Research Article

Gene polymorphism associated with angiotensinogen (M235T), endothelial lipase (584C/T) and susceptibility to coronary artery disease: a meta-analysis

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Objective: To explore the association between the variant M235T locus of angiotensinogen (AGT) gene, 584C/T locus of Endothelial lipase (EL) gene, and coronary artery disease (CAD) by meta-analysis.
Methods: The case–control studies on the association between AGT/EL gene polymorphism and CAD were collected through searching PubMed, Excerpta Medica Database (EMBASE), Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases up to 1 March 2020. Stata 15.0 software was used for analysis.
Results: A total of 29 articles met the inclusion criteria. After analyzing, it was found that the M235T polymorphism of AGT gene was associated with the occurrence of CAD. In the allele model (T vs. M), OR = 1.38 ($P<v$0.05). In other heredity, there was also statistical significance. Subgroup analysis indicated that except the heterozygous genetic model of the Chinese population, other genetic models of the Caucasian and Chinese population were also statistically significant. The 584C/T polymorphism of EL gene was associated with the occurrence of CAD, with OR = 0.83 ($P<$0.05) in the allele model (T vs. C) and OR = 0.80 ($P<$0.05) in the dominant gene model. Also, in the allele model of Caucasian subgroup, OR = 0.83 ($P<$0.05), while in Asian subgroup, there was no statistically significant genetic model.
Conclusion: AGT M235T and EL 584C/T polymorphisms are associated with CAD susceptibility. The genotype TT, TC or allele T of AGT M235T and genotype CC or allele C of EL 584C/T might be the genetic risk factors for the development of CAD.

Introduction

Coronary artery disease (CAD), the incidence of which is increasing year by year in both developed and developing countries, is the leading cause of deaths and seriously endangers human health [1,2]. With the increase in age, the incidence of CAD increases gradually [3]. Common risk factors, such as dyslipidemia, hypertension and diabetes, are affected by both environmental and genetic factors [4]. Also, these traditional risk factors could not directly lead to CAD, and there might be other factors directly leading to atheromatous plaques formation that are related to genetic susceptibility. Moreover, increasing studies have demonstrated that the renin–angiotensin system (RAS) plays a vital role in CAD [5].

Renin is mainly secreted by renal juxtaglomerular cells, and it can catalyze the conversion of plasma pro-angiotensin (AGT) into Angiotensin I. Also, Angiotensin I can be further converted into angiotensin II, III, IV, to play the role of vasoconstriction. It has been found that AGT M235T polymorphism is closely related to the occurrence of cardiovascular disease. M235T refers to the substitution of nucleotide T at

location 704 of the second exon by C, resulting in the conversion of amino acid at position 235 from methionine (M) into threonine (T). Some studies have confirmed that Angiotensinogen (AGT) M235T polymorphism is closely related to the severity of CAD [6]. Van et al. [7] have suggested that the haplotype of AGT gene is associated with coronary heart disease in familial hypercholesterolemia. While, AGT M235T polymorphism is not associated with CAD in diabetic patients [8]. Khatami et al. [9] suggested that allele T of the AGT gene would increases the risk of CAD, while Zhu et al. [10] indicated that allele T would not increase the risk of CAD.

Related studies have shown that low plasma high-density lipoprotein cholesterol (HDL-C) concentration is closely related to the incidence of coronary heart disease (CAD). In contrast, high HDL-C levels can reduce the risk of CAD [11]. The concentration of HDL-C in plasma is not only affected by environmental factors, but also highly hereditary. Current genetic studies indicate that the genetic heterogeneity of HDL-C is associated with the gene polymorphism of endothelial lipase (LIPG), which could regulate the metabolism of HDL [12]. Endothelial lipase (EL), a member of the triglyceride lipase family, has high homology with Lipoprotein lipase (LPL) and Hepatic lipase (HL), and plays a critical role in the regulation of lipid metabolism, especially in the process of HDL-C metabolism. The main activity of EL is phospholipase activity, and HDL granules are its preferred substrate. Plasma EL activity affects human high-density lipoprotein metabolism and coronary artery risk factors [13]. The relationship between EL 584C/T polymorphism and CAD susceptibility has been discussed, but there is not consistent conclusion. Solim et al. [14] believed that allele T of EL gene was a protective factor of CAD, but Xie et al. [15] did not find this association in the Chinese population.

Furthermore, to compare different research results more scientifically and objectively, meta-analysis is used to conduct a comprehensive study on this issue. On this basis, a meta-analysis of the genotypic data from all eligible surveys in recent years was administered to more accurately evaluate the relationship between AGT (M235T), Endothelial (584C/T) polymorphism and susceptibility to CAD, thus providing evidence-based medicine for cardiovascular clinic.

Methods
Literature search
A combination of following terms: Angiotensinogen, Endothelial lipase, myocardial infarction, coronary artery disease, acute myocardial infarction, cardiovascular disease, ischemic heart disease, coronary heart disease, cute coronary syndrome and polymorphism. We systematically searched the relevant literatures of relationship between Angiotensinogen, Endothelial lipase Polymorphism and Coronary artery Disease on PubMed, Excerpta Medica Database (EMBASE), Web of Science, China National Knowledge Infrastructure (CNKI) and China Wanfang databases up to 1 March 2020. The retrieval strategy was as follows: (myocardial infarction OR coronary artery disease OR acute myocardial infarction OR cardiovascular disease OR ischemic heart disease OR coronary heart disease OR cute coronary syndrome) AND (Angiotensinogen OR Endothelial lipase) AND (polymorphism OR Single nucleotide mutation). There were no language restrictions.

Inclusion and exclusion criteria
Inclusion criteria
(1) It was case–control study; (2) CAD was defined as coronary heart disease, coronary artery disease, myocardial infarction, acute Myocardial infarction, acute coronary syndrome, cardiovascular disease; (3) the number of genotypes should be provided in both the case group and the control group.

Exclusion criteria
(1) No specific amount of genotypes was provided, or the data of each genotype cannot be obtained by calculation, (2) repeated studies of the same ethnic group, (3) Newcastle–Ottawa Scale (NOS) score was less than 6.

