M235T polymorphism in the angiotensinogen gene and cardiovascular disease: An updated meta-analysis of 39 case–control comparisons

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Abstract

Objective: M235T polymorphism of the angiotensinogen (AGT) gene has been linked with cardiovascular disease (CVD). The aim of this meta-analysis was to investigate whether combined evidence supports this association.
Methods: A systematic search was conducted for studies published up to October 2018 that evaluate the association between AGT M235T polymorphism and risk of CVD. Case–control studies were identified, and the association between AGT M235T polymorphism and CVD risk was assessed using genetic models.
Results: Thirty-nine comparisons from 38 studies were collected, and a meta-analysis and subgroup analysis was performed based on ethnicity. In the overall population (9225 cases and 8406 controls), the occurrence of CVD was found to be associated with AGT M235T polymorphism in both allelic [T vs. M: odds ratio (OR)=1.16] and recessive (TT vs. MT+MM: OR=1.14) models. In subgroup analyses, a significant association was identified between AGT M235T polymorphism and CVD risk in East Asian subgroups in allelic (T vs. M: OR=1.46), homozygous (TT vs. MM: OR=1.78), dominant (MT+TT vs. MM: OR=1.47), and recessive (TT vs. MT+MM: OR=1.68) models, but there was no significant association in Caucasian populations.
Conclusion: Among East Asians, the AGT variant M235T is associated with CVD risk. However, current evidence suggests that there is no such association in the Caucasian population. *(Anatol J Cardiol 2019; 21: 222-32)*
Keywords: angiotensinogen, genetic polymorphism, cardiovascular disease

Introduction

Cardiovascular disease (CVD) is the main cause of death and leads to over 30% of mortality annually worldwide (1). The general risk factors for CVD include smoking, high body mass index, hypertension, lipid metabolism disorders, and diabetes mellitus, among several other factors (2). Emerging evidence has demonstrated that genetic and environmental factors and polymorphisms also play a crucial role in the occurrence and development of CVD (3, 4). The advancement in single-nucleotide polymorphism (SNP) and genome-wide sequencing technologies has led to an increased number of in-depth studies on the genetics of CVD, and a number of candidate genes have been identified, such as those involved in the regulation of lipid metabolism (5), inflammatory cytokines (6), and the renin–angiotensin–aldosterone system (RAAS) (7).

The RAAS plays a critical role in the pathogenesis of coronary heart disease, and previous studies have determined that it is involved in the progression of hypertension and vascular and left ventricular remodeling (8). Much accumulated evidence has indicated that the RAAS is significantly associated with the initiation and progression of coronary atherosclerosis and thrombogenesis (9). In addition, studies involving angiotensin-converting enzyme (ACE) inhibition and angiotensin II receptor blockade have highlighted the vital role of the RAAS, and gene polymorphism of the RAAS may also affect the efficacy of drug (10). Recently, several genetic variants in the RAAS have been found to be significantly associated with

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CVD risk, such as an insertion/deletion polymorphism in the ACE gene, and T175M and M235T polymorphisms in the angiotensinogen (AGT) gene (11-13). AGT is a crucial determinant of angiotensin II levels, which is an important component of the RAAS. Furthermore, polymorphism in the AGT gene may contribute to atherogenesis in the coronary artery and may be related to the development of CVD (14, 15). The M235T polymorphism has been most widely studied; however, several inconsistent results regarding this polymorphism and CVD risk have been reported. Raygan et al. (16), Bonfim-Silva et al. (17), and Isordia-Salas et al. (18) detected positive correlations, whereas Renner et al. (19), Ranjith et al. (20), and Erbas et al. (21) determined that the AGT M235T polymorphism has no significant effect on the development of CVD. Meta-analyses have been performed to resolve these discrepancies; however, these analyses have been compromised by deficiencies in the sample size, and the results have been either inconclusive or only weakly significant (16). Some of the studies have been limited to Asian populations (22, 23), and several of the most recent studies have not been considered. The aim of the present study was to compile case–control research and updated meta-analyses to explore the association between AGT M235T polymorphism and susceptibility for CVD in a range of populations for more accurate assessment.

Methods

Search strategy

A systematic search of MEDLINE, Embase, China National Knowledge Infrastructure, OVID, ScienceDirect, and WanFang databases was performed to identify epidemiological studies on M235T polymorphisms of the AGT gene and CVD that were published up to October 2018. In the literature searches, various combinations of the keywords "angiotensinogen gene," "AGT," "M235T gene," "genetic polymorphism," "variants," or "variations," "coronary heart disease," "coronary artery disease," "cardiovascular disease," "myocardial infarction," "ischemic heart disease," and "coronary stenosis" were used. Only studies published in English or Chinese were included in the study. The references of all full text papers were examined to identify additional relevant studies. Secondary searches of gray literature were not performed. All retrieved articles were organized using reference manager software (Endnote 6).

