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Association of *AT1R* polymorphism with hypertension risk: An update meta-analysis based on 28,952 subjects

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Abstract

Background: Previous studies have shown that angiotensin II AT1 receptor gene (*AT1R*) polymorphisms are associated with the risk for hypertension. However, the results remain controversial. In the present study, we performed a meta-analysis to systematically summarize the association between *AT1R* genetic polymorphisms and the risk for hypertension.
Methods: We searched the literature in PubMed, EMBASE, ISI Web of Science, Wanfang, and Chinese National Knowledge Infrastructure databases (CNKI) to find case-control studies on the associations of AT1R genetic polymorphisms with the risk for hypertension. The meta-analysis was performed by using RevMan 5.0 software. The association of hypertension risk with *AT1R* genetic polymorphism was estimated by pooled odds ratios (ORs) and 95% confidence intervals (95% CIs).
Results: Fifty-six studies involving 28,952 subjects were included in the present meta-analysis. Our results suggest that the polymorphism (A1166C) of *AT1R* gene is associated with a statistically increased hypertension risk, not only in Asian populations but also in Caucasian populations. We did not find any association in African populations.
Conclusions: This meta-analysis suggests that A1166C polymorphism in the *AT1R* gene is associated with the risk of hypertension in Asian and Caucasian populations.

Keywords

Genetic polymorphism, hypertension, meta-analysis, angiotensin II AT1 receptor

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Introduction

Hypertension is a major public health problem throughout the world.[1] However, the pathogenesis of hypertension remains unclear. It is considered that hypertension is a complex disease resulting from the interaction between genetic polymorphisms and environmental factors.[2] Recently, many genes have been identified as candidates for contribution to hypertension.[3] Of these, the angiotensin II AT1 receptor (AT1R) plays an important role in normal blood pressure regulation and in the pathophysiological progression of hypertension.[4–6] The polymorphisms of the *AT1R* gene have been reported to be associated with the pathogenesis of hypertension.[7–9] In particular, a single nucleotide polymorphism (SNP), A1166C, is the most studied variant being located in the 3′ untranslated region of the *AT1R* gene.[10]

Several studies have indicated that A1166C polymorphism is associated with hypertension.[11,12] However, this association has not been confirmed in other reports.[13,14] In 2010, Wang et al. conducted a meta-analysis assessing the

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association of the *AT1R* gene A1166C polymorphism with hypertension in the Chinese population; this indicated that the *AT1R* C allele carriers have a higher risk for hypertension.[15] Niu and Qi also performed a meta-analysis and found that the *AT1R* C allele conferred