Data extraction and methodological quality
According to the NOS [16], the full text was carefully read and evaluated. The literature below 6 stars was of low quality, and the research above 6 stars was of high quality, among which only the research above 6 stars was included. The evaluation was conducted independently by two evaluators according to the uniform quality standard, and they extracted the data from the literature and then cross-checked it. When they encountered some differences, they solve these problems through discussion, or with the help of a third party. The extracted data included the number of AGT M235T and EL 584C/T genotypes in the case group and the control group, first author, publication time, source of the control group, and country.
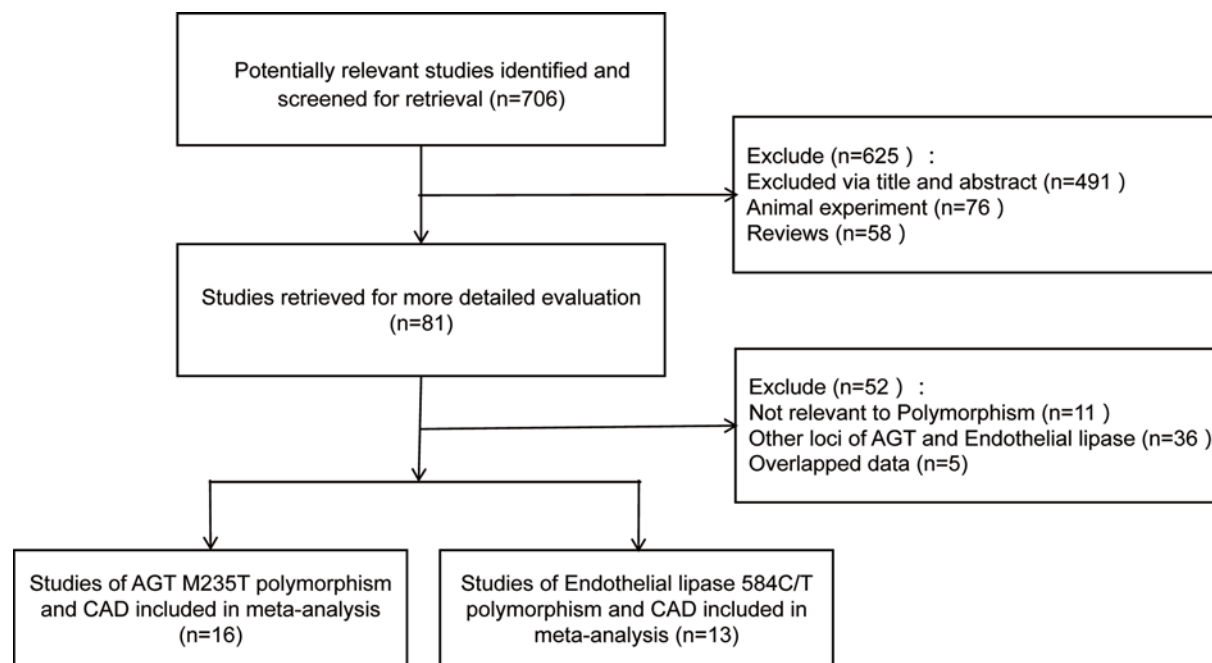
Figure 1. A flow diagram of the study selection process

Statistical analysis

The odds ratio (OR) and its 95% confidence interval were used to evaluate the association between AGT/EL gene polymorphism and CAD. The data were merged and analyzed by statistical software Stata 15.0. Q test was applied to verify the heterogeneity of the included studies. When $I^2 \geq 50\%$ or $P \leq 0.05$, heterogeneity was considered to exist, the random-effects model (REM) was selected; when $I^2 < 50\%$ and $P > 0.05$, heterogeneity was deemed to be low, and the fixed-effects model (FEM) was used for data integration. Z test was used to test the significance of the combined OR value. The funnel plot was performed to evaluate publication bias, and the criterion was whether the funnel plot was symmetric or not. If the funnel chart was asymmetric, there might be publication bias. Egger's test was also used for checking publication bias. Subgroup analysis was carried out to assess whether Hardy–Weinberg equilibrium (HWE) was satisfied in the ethnicity and control groups. Finally, the sensitivity of the results was analyzed to determine the robustness of the research results.

Results
Search results

According to the inclusion and exclusion criteria, 29 articles were collected in this meta-analysis, including 16 studies on the relationship between AGT M235T polymorphism and CAD susceptibility [17–31], and 13 studies on EL 584C/T polymorphism and CAD susceptibility [32–43]. The specific literature screening process was displayed in Figure 1. The characteristics of the study, the distribution frequency of genotypes, and the results of the literature quality score were shown in Tables 1 and 2. The detailed quality assessment included in the study was shown in Supplementary Table S1.

Meta-analysis results
Comparison of alleles

The main results of meta-analysis of AGT M235T polymorphism and CAD susceptibility were shown in Table 3 and Figure 2, while the main findings of meta-analysis of EL 584C/T polymorphism and CAD susceptibility are shown in Table 4 and Figure 3. The comparison of allele T and allele M at M235T locus of AGT gene suggested that there were significant differences in heterogeneity among different studies ($I^2 = 69.2\%$, $P<0.05$). Therefore, the REM was applied. The results indicated that OR = 1.38 (95% CI: 1.15–1.65), the difference was statistically significant. The same conclusion was obtained from the subgroup analysis of Chinese and Caucasian populations. The allele model

Table 1 The basic characteristics of AGT M235T polymorphism included in the literature

First author	Year	Country	Age (CAD)	End point	Source of controls	Cases			Controls			HWE (control)	NOS score
						TT	MT	MM	TT	MT	MM		
Ko	1997	China	61.50 ± 5.60	CAD	HB	225	36	6	279	54	4	0.454	8
Chen	1998	China	67.70 ± 8.50	MI	PB	40	13	4	32	31	13	0.258	8
Sheu	1998	China	62.00 ± 1.00	CAD	PB	75	26	1	107	37	1	0.247	7
Xie	2001	China	61.40 ± 9.50	CAD	HB	69	29	8	45	30	11	0.109	7
Zhu	2002	China	58.90 ± 9.20	CAD	HB	56	48	14	54	42	10	0.661	8
Gu	2003	China	65.83 ± 9.23	CAD	PB	86	31	12	53	30	7	0.568	8
Zhu	2004	China	55 (median)	CAD	HB	105	75	12	54	36	8	0.355	8
Li	2004	China	61.60 ± 11.80	CAD	PB	49	60	11	25	41	14	0.689	7
Ren	2005	China	60.40 ± 9.77	CAD	HB	67	24	9	31	26	13	0.087	7
Yang	2013	China	61.47 ± 9.95	CAD	HB	73	27	10	34	29	17	0.031	7
Huang	2013	China	59.30 ± 12.10	CAD	HB	104	23	10	54	51	20	0.184	7
Al-Hazzani	2014	Caucasian	46.61 ± 16.15	CAD	HB	73	98	54	31	50	29	0.342	8
Bonfim(a)	2016	African-Brazilians	55.70 ± 7.90	CAD	HB	71	104	25	27	28	11	0.4234	8
Bonfim(b)	2016	Caucasian-Brazilians	55.70 ± 6.70	CAD	HB	103	146	73	25	67	34	0.439	8
Khatami	2017	Iran	52.60 ± 7.20	CAD	HB	15	50	83	10	31	94	0.004	8
Isordia-Salas	2018	Mexico	41.00 ± 5.30	MI	PB	6	98	138	10	62	170	0.163	8
Zhu	2019	China	65.24 ± 10.69	CAD	HB	23	11	3	123	42	5	0.545	8

Abbreviations: HB, hospital-based; MI, myocardial infarction; PB, population-based.

Table 2 The basic characteristics of EL 584C/T polymorphism included in the literature

First author	Year	Country	Age (CAD)	End point	Source of controls	CAD			Control			HWE (control)	NOS score
						CC	CT	TT	CC	CT	TT		
Rimm	1992	America	NR	CAD	PB	129	117	16	240	239	40	0.060	8
Colditz	1997	America	NR	CAD	PB	115	110	16	224	214	39	0.220	8
Tjonneland	2007	Danmark	50–64	CAD	PB	509	406	83	837	673	133	0.840	8
Zhu	2007	China	64.74 ± 9.52	CAD	PB	186	56	0	150	46	0	0.063	7
Shimizu	2007	Japan	60.10 ± 0.80	CAD	PB	70	36	1	54	50	3	0.030	8
Tang	2008	China	62.80 ± 0.60	CAD	HB	174	85	6	125	122	18	0.100	8
Zhang	2009	China	54–71	CAD	HB	493	379	69	405	333	56	0.264	7
Vergeer	2010	Netherlands	45–79	CAD	PB	97	413	87	207	857	207	0.000	8
Cai	2014	China	51.81 ± 7.76	CAD	HB	84	45	6	97	64	5	0.146	8
Xie	2015	China	59.88 ± 9.20	CAD	HB	160	116	11	216	139	12	0.065	8
Toosi	2015	Iran	64 ± 4.2	CAD	HB	67	70	3	28	46	6	0.029	8
Elnaggar	2018	Egypt	55.90 ± 6.30	CAD	HB	58	23	2	17	21	4	0.492	8
Solim	2018	Turkish	63.04 ± 8.92	CAD	HB	40	27	6	26	33	14	0.545	8

Abbreviations: HB, hospital-based; MI, myocardial infarction; NR, not reported; PB, population-based.

was also statistically significant after the control group was removed from the study that did not meet HWE. The funnel plot (Figure 4A) was symmetrical. Egger's test results showed that $P > 0.05$, suggesting no publication bias.