Inclusion and exclusion criteria

Inclusion criteria were the following: (1) the study evaluated AGT M235T and CVD risk, (2) original research (case–control studies) or AGT M235T genotype frequencies were provided by case–control status, (3) the study had sufficient data to allow the association between AGT M235T and CVD risk, (4) the study included original data, independent of other studies, and (5) the language of the report was in English or Chinese. Exclusion criteria were the following: (1) overlapping data, (2) missing information (particularly genotype distributions and studies without controls), after having not received the requested information from the corresponding author, and (3) genome scans investigating linkages without detailed genotype frequencies between cases and controls. Two reviewers independently screened the titles and abstracts for eligibility criteria. Thereafter, the reviewers read the full text of the studies that potentially met the inclusion criteria, and the literature was reviewed to determine the final inclusion of data. For each study, the following information was recorded: first author, year of publication, geographical area, ethnicity, number of cases and controls, genotypes for cases and controls, and evidence of Hardy–Weinberg equilibrium in the controls. If the two reviewers disagreed regarding the inclusions of a study, a consensus was reached through additional review and discussion.

Data extraction

The two reviewers extracted data from each study independently, and any discrepancies were resolved. The information extracted from each article in Tables 1 and 2, including first author, year of publication, country of origin, ethnicity of patients, numbers of cases and controls, AGT genotypes, allele distribution of cases and controls, and outcome, was summarized.

Statistical analysis

Data analysis was conducted using STATA 12.0 software (StataCorp, College Station, TX, USA). The association between AGT M235T polymorphism and CVD susceptibility was assessed in the following genetic models: T versus M (allelic), TT versus MM (co-dominant), MT versus MM (co-dominant), MT+TT versus MM (dominant), and MT+MM versus TT (recessive). Inter-study heterogeneity was tested using Q-statistics. The Mantel–Haenszel method for fixed effects and the DerSimonian and Laird method for random effects were used to estimate pooled effects (24). The fixed effects method was used if the result of the Q test was not significant. Otherwise, the pooled odds ratio (OR) and 95% confidence interval (CI), assuming a random effects model, were calculated. Fixed effects assume that genetic factors have similar effects on CVD susceptibility across all studies, and that the observed variations among studies are caused by chance alone (25). The random effects model assumes that different studies may have substantial diversity and assesses both intra- and inter-study variations (26). A recently developed measure, I^2, was used to quantify the inconsistency among the studies' results for values of ≥50%, with large heterogeneity among values of ≥75% (27). Data are expressed as OR with 95% CI and two-tailed p-values. A p-value <0.05 was considered statistically significant. Assessment of publication bias was conducted both visually by using a funnel plot and statistically via Begg's funnel plots

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and Egger's bias test, which measures the degree of funnel plot asymmetry (28, 29). The Begg's adjusted rank correlation test was used to assess the correlation between test accuracy estimates and their variances. The deviation of Spearman's rho values from zero provides an estimate of funnel plot asymmetry, where positive values indicate a trend toward higher levels of test accuracy in studies with smaller sample sizes. The Egger's bias test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision. Meta-regression analysis was applied to evaluate the heterogeneity of the studies.

Results

Search results and characteristics of included studies

Initially, 427 potentially relevant articles were obtained; however, after screening the abstracts, most were determined to be irrelevant to our analysis. Of the remaining 51 articles, 13 articles were removed because of an insufficient number of cases or unusable data. Eventually, 23 studies in English (12-21, 30-42) and 15 in Chinese (43-57), including 39 comparisons of the AGT M235T polymorphism that all adopted the observational study design, satisfied the eligibility criteria (Fig. 1). A total of 39 comparisons from the 38 studies of the AGT M235T polymorphism were included in this updated meta-analysis.

The relevant studies included 9225 cases and 8406 controls (Tables 1 and 2). Reference to the "overall population" indicates meta-analysis without ethnic subdivisions. Ethnicity-specific meta-analysis was categorized by Caucasian, East Asian, and other races (miscellaneous subgroup).

