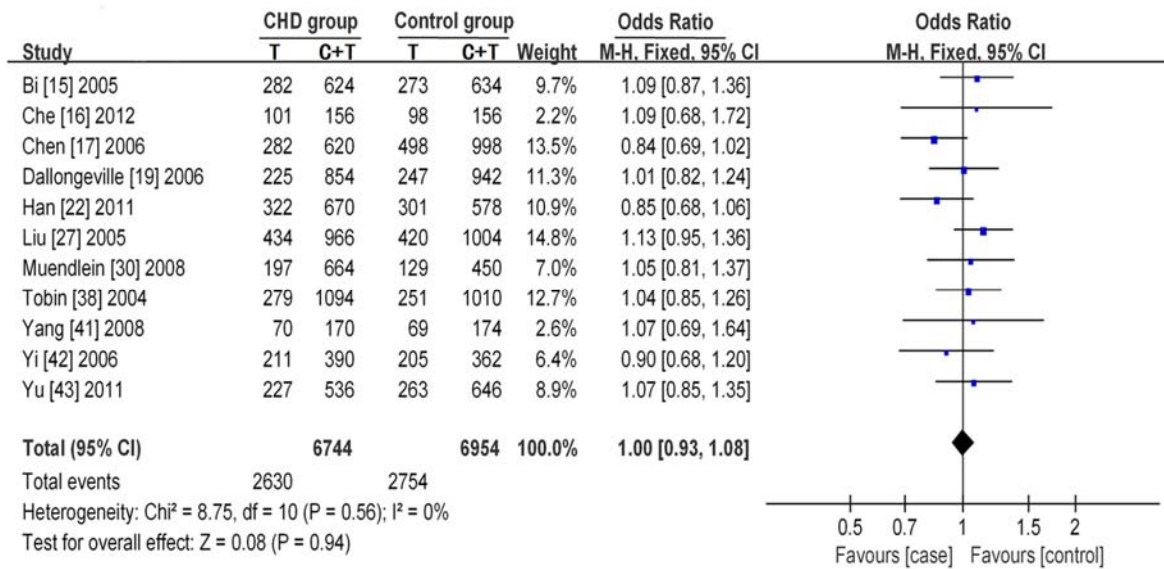


Figure 4. Forest plot of the association between the APOC3 C-482T polymorphism and CHD under the allelic contrast model (T vs. C). The horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of the OR and the 95% CI.

DISCUSSION

CHD is a multi-factorial and polygenic disorder disease, which is thought to result from complex gene-gene and gene-environment interactions [44]. The association between APOC3 gene polymorphisms and the risk of CHD has been intensively studied, but the results remain inconclusive [12–43]. To generate more robust data regarding the APOC3 gene polymorphisms and CHD risk, we conducted a comprehensive genetic meta-analysis on

the basis of data from 8311, 5653 and 6828 samples for the SstI, T-455C and C-482T polymorphisms, respectively. The results showed that the APOC3 SstI and T-455C polymorphisms significantly increase CHD susceptibility. No significant association between the APOC3 C-482T polymorphism and an increased risk of CHD was observed.

Abd El-Aziz [36] and Abd El-Aziz [37] had an undue influence on the summary ORs under the dominant genetic model in the SstI polymorphism; there was no

observed effect on the pooled P or OR in the subgroup.

Heterogeneity is a potential problem that may affect the interpretation of the results. Heterogeneity may be attribute to potential confounding resulting from diversity in sample-sizes, design differences, variations in the ethnicities and regions under study, CHD severity, subject gender, methods of genotyping, and/or the interaction with other risk factors. When the study of Abd El-Aziz [37] was included in the Forest plot of the association between APOC3 SstI polymorphism and CHD, significant heterogeneity was found under the allelic contrast and dominant genetic models. Initially, we included two studies conducted by Abd El-Aziz investigating the Severity of Coronary Artery diseases [36] and acute myocardial infarction in diabetic patients [37] in patients with an APOC3 SstI polymorphism. According to the Newcastle-Ottawa scale, these two studies ranked as having six stars, indicating them as possessing medium quality. We found that the publication bias of these two articles was huge, and the heterogeneity analysis found that heterogeneity is large in the study of Apolipoprotein C3 Genes with the Severity of Coronary Artery diseases [36]. Because the two articles were published at a similar

time and both investigated the association between Apolipoprotein C3 genes and CHD, we are unsure if they made use of repeated samples. We contacted the corresponding authors by email but did not receive any reply. To increase the credibility of the meta-analysis, we therefore eliminated this article, as it had an excessive impact on the overall publication bias.