Comparing allele C with allele T at 584C/T locus of EL gene, the heterogeneity between studies was significant ($I^2 = 69.5\%$, $P < 0.05$). Therefore, the REM was used for data merging. The results showed that OR = 0.83 (95% CI: 0.73–0.95), the difference was statistically significant. The analysis of the Caucasian population subgroup and the subgroup without the control group that did not meet HWE showed statistically significant differences. In the Asian population, the allele model was not statistically significant. The funnel plot (see in Figure 5A) was generally symmetrical, and the P-value of Egger's test was less than 0.05, indicating a particular publication bias.

Table 3 The results of meta-analysis of AGT M235T polymorphism and CAD susceptibility

Gene model	Subgroup	n	OR	95% CI	P	I²	P for hetero-geneity	Model	P for publication bias (Egger)
T vs. M	Overall	17	1.38	1.15–1.65	0.001	69.2	0.000	REM	0.459
	China	12	1.42	1.08–1.87	0.011	76.7	0.000	REM	0.767
	Caucasian	4	1.37	1.16–1.61	0.000	0.0	0.601	FEM	0.532
	HWE satisfied	15	1.32	1.09–1.60	0.005	68.9	0.000	REM	0.590
TT+TM vs. MM	Overall	17	1.51	1.28–1.80	0.000	17.3	0.251	FEM	0.764
	China	12	1.53	1.15–2.02	0.003	32.8	0.128	FEM	0.205
	Caucasian	4	1.52	1.21–1.90	0.000	0.0	0.402	FEM	0.337
	HWE satisfied	15	1.43	1.19–1.73	0.000	16.0	0.274	FEM	0.670
TT vs. TM+MM	Overall	17	1.42	1.11–1.83	0.006	68.1	0.000	REM	0.884
	China	12	1.54	1.12–2.12	0.008	73.3	0.000	REM	0.458
	Caucasian	4	1.39	1.03–1.89	0.033	32.5	0.217	FEM	0.395
	HWE satisfied	15	1.36	1.04–1.78	0.023	69.3	0.000	REM	0.891
TT vs. MM	Overall	17	1.56	1.15–2.12	0.004	43.9	0.027	FEM	0.759
	China	12	1.66	1.05–2.12	0.029	54.8	0.011	REM	0.272
	Caucasian	4	1.45	1.01–2.08	0.042	0.0	0.425	FEM	0.443
	HWE satisfied	15	1.46	1.05–2.03	0.026	43.8	0.036	REM	0.746
TM vs. MM	Overall	17	1.32	1.10–1.59	0.003	2.5	0.425	FEM	0.037
	China	12	1.07	0.79–1.46	0.650	0.0	0.755	FEM	0.201
	Caucasian	4	1.48	1.16–1.88	0.001	50.7	0.107	FEM	0.334
	HWE satisfied	15	1.25	1.03–1.53	0.027	4.3	0.425	FEM	0.055

Table 4 The results of meta-analysis of EL 584C/T polymorphism and CAD susceptibility

| Gene model	Subgroup	n	OR	95% CI	P	I²	P for hetero-geneity	Model	P for publication bias (Egger)
T vs. C	Overall	13	0.83	0.73–0.95	0.006	69.5	0.000	REM	0.011
	Asian	6	0.84	0.66–1.07	0.151	74.5	0.001	REM	0.462
	Caucasian	7	0.83	0.70–0.98	0.029	68.9	0.004	REM	0.000
	HWE satisfied	10	0.84	0.72–0.98	0.031	72.9	0	REM	0.064
TT+TC vs. CC	Overall	13	0.80	0.68–0.95	0.009	66.8	0.000	REM	0.013
	Asian	6	0.80	0.60–1.06	0.116	73.5	0.002	REM	0.443
	Caucasian	7	0.81	0.65–1.01	0.057	64.0	0.011	REM	0.003
	HWE satisfied	10	0.82	0.68–0.99	0.036	70.1	0.000	REM	0.072
TT vs. TC+CC	Overall	12	0.87	0.75–1.02	0.078	32.3	0.132	FEM	0.100
	Asian	5	0.92	0.68–1.23	0.563	43.8	0.130	FEM	0.668
	Caucasian	7	0.86	0.72–1.02	0.090	32.8	0.177	FEM	0.009
	HWE satisfied	9	0.90	0.75–1.08	0.244	37.2	0.121	FEM	0.173
TT vs. CC	Overall	12	0.73	0.55–0.98	0.034	52.9	0.016	REM	0.043
	Asian	5	0.75	0.39–1.45	0.396	60.0	0.040	REM	0.647
	Caucasian	7	0.70	0.49–1.00	0.050	54.9	0.038	REM	0.001
	HWE satisfied	9	0.74	0.53–1.05	0.092	56.9	0.017	REM	0.141
TC vs. CC	Overall	13	0.84	0.72–0.97	0.019	57.2	0.005	REM	0.017
	Asian	6	0.81	0.62–1.04	0.100	66.4	0.011	REM	0.429
	Caucasian	7	0.87	0.72–1.05	0.143	50.7	0.058	REM	0.008
	HWE satisfied	10	0.85	0.71–1.00	0.055	57.2	0.005	REM	0.083