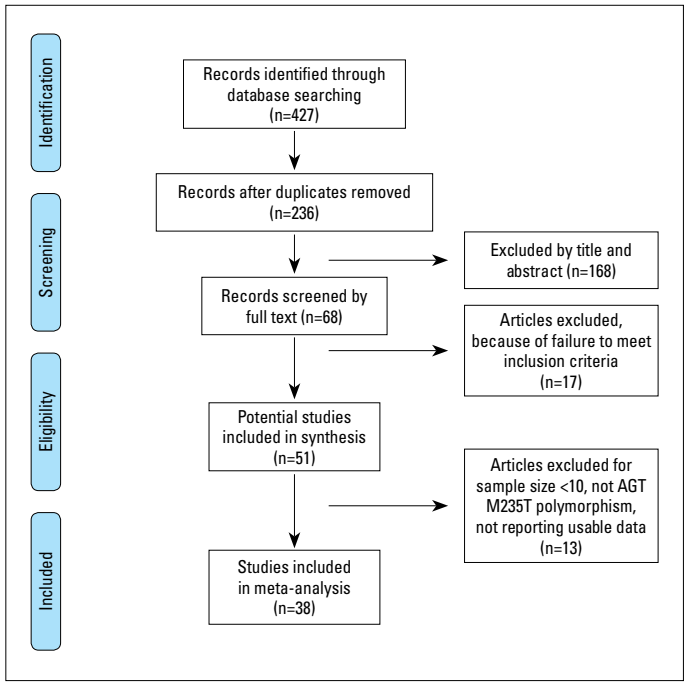

Figure 1. Flow of studies for meta-analysis

Association of the AGT M235T polymorphism with CVD risk in the overall population

As shown in Figure 2, significant heterogeneity among studies was observed for the overall population (P_h<0.10 or I^2≥50%). Using the random effect models, M235T was found to be associated with an increased risk of CVD in the allelic (T vs. M: OR=1.16, 95% CI=1.05–1.27, p<0.001) and recessive (TT vs. MT+MM: OR=1.14, 95% CI=1.06–1.23, p<0.001) models.

Association of the M235T polymorphism of the AGT gene with CVD risk in subgroups analysis

When analyses were subdivided according to ethnicity, no associations were noted for Caucasians using any of the five genetic models. However, for the East Asian subgroup, M235T was significantly associated with CVD risk in allelic (T vs. M: OR=1.46, 95% CI=1.13–1.90, p<0.001), homozygous (TT vs. MM: OR=1.78, 95% CI=1.18–2.67, p=0.01), dominant (MT+TT vs. MM: OR=1.47, 95% CI=1.05–2.04, p=0.02), and recessive (TT vs. MT+MM: OR=1.68, 95% CI=1.25–2.27, p<0.001) models. In miscellaneous populations, a significant association between M235T and CVD risk was observed in the allelic model (T vs. M: OR=1.21, 95% CI=1.07–1.36, p<0.001), but no association was observed in the other four genetic models. In subgroup analysis, neither moderate nor large heterogeneity was observed among Caucasians, but true heterogeneity was noted among East Asians (T vs. M: P_h<0.10, I^2=83% and TT vs. MT+MM: P_h<0.10, I^2=81%) and miscellaneous populations (MT vs. MM: P_h=0.05, I^2=51.1%) (Table 3).

Publication bias and sensitivity analysis

Publication bias was not detected in the analyses of the homozygote, heterozygote, or dominant models (p>0.05, for all). However, publication bias was noted in the analyses of the associations between M235T polymorphisms and CVD risk (allelic model: P_{Egger}=0.01, P_{Begg}=0.02 and recessive model: P_{Egger}=0.01) (Table 4). Sensitivity analyses showed that the present meta-analysis was relatively stable and credible (Fig. 3).

Meta-regression

A meta-regression analysis for several potential sources of heterogeneity, including published year, sample size, age, gender, outcome, and ethnic background, was performed. Single covariates were added in the allelic, homozygote, dominant, and recessive models. The results suggest that the East Asian population (allelic model: p=0.006, homozygote model: p=0.010, dominant model: p=0.022, and recessive model: p=0.005) and study size (homozygote model: p=0.042 and recessive model: p=0.010) contributed to the observed heterogeneity across all studies of the association between AGT M235T polymorphisms and CVD susceptibility.

Table 1. Characteristics and genotype frequencies for AGT M235T polymorphism in the included studies