To better interpret the results, other limitations of this meta-analysis should also be acknowledged. For one thing, some inevitable publication bias may exist in the results. Only full text articles published in English and Chinese were included in this meta-analysis. Thus, some eligible studies that were unpublished or reported in other languages were likely missed. Cultural background factors can also affect the decision to publish, making researchers more or less likely to report or edit negative results in some areas of research. Furthermore, CHD is a complex disease involving potential interactions among gene-gene and gene-environment factors. However, many eligible studies included in this meta-analysis failed to consider environmental factors, which could also influence the study results.

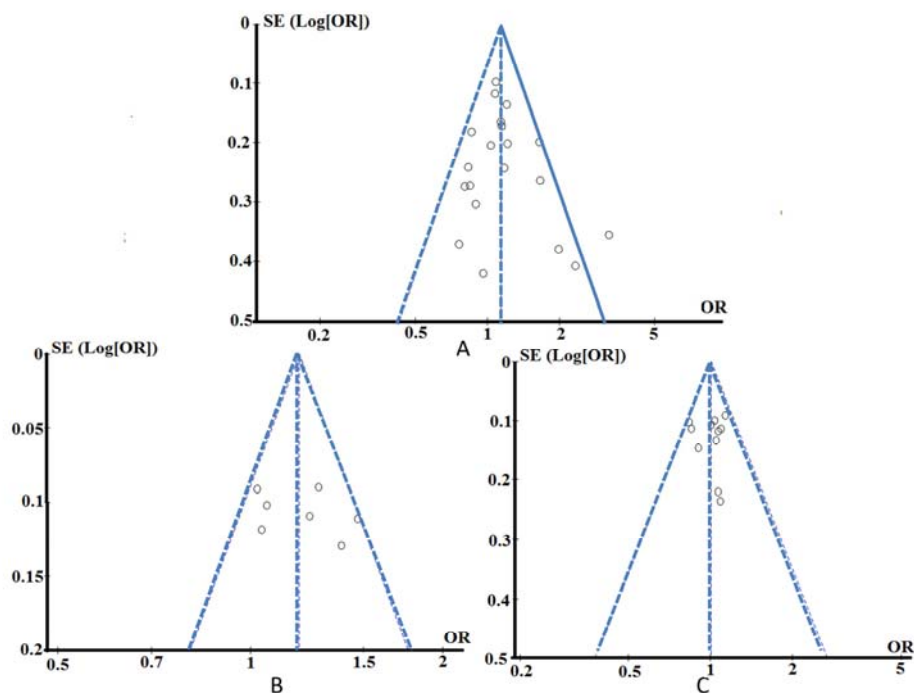


Figure 5. Funnel plot for the publication bias tests. Each point represents a separate study for the indicated association. The horizontal and vertical axis correspond to the OR and confidence limits (OR: odds ratio, SE: standard error). A: SstI polymorphism under the allelic contrast model (S2 vs. S1); B: T-455C polymorphism under the allelic contrast model (C vs. T); C: C-482T polymorphism under the allelic contrast model (T vs. C).

Despite these limitations or disadvantages, our meta-analysis did have some advantages. First, a systematic review of the association of the APOC3 gene (SstI, T-455C and C-482T) polymorphisms with CHD risk is able to overcome the limitation of the small sample sizes of the study populations by increasing the sample size, thus generating more robust data. Second, the quality of the case-control studies included in our meta-analysis was satisfactory and met our inclusion criteria.

Conclusion

In conclusion, this meta-analysis reveals that the APOC3 SstI and T-455C polymorphisms significantly increased CHD susceptibility. No significant association between APOC3 C-482T polymorphism and the susceptibility of CHD was observed. However, the results should be interpreted with caution because of the discussed study limitations. Further studies with larger sample sizes that consider gene-gene and gene-environment interactions are thus needed to confirm our findings.

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