Comparison of dominant gene inheritance models

The comparison of genotype TT+MT with genotype MM at M235T locus of the AGT gene showed that the heterogeneity between studies was not significant ($I^2 = 17.3\%$, $P>0.05$). Therefore, the FEM was used for data merging. The results showed that OR = 1.51 (95% CI: 1.28–1.80), the difference was statistically significant. The same conclusion was obtained in the subgroup analysis of Chinese and Caucasian populations. After excluding the study that
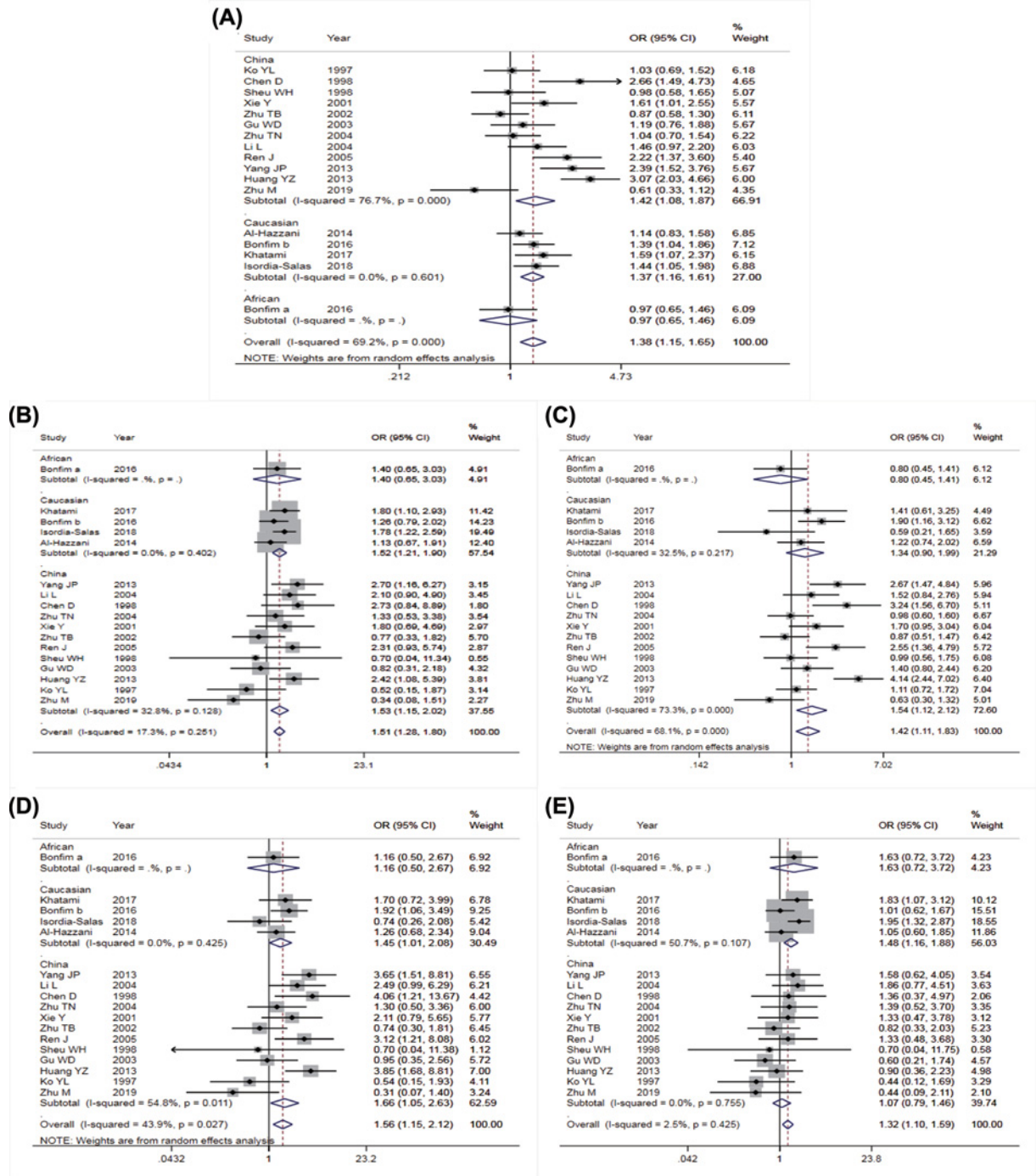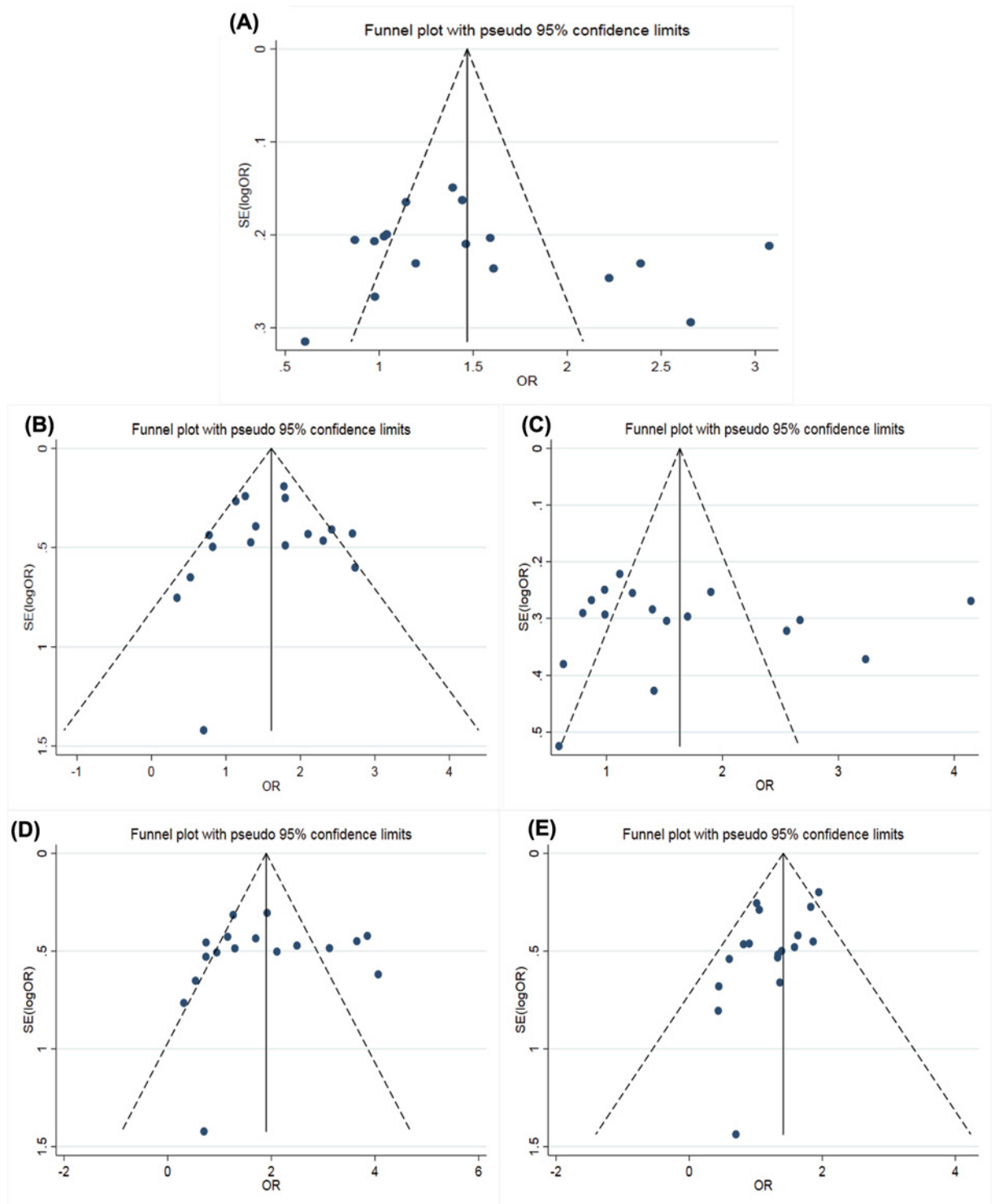
Figure 2. Forest plots of Angiotensinogen M235T polymorphism and susceptibility to coronary artery disease

Forest plots of AGT M235T polymorphism and CAD susceptibility (**A**) allele model; (**B**) dominant model; (**C**) recessive model; (**D**) homozygous model; (**E**) heterozygous model.

the control group did not meet HWE, the dominant gene model was also statistically significant. The funnel diagram was symmetrical (see in Figure 4B). Egger's test results indicated that there was no publication bias with $P > 0.05$.