Study	Year	ID	Country	Enthic	Sample size	Genotypes and allele distribution									
					Case/Control	Cases					Controls				
						MM	MT	TT	M	T	MM	MT	TT	M	T
Tiret et al.	1995	1	France	Caucasian	630	741	229	301	100	759	501	258	372	111	888	594
Kamitani et al.	1995	2	Japan	East Asian	103	103	6	31	66	43	163	10	41	52	61	145
Ko et al.	1997	3	China	East Asian	150	338	4	22	124	30	270	4	54	279	62	612
Chen et al.	1998	4	China	East Asian	57	76	4	13	40	21	93	13	31	32	57	95
Sheu et al.	1998	5	China	East Asian	102	145	1	26	75	28	176	1	37	107	39	251
Pastinen et al.	1998	6	Finland	Caucasian	122	122	48	66	37	162	140	53	64	34	170	132
Frossard et al.	1998	7	UAE	Caucasian	40	61	14	18	8	46	34	16	26	19	58	64
Gardemann et al.	1999	8	Germany	Caucasian	1058	511	319	582	157	1220	896	385	585	222	1355	1029
Winkelmann et al.	1999	9	Germany	Caucasian	122	92	38	54	30	130	114	28	53	11	109	75
Batalla et al.	2000	10	Spain	Caucasian	220	200	69	99	52	237	203	64	96	40	224	176
Fomicheva et al.	2000	11	Russia	Caucasian	198	152	63	85	50	211	185	43	75	34	161	143
Olivieri et al.	2001	12	Italy	Caucasian	247	245	63	124	60	250	244	54	76	27	184	130
Xie et al.	2001	13	China	East Asian	106	86	8	29	69	45	167	11	30	45	52	120
Fernández-Arcás et al.	2001	14	Spain	Caucasian	212	180	59	121	32	239	185	34	97	49	165	195
Ermis et al.	2002	15	Turkey	Miscellaneous	102	114	32	48	22	112	92	39	59	16	137	91
Hooper et al.	2002	16	USA	Miscellaneous	110	185	4	29	67	37	163	2	31	67	35	165
Zhu et al.	2002	17	China	East Asian	41	116	2	7	32	11	71	18	47	51	83	149
Zhu et al.	2002	18	China	East Asian	118	106	14	48	56	76	160	10	42	54	62	150
Bis et al.	2003	19	USA	Caucasian	208	717	71	98	39	240	176	215	349	153	779	655
Gu et al.	2003	20	China	East Asian	129	90	12	31	86	55	203	7	30	53	44	136
Ranjith et al.	2004	21	India	Miscellaneous	195	300	24	80	91	128	262	29	127	144	185	415
Zhu et al.	2004	22	China	East Asian	192	98	12	75	105	99	285	8	36	54	52	144
Li et al.	2004	23	China	East Asian	120	80	11	60	49	82	158	14	41	25	69	91
Tobin et al.	2004	24	England	Caucasian	547	505	212	252	83	676	418	197	226	82	620	390
Ren et al.	2005	25	China	East Asian	100	70	2	10	35	14	80	13	26	31	52	88
Araujo et al.	2005	26	Brazil	Caucasian	110	104	46	52	12	144	76	43	51	10	137	71
Renner et al.	2005	27	Austria	Caucasian	1370	733	NA	NA	NA	1537	1203	NA	NA	NA	832	634
Liang et al.	2006	28	China	East Asian	133	154	2	30	101	34	232	10	60	84	80	228
Tsai et al.	2007	29	China	East Asian	735	519	15	195	525	225	1245	5	111	403	121	917
Niu et al.	2008	30	China	East Asian	105	110	8	32	65	48	162	9	47	54	65	155
Zhu et al.	2010	31	China	East Asian	151	127	9	27	115	45	257	20	51	56	91	163
Peng et al.	2011	32	China	East Asian	196	200	14	54	128	82	155	18	86	96	122	278
Konopka et al.	2011	33	Poland	Caucasian	100	95	30	46	24	106	94	22	44	29	88	102
Mehri et al.	2011	34	Tunisia	Miscellaneous	123	144	29	53	41	111	135	53	61	30	167	121
Raygan et al.	2016	35	Iran	Miscellaneous	155	185	42	79	34	163	147	71	85	29	227	143
Bonfim-Silva et al.	2016	36	Brazil	Miscellaneous	153	113	23	69	61	115	191	13	63	37	89	137
				Caucasian	306	142	73	145	88	291	321	34	68	40	136	148
Erbas et al.	2017	37	Turkey	Miscellaneous	117	106	11	104	2	126	108	16	85	5	117	95
Isordia-Salas et al.	2018	38	Mexico	Miscellaneous	242	242	138	98	6	374	110	170	62	10	402	82

NA - not available

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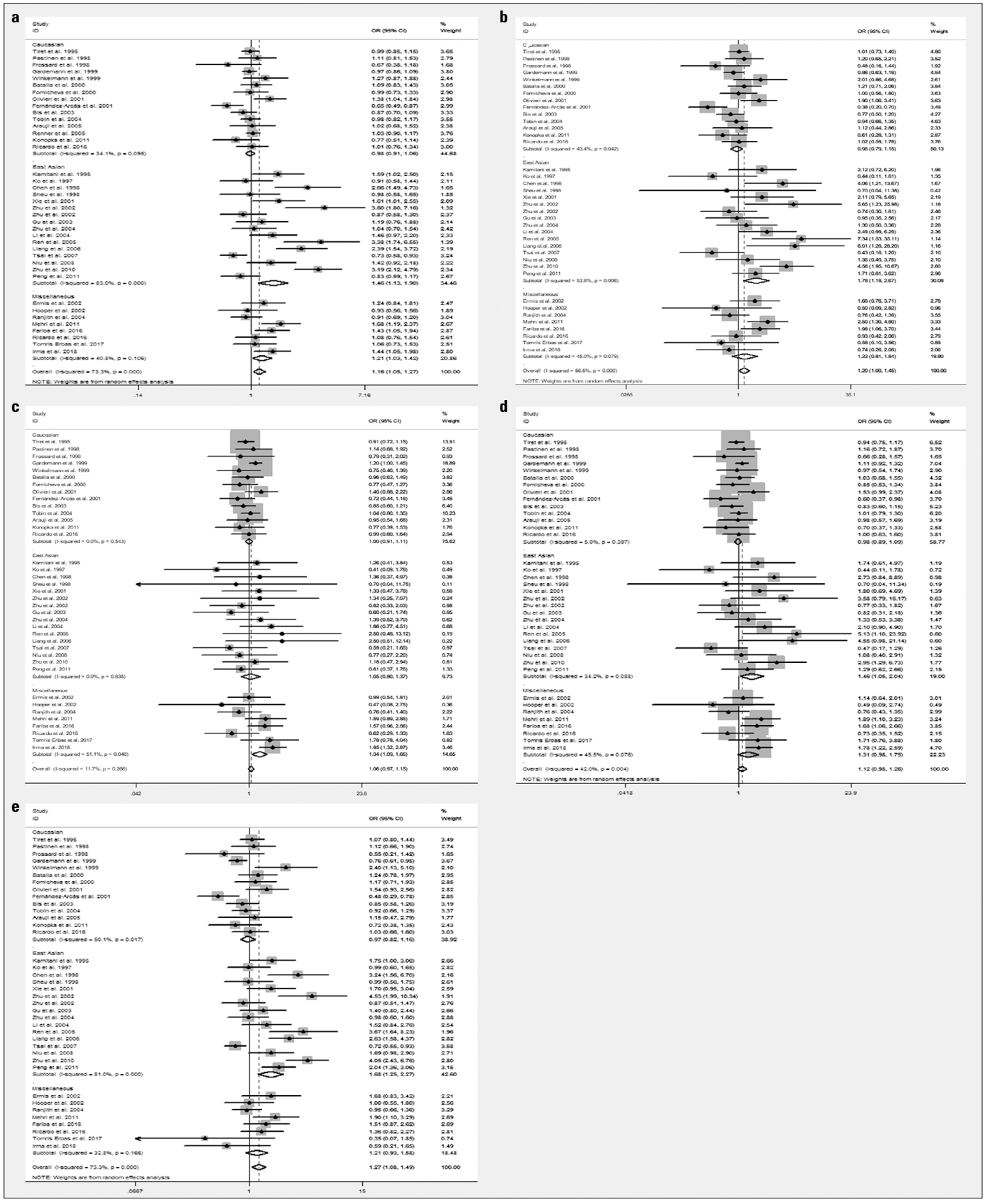

Figure 2. Forest plots of the association between AGT M235T polymorphism and CVD risk. (a) Allelic model, (b) homozygote model, (c) heterozygote model, (d) dominant model, and (e) recessive model