The heterogeneity between the genotype TT+TC and genotype CC of EL 584C/T was significant ($I^2 = 66.8\%$, $P < 0.05$), so, the REM was used for data integration. The results showed that OR = 0.80 (95% CI: 0.68–0.95), the difference was statistically significant. Excluding the subgroup analysis of the control group that did not meet HWE,
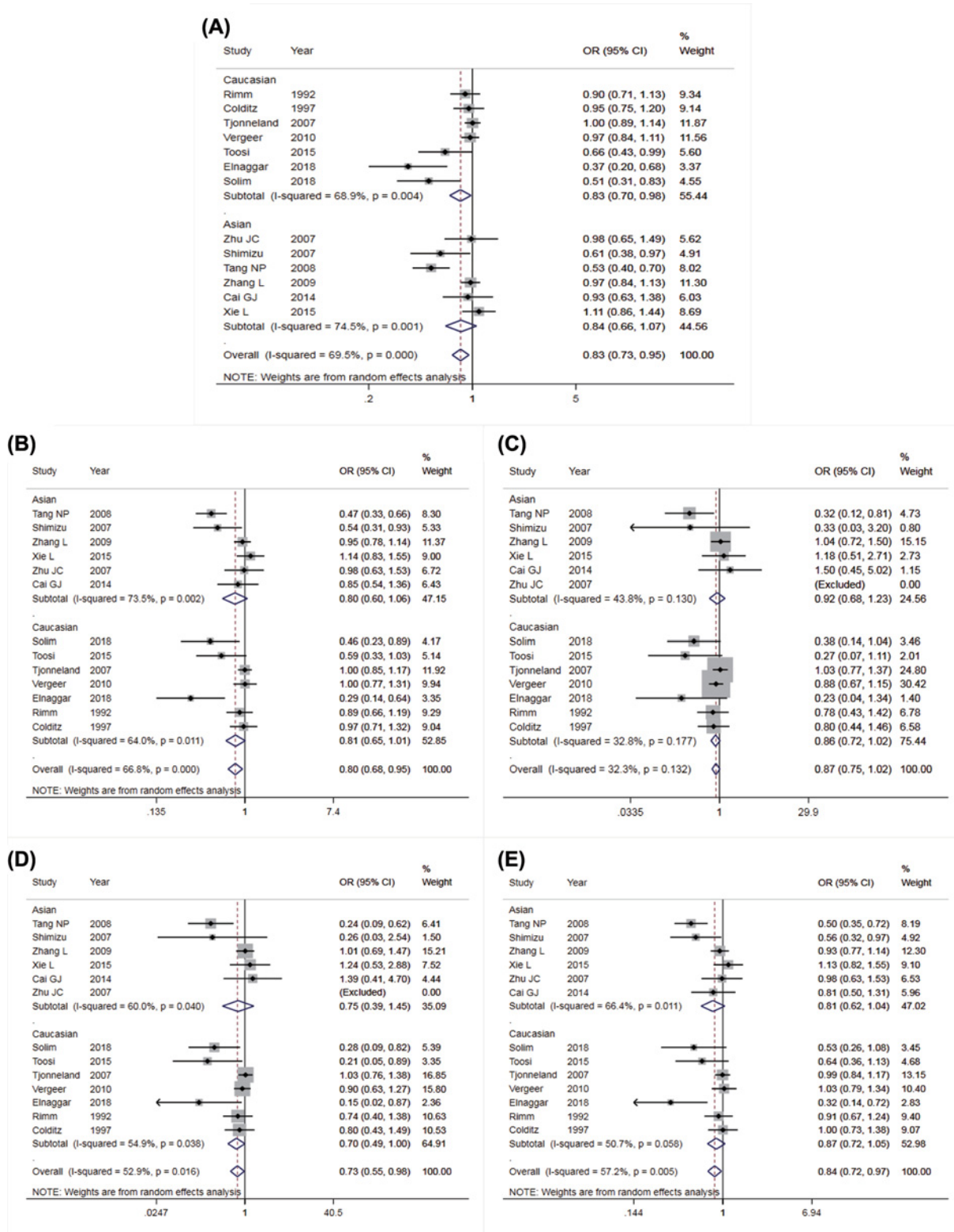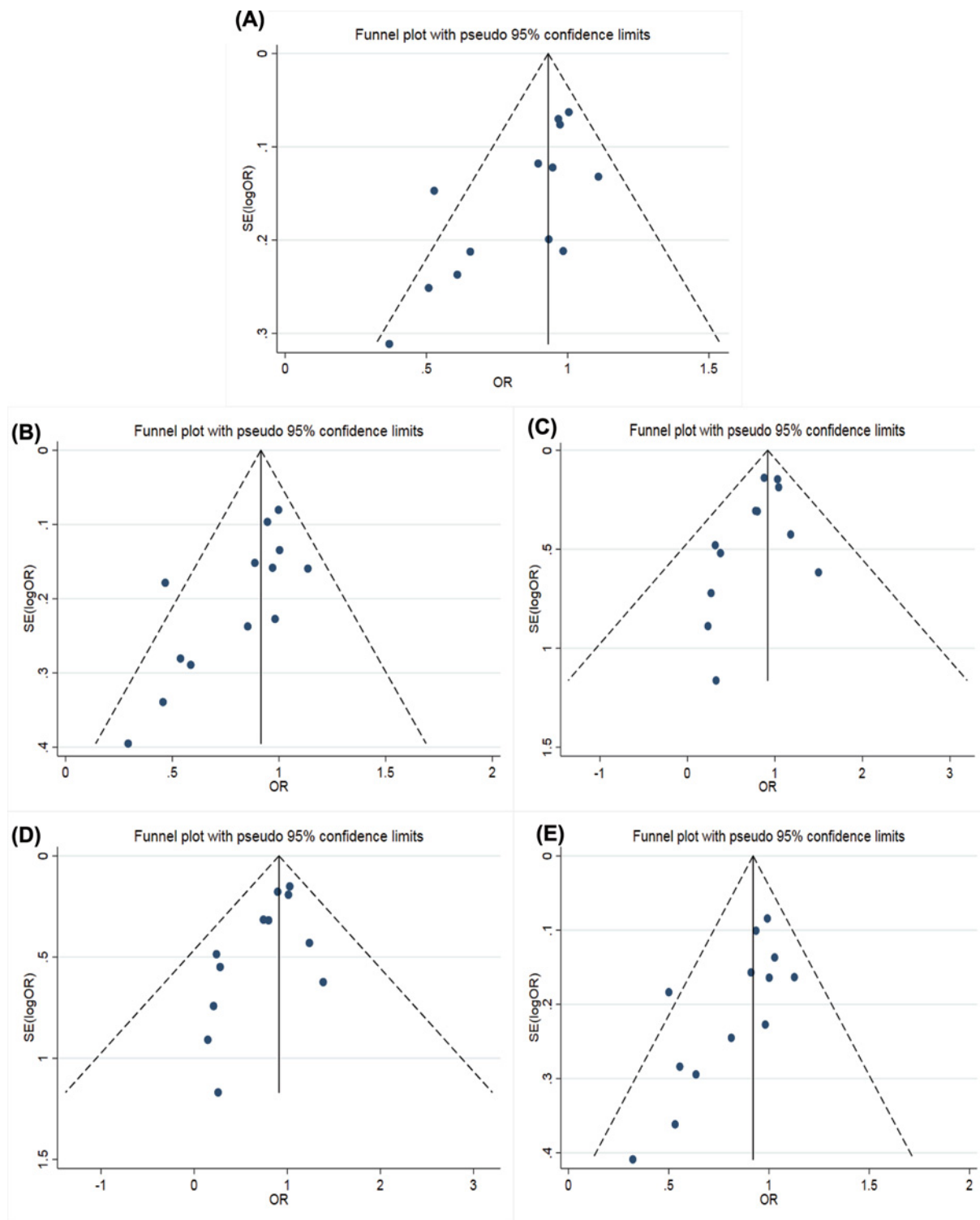
Figure 3. Forest plots of Endothelial lipase 584C/T and susceptibility to coronary artery disease

Forest plots of EL 584C/T polymorphism and CAD susceptibility (**A**) allele model; (**B**) dominant model; (**C**) recessive model; (**D**) homozygous model; (**E**) heterozygous model.