Table 2. Baseline characteristics of the included studies

Study	Enthic	Outcome	Genotyping-methods	Age		Gender (M/F)		HWE
				Case	Control	Case	Control	
Tiret et al.	C	MI	PCR	53.0±0.3	54.0±0.3	630/0	741/0	Y
Kamitani et al.	EA	MI	PCR	52±1	54±1	103/0	103/0	Y
Ko et al.	EA	MI	PCR	61.5±0.6	56.0±0.6	NR	181/157	Y
Chen et al.	EA	MI	PCR	67.7±8.5	65.7±8.2	50/7	69/7	Y
Sheu et al.	EA	CAD	PCR	NR	NR	102/0	145/0	Y
Pastinen et al.	C	MI	PCR	57.7±4.9	57.7±4.9	122/0	122/0	Y
Frossard et al.	C	MI	PCR	55.0±11.3	53.7±14.0	25/15	31/30	Y
Gardemann et al.	C	MI	PCR	62.2±9.5	58.5±10.6	1058/0	511/0	Y
Winkelmann et al.	C	MI	PCR	55.7±9.6	55.7±9.6	122/0	92/0	Y
Batalla et al.	C	MI	PCR	43±5	42±6	220/0	200/0	Y
Fomicheva et al.	C	MI	PCR	67 (55-85)	11 (6-17)	198/0	152/0	Y
Olivieri et al.	C	MI	PCR	57.7±12.8	59.6±9.5	160/85	221/26	Y
Xie et al.	EA	CAD	PCR	61.4±9.5	52.8±8.7	82/24	54/32	Y
Fernández-Arcás et al.	C	MI	PCR	54±13	56±15	212/0	180/0	Y
Ermis et al.	M	MI	PCR	42.1±11.8	40.3±12.8	NR	NR	Y
Hooper et al.	M	MI	PCR	NR	NR	NR	NR	Y
Zhu et al.	EA	MI	PCR	59.6±10.4	56.6±10.4	27/14	67/49	Y
Zhu et al.	EA	CAD	PCR	NR	NR	NR	NR	Y
Bis et al.	C	MI	PCR	63.6	64.4	128/80	371/346	Y
Gu et al.	EA	CAD	PCR	65.8±9.2	65.3±9.8	81/48	54/36	Y
Ranjith et al.	M	MI	PCR	18-45	18-45	NR	NR	Y
Zhu et al.	EA	CAD	PCR	NR	NR	NR	NR	Y
Li et al.	EA	CAD	PCR	61.5±11.8	59.3±10.5	80/40	47/33	Y
Tobin et al.	C	MI	PCR	61.9±9.2	58.6±10.7	372/175	313/192	Y
Ren et al.	EA	CAD	PCR	60.0±9.8	57.9±11.6	71/29	38/32	Y
Arauji et al.	C	MI	PCR	>18	>18	73/37	44/60	Y
Renner et al.	C	MI	PCR	63.1±10.4	58.4±12.1	1081/289	378/355	NR
Liang et al.	EA	CAD	PCR	64±8	63±8	100/33	116/38	Y
Tsai et al.	EA	CAD	PCR	63.8±11.4	58.6±13.1	531/204	269/250	Y
Niu et al.	EA	CAD	PCR	59±7	57±9	69/36	71/39	Y
Zhu et al.	EA	CAD	PCR	59.7±11.3	58.1±10.8	96/55	71/56	Y
Peng et al.	EA	CAD	PCR	70.0±8.3	69.0±6.4	128/68	132/68	Y
Konopka et al.	C	MI	PCR	57±10	38±11	79/21	76/19	Y
Mehri et al.	M	MI	PCR	62.3±11.8	60.4±10.3	71/52	83/61	Y
Raygan et al.	M	MI	PCR	62.4±3.2	61.7±4.3	102/53	127/58	Y
Bonfim-Silva et al.	M	CAD	PCR	55.7±7.9	51.8±8.4	99/54	49/64	Y
	C	CAD	PCR	55.7±6.7	53.0±7.7	204/102	65/77	Y
Erbas et al.	M	CAD	PCR	50.2±12.3	41.4±11.3	55/62	14/92	Y
Isordia-Salas et al.	M	MI	PCR	41.0±5.3	39.7±5.0	191/51	192/50	Y

C - Caucasian; EA - East Asian; M - Miscellaneous; MI - myocardial infarction; CAD - coronary artery disease; PCR - polymerase chain reaction; NR - no reported; HWE - Hardy-Weinberg equilibrium; Y - yes

Discussion

The AGT gene (on chromosome 1q42–43) comprises five exons and four introns spanning 12 kb, with the M235T polymorphism in exon 2. The M235T variant has been demonstrated to alter plasma AGT levels (58, 59), with elevated levels of serum AGT for patients carrying the T allele (60). Furthermore, a positive correlation exists between AGT M235T genotype and

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Table 3. Overall and subgroup meta-analysis of the association between AGT M235T polymorphism and risk of cardiovascular disease

Categories	n	T vs. M			TT vs. MM			MT vs. MM			MT+TT vs. MM			TT vs. MM+MT		
		OR (95% CI)	*P*	I^2 (%)/P_h	OR (95% CI)	*P*	I^2 (%)/P_h	OR (95% CI)	*P*	I^2 (%)/P_h	OR (95% CI)	*P*	I^2 (%)/P_h	OR (95% CI)	*P*	I^2 (%)/P_h
Overall	22	1.16 (1.05-1.27)	**0.003**	73.3/0.00	1.20 (1.00-1.45)	0.05	56.5/0.00	1.06 (fixed) (0.97-1.15)	0.20	11.7/0.27	1.12 (0.99-1.26)	0.085	42.0/0.00	1.14 (1.06-1.23)	**0.003**	73.3/0.00
Subgroup (by population)																
Caucasian		0.99 (fixed) (0.93-1.04)	0.584	34.1/0.10	0.95 (0.79-1.16)	0.63	43.4/0.04	1.00 (fixed) (0.91-1.11)	0.94	00.0/0.54	0.99 (0.89-1.09)	0.761	05.0/0.40	0.97 (0.82-1.16)	0.743	50.1/0.02
East Asian		1.46 (1.13-1.90)	**0.004**	83.0/0.00	1.78 (1.18-2.67)	**0.01**	53.8/0.01	1.05 (fixed) (0.80-1.38)	0.73	00.0/0.84	1.47 (1.05-2.04)	**0.023**	34.2/0.09	1.68 (1.25-2.27)	**0.001**	81.0/0.00
Miscellaneous		1.21 (fixed) (1.07-1.36)	**0.002**	40.8/0.11	1.22 (0.81-1.84)	0.33	45.0/0.08	1.23 (0.90-1.70)	0.20	51.1/0.05	1.31 (0.98-1.75)	0.065	45.5/0.08	1.20 (fixed) (0.98-1.46)	0.082	32.8/0.17

n- study numbers, OR- odds ratio, CI- confidence interval, bold values represent statistically significant findings, P_h - P heterogeneity (P<0.1 was considered as a significant difference), fixed - the fixed effects model

Table 4. Publication bias assessment of this meta-analysis

Genetic model	Egger's test t-value	*P*	Begg's test t-value	*P*
Allelic model	2.70	0.01	2.42	0.02
Homozygote model	1.84	0.07	1.28	0.20
Heterozygote model	-0.2	0.85	0.10	0.92
Dominant model	1.18	0.24	0.85	0.39
Recessive model	2.83	0.01	1.91	0.06

P<0.05 was considered as a significant difference

plasma AGT levels in survivors of myocardial infarction (MI) (14). Elevation circulating AGT levels are associated with an increase in the concentration of angiotensin II, which activates cardiomyocyte hypertrophy and fibroblast proliferation by stimulation the AT1 receptor (61, 62). In addition, angiotensin II stimulates vascular apoptosis and may promote the retention of low-density lipoprotein in the coronary arteries, oxidize, and be assimilated by phagocytes, ultimately contributing to the dysfunction of the vascular endothelium and myocardial ischemia and rupture of atherosclerotic plaque (63-65). These processes all play critical roles in promoting the pathological development of CVD.

In previous studies, the distribution of the AGT M235T variant has been shown to differ significantly among various populations. Katsuya et al. (66) demonstrated that homozygous AGT T235 is an independent risk factor, which carries a two-fold increased risk of CVD. In contrast, Tiret et al. (31) suggested that the AGT genetic polymorphism can lead to predisposition to hypertension, with no relationship to CVD. Renjith et al. (20) and Renner et al. (19) reported similar results showing that AGT genotypes are neither related to CVD nor high blood pressure. Batalla et al. (12) and Bonfim-Silva et al. (17) provided evidence of the synergistic effect between AGT polymorphism and CVD, suggesting that M235T polymorphism is significantly correlated with MI and hypertension. Recently, Raygan et al. (16) suggested that M235T polymorphism in Asians can be a useful biomarker for screening of individuals susceptible to MI. Given the disparity of the results, we sought to provide an updated meta-analysis to resolve the discrepancies among studies.

Our results clearly demonstrate a difference in the association of M235T polymorphism among Asians and Caucasians, suggesting that there is heterogeneity based on ethnicity. Our results suggest that the T allele is a genetic risk factor for CVD in Asians, as well as in the miscellaneous population. Previous meta-analyses based on Chinese populations have shown similar positive results (22, 23). Although two recent meta-analyses (16, 67) reported an association between the AGT M235T variant and MI, they did not include recently published studies, and the literature sample size was smaller than the current analysis. Thus, an update of previous meta-analyses that included diverse populations was warranted. Our results include the largest sam-