Figure 4. Funnel plots of Angiotensinogen M235T polymorphism and susceptibility to coronary artery disease
Funnel plots of AGT M235T polymorphism and CAD susceptibility (**A**) allele model; (**B**) dominant model; (**C**) recessive model; (**D**) homozygous model; (**E**) heterozygous model.

Figure 5. Funnel plots of Endothelial lipase 584C/T and susceptibility to coronary artery disease

Funnel plots of EL 584C/T polymorphism and CAD susceptibility (**A**) allele model; (**B**) dominant model; (**C**) recessive model; (**D**) homozygous model; (**E**) heterozygous model.

the difference was statistically significant. In the subgroup analysis of the Caucasian and Asian populations, the dominant gene model was not statistically significant. The symmetry of the funnel plot (Figure 5B) was general, *P*-value of Egger's test was less than 0.05, indicating that there was a particular publication bias.

Comparison of recessive gene inheritance models

The comparison of genotype TT with genotype MT+MM at M235T locus of AGT gene showed that the heterogeneity between the studies was significant (I^2 = 68.1%, $P<0.05$), then, the REM was used to integrate data. The results indicated that OR = 1.42 (95% CI: 1.11–1.83), the difference was statistically significant. The same conclusion was reached in the subgroup analysis of Chinese and Caucasian populations. The recessive gene model was also statistically significant after removing the control groups that did not satisfy HWE. The funnel plot was symmetrical, shown in Figure 4C. Egger's test results suggested that there was no publication bias ($P>0.05$).

Compared genotype TT with genotype TC+CC at 584C/T locus of EL gene, there was no significant heterogeneity between studies (I^2 = 32.3%, $P>0.05$), and the FEM was used. The results showed that there was no significant difference with OR = 0.87 (95% CI: 0.75–1.02). Subgroup analysis that removed the control group that did not meet HWE showed no statistically significant difference. The recessive gene model was also not statistically significant in the Caucasian and Asian subgroups. The funnel plot (Figure 5C) was symmetrical. The *P*-value of Egger's test was higher than 0.05, indicating a low publication bias.

Comparison of homozygous genetic models

The comparison between genotype TT and genotype MM at M235T locus of the AGT gene showed no significant heterogeneity between studies (I^2 = 43.9%, $P>0.05$). Therefore, the FEM was applied. The results showed that OR = 1.56 (95% CI: 1.15–2.12), the difference was statistically significant. The same conclusion was obtained from the subgroup analysis of Chinese and Caucasian populations. After excluding the study that the control group did not meet HWE, the homozygous genetic model was statistically significant. The funnel plot was symmetrical (see in Figure 4D). Egger's test results suggested that there was no publication bias ($P>0.05$).

Compared genotype CC with genotype TT at 584C/T locus of EL gene, there was significant heterogeneity (I^2 = 52.9%, $P<0.05$), then, the REM was applied. The results showed that OR = 0.0.73 (95% CI: 0.55–0.98), the difference was statistically significant. Subgroup analysis that removed the control group that did not meet HWE showed no statistically significant difference. In the subgroup analysis of Caucasian and Asian populations, the heterogeneity was not significantly decreased, and the homozygous gene model was not statistically significant. The symmetry of the funnel chart shown in Figure 5D was general, and the *P*-value of Egger's test was slightly less than 0.05, indicating partial publication bias.

Comparison of heterozygous genetic models

The comparison of genotype TM at M235T locus of the AGT gene with genotype MM suggested that the heterogeneity was not significant (I^2 = 2.5%, $P>0.05$). Therefore, the FEM was used for data merging. The results showed that OR = 1.32 (95% CI: 1.10–1.59), the difference was statistically significant. The same conclusion was obtained in the Caucasian population subgroup after removal of the control group that did not satisfy HWE. While, the heterozygous genetic model had no statistical significance in the Chinese population. The symmetry of the funnel plot was general (see in Figure 4E). Egger's test results showed that $P<0.05$, indicating that there was a partial publication bias.

Compared genotype CC with genotype TC at 584C/T locus of EL gene, significant heterogeneity was found (I^2 = 57.2%, $P<0.05$), then the REM was applied for data merging. The results showed that OR = 0.84 (95% CI: 0.72–0.97), the difference was statistically significant. Subgroup analysis that removed the control group that did not meet HWE showed no statistically significant difference. In the subgroup analysis of the Caucasian and Asian populations, the heterozygous gene model was also not statistically significant. The funnel plot shown in Figure 5E was generally symmetrical. Egger's test result indicated partial publication bias with *P*-value that was slightly less than 0.05.
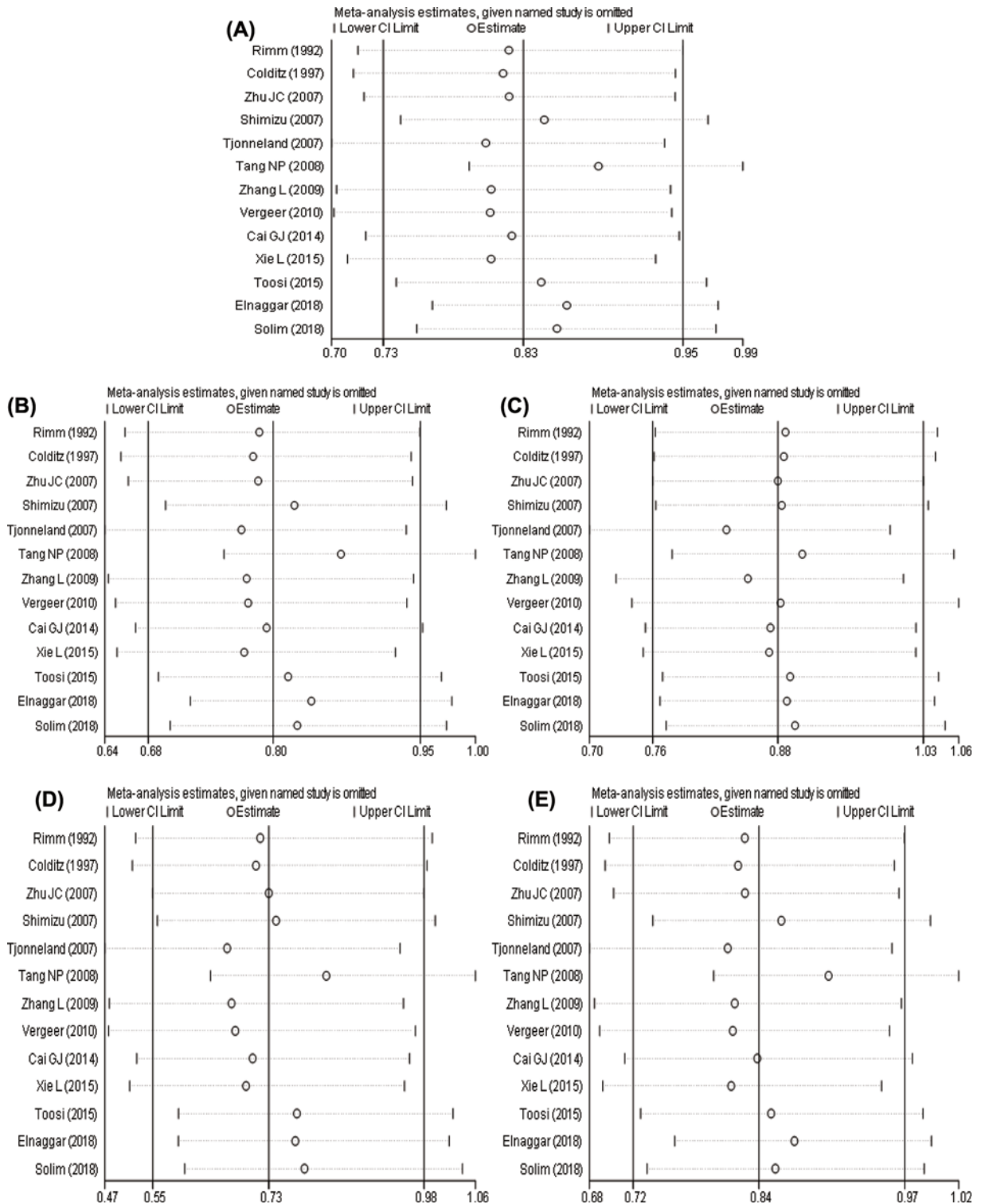
Sensitivity analysis

The result of susceptibility analysis between AGT M235T polymorphism and susceptibility to CAD is shown in Figure 6. It indicated that there was a statistically significant change in the heterozygous genetic model after elimination of one study. In contrast, no statistically significant change manifested in the allele model and other genetic models after removing the single literature, suggesting that the result was robust.

The sensitivity analysis result of EL 584C/T polymorphism and CAD susceptibility is shown in Figure 7. It showed that there was no statistically significant change in the allele model after a single study was eliminated, indicating that the result of the allele model was robust. The dominant gene model, recessive gene model, homozygous gene
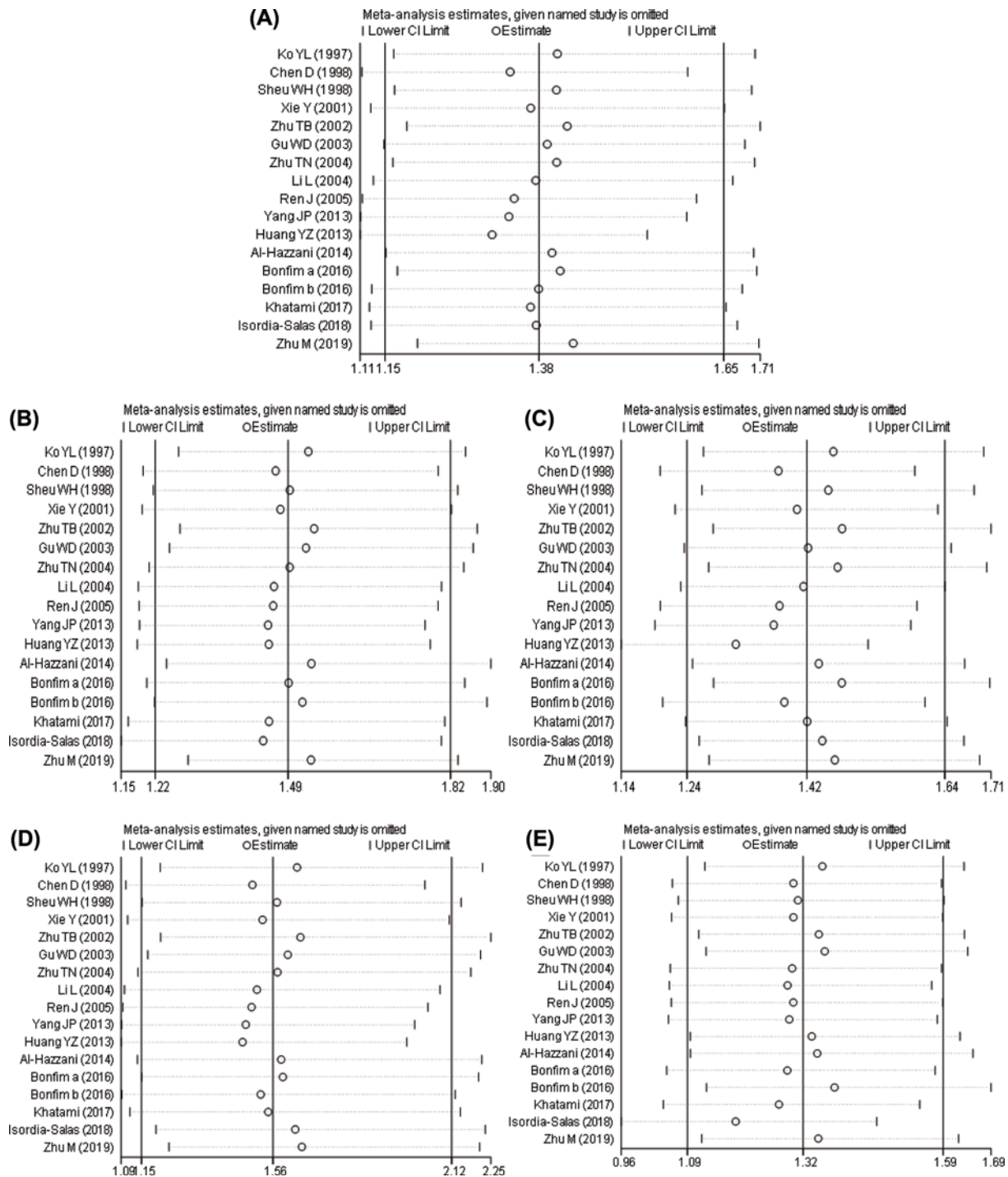
Figure 6. The results of sensitivity analysis between Angiotensinogen M235T polymorphism and susceptibility to coronary artery disease

The result of susceptibility analysis between AGT M235T polymorphism and susceptibility to CAD (**A**) allele model; (**B**) dominant model; (**C**) recessive model; (**D**) homozygous model; (**E**) heterozygous model.

Figure 7. The results of sensitivity analysis between Endothelial lipase 584C/T polymorphism and susceptibility to coronary artery disease

The result of sensitivity analysis between EL 584C/T polymorphism and susceptibility to CAD (**A**) allele model; (**B**) dominant model; (**C**) recessive model; (**D**) homozygous model; (**E**) heterozygous model.

model and heterozygous gene model had one, one, four, one study, respectively, and they were excluded one by one; the differences were statistically significant.