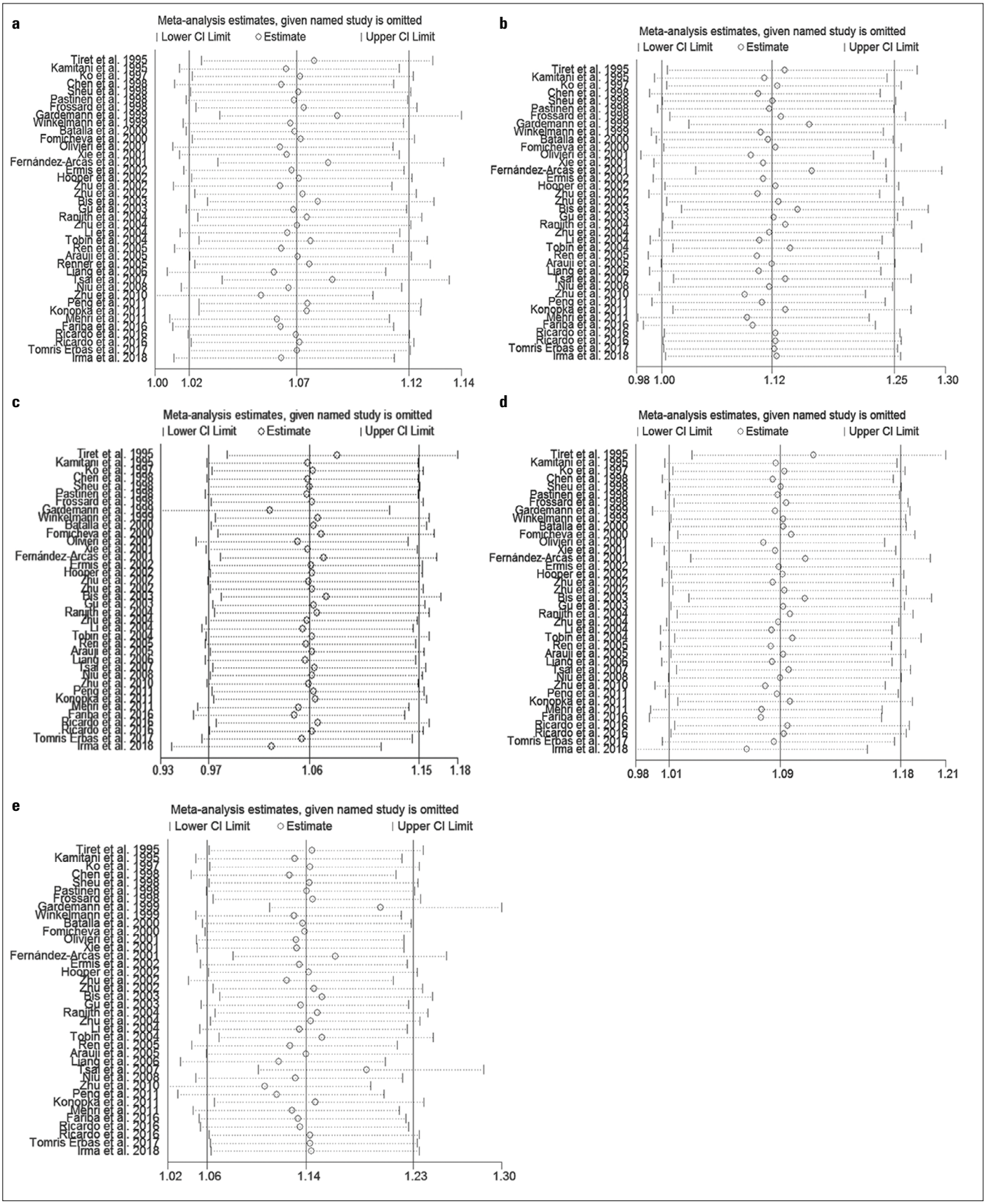

Figure 3. Sensitivity analyses of the association between AGT M235T polymorphism and CVD risk. (a) Allelic model, (b) homozygote model, (c) heterozygote model, (d) dominant model, and (e) recessive model

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ple size to date and provide an ethnicity-based explanation for different results among studies. The association of AGT M235T with stroke was not addressed in the present study but would be an important topic for consideration in future studies to maintain a relatively narrow focus.

The following potential factors may account for differences observed among the various ethnic groups: (1) population diversity (68), (2) different habits among populations (69), and (3) environmental factors leading to differences in susceptibility to CVD (70). Furthermore, we speculate that the non-significant association among Caucasians may be due to the relatively low frequency of the TT genotype in this population. Moreover, owing to the limited number of these studies, the miscellaneous ethnic subgroups were not analyzed further. Therefore, more studies with a larger sample size may reveal factors that influence differences in the association of AGT M235T and CVD, especially among Caucasians and other ethnic populations. The association between AGT M235T and CVD among Asians is evident.

The heterogeneity of associations across all included studies should be noted as it may potentially affect the strength of the present study. Thus, the random effects model was used, and our analysis was based on different ethnic subgroups. Ethnic background and sample size were found to be factors of heterogeneity. However, heterogeneity was still high within the East Asian subgroup. The heterogeneity of results among those included in these studies may be explained by the quality of the included studies, classification of CVD, and sampling criteria. The heterogeneity of genetic effects among individual studies may also be caused by the existence of genetic and environmental or genetic interactions.

Study limitations

The primary limitations of our meta-analysis include: (1) significant publication bias in the allelic and recessive models, (2) insufficient genotyping data of AGT M235T in miscellaneous races, which limited the ability to draw conclusions regarding this population, and (3) potential heterogeneity of clinical variables, such as the general condition of subjects, their medical history, medication compliance, complications of CVD, and other factors.

Conclusion

The genetic polymorphism of AGT M235T is associated with a critical risk of CVD in East Asian populations, with no detectable association in Caucasian populations. However, further studies with multiple ethnicities and rigorous designs should be performed to confirm these conclusions.

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