Discussion

The purpose of the present study was to explore the association between AGT M235T, EL 584C/T polymorphisms and CAD. In recent years, the polymorphism of AGT and EL genes have attracted considerable attention of researchers. It has been found that both AGT and EL genes have gene polymorphisms, which may affect gene transcription and expression, and are closely associated with the significant increase in coronary heart disease risks [44,45]. Also, AGT polymorphism may affect restenosis after stent implantation in patients with coronary heart disease [46]. Junusbekov et al. [47] suggests that AGT rs699 gene mutations are associated with cardiovascular phenotypes in atherosclerotic peripheral arterial obstructive disease. Moreover, AGT polymorphism was associated with cardiovascular risk in patients with acromegaly [48]. Studies have shown that serum concentration of full-length EL and carboxyl-terminal fragments could predict cardiovascular risk in patients with coronary heart disease [49]. Therefore, it is of considerable significance to study the polymorphism of AGT and EL genes and the susceptibility to CAD.

The results of AGT M235T polymorphism and CAD showed that the differences were statistically significant in the dominant, recessive, homozygous, heterozygous, and allelic gene models. Allele T could be a risk factor for CAD. After removing two studies, in which the control group did not satisfy HWE, the results of meta-analysis were consistent with those before exclusion. The ethnicity subgroup analysis results suggested that except the heterozygous genetic model of the Chinese population, it was statistically significant in other genetic models of the Chinese population and all genetic models of the Caucasian population. Also, the funnel plot of publication bias was symmetrical, and the *P*-value of Egger's test was greater than 0.05, suggesting that there was no publication bias and the correlation between AGT M235T polymorphism and CAD susceptibility was robust, which was also verified by sensitivity analysis results. In a meta-analysis involving nine studies, Wang et al. [50] indicated that the genotype TT of AGT M235T might increase the risk of CAD, which is consistent with the results of this study. We have included more recent studies to demonstrate such a correlation.

The results of EL 584C/T polymorphism and CAD showed that the differences were statistically significant in dominant, homozygous, heterozygous, and allelic gene models, and the recessive genetic model had no statistical significance. Allele model and dominant gene model were still statistically significant after the control groups not meeting HWE were removed, which indicated that the two models were robust. While, in the results of the ethnicity subgroup analysis, there was no statistical significance in dominant, recessive, homozygous, and heterozygous genetic models of Asian and Caucasian populations. Also, the heterogeneity did not decrease significantly, suggesting that ethnicity may not be the primary source of heterogeneity. The results of publication bias showed that the symmetry of funnel plots in many genetic models were general, and the *P*-values of Egger's test were all slightly less than 0.05, indicating the robustness deviation of the conclusion. Also, there may be a potential publication bias having a significant impact on the outcome. It can also be seen from the results of sensitivity analysis that, except the allele genetic model, the differences in other genetic models were statistically significant after excluding some of the literatures, which indicated that the conclusion of 584C/T polymorphism of the EL gene and susceptibility to CAD should be taken seriously. A meta-analysis of EL 584C/T polymorphism and coronary heart disease susceptibility by Cai et al. [51] suggested that there were significant differences between allele model and homozygote model in the Asian population. At the same time, there were no statistical differences in allele model of the Caucasian population, which is not consistent with the conclusion of this study, as more high-quality researches are included in the present study.

Furthermore, the present study also had some limitations: (1) there was heterogeneity in allele model, recessive gene model and homozygous model of AGT M235T gene, and the heterogeneity did not decrease significantly according to ethnic subgroup analysis, (2) the heterogeneity of the EL 584C/T gene was significant in all genetic models except the recessive gene model, and there was no significant decrease in the heterogeneity after analysis by ethnic subgroup, (3) except recessive gene model, EL 584C/T gene had publication bias in other genetic models, especially in Caucasian population, (4) the interactions between gene and gene, gene and environment were not analyzed.

In conclusion, AGT M235T and EL 584C/T genes are associated with CAD susceptibility. Allele T, genotype TT and TC of AGT M235T gene and allele C, genotype CC of EL 584C/T gene could increase the risk of CAD. In particular, the relationship between the AGT M235T gene and CAD is robust, while the relationship between the EL 584C/T gene and CAD susceptibility is unstable. Furthermore, considering the limitations of the present study, further studies are required on a larger scale to explore the relationship between AGT and EL polymorphisms, and CAD susceptibility.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution

Hongyan Zhao, Jidong Rong: critical revision of the manuscript. Hongyan Zhao, Ranzun Zhao, Jidong Rong: substantial contribution to the conception and design of the work, manuscript drafting. Hongyan Zhao, Shan Hu: acquisition, analysis, and interpretation of the data. Hongyan Zhao,Ranzun Zhao: revising the manuscript critically, final approval of the version to be published.

Abbreviations

AGT, angiotensinogen; CAD, coronary artery disease; EL, endothelial lipase; FEM, fixed-effects model; HDL-C, high-density lipoprotein cholesterol; HWE, Hardy–Weinberg equilibrium; NOS, Newcastle–Ottawa Scale; OR, odds ratio; REM, random-effects model.

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Supplementary table 1 Quality assessment included in the study(NOS)

First author	Year	Case selection				Comparability between groups		Exposure factor measurement			NOS score
		1	2	3	4	5	6	Blind method	7	Response rate	
Ko YL	1997	*	*	*	*	*	*	?	*	*	8
Chen D	1998	*	*	*	*	*	*	?	*	*	8
Sheu WH	1998	*	*	*	*	*	*	?	*	?	7
Xie Y	2001	*	*	*	*	*	*	?	*	?	7
Zhu TB	2002	*	*	*	*	*	*	?	*	*	8
Gu WD	2003	*	*	*	*	*	*	?	*	*	8
Zhu TN	2004	*	*	*	*	*	*	?	*	*	8
Li L	2004	*	*	*	*	*	*	?	*	?	7
Ren J	2005	*	*	*	*	*	*	?	*	?	7
Yang JP	2013	*	*	*	*	*	*	?	*	?	7
Huang YZ	2013	*	*	*	*	*	*	?	*	?	7
Al-Hazzani	2014	*	*	*	*	*	*	?	*	*	8
Bonfim a	2016	*	*	*	*	*	*	?	*	*	8
Bonfim b	2016	*	*	*	*	*	*	?	*	*	8
Khatami	2017	*	*	*	*	*	*	?	*	*	8
Isordia-Salas	2018	*	*	*	*	*	*	?	*	*	8
Zhu M	2019	*	*	*	*	*	*	?	*	*	8
Rimm	1992	*	*	*	*	*	*	?	*	*	8
Colditz	1997	*	*	*	*	*	*	?	*	*	8
Tjonneland	2007	*	*	*	*	*	*	?	*	*	8
Zhu JC	2007	*	*	*	*	*	*	?	*	?	7
Tang NP	2008	*	*	*	*	*	*	?	*	*	8
Zhang L	2009	*	*	*	*	*	*	?	*	?	7
Cai GJ	2014	*	*	*	*	*	*	?	*	*	8
Xie L	2015	*	*	*	*	*	*	?	*	*	8
Elnaggar	2018	*	*	*	*	*	*	?	*	*	8
Solim	2018	*	*	*	*	*	*	?	*	*	8
Shimizu	2007	*	*	*	*	*	*	?	*	*	8
Vergeer	2010	*	*	*	*	*	*	?	*	*	8
Toosi	2015	*	*	*	*	*	*	?	*	*	8

Note:*:Yes;?:unclear;1:Case identification appropriate;2:Case representativeness;3:The source of the control clear;4:control group choosed properly;5:Controls the most important confounding factors;6:Control other confounding factors;7:same exposure determination method; NOS:Newcastle-Ottawa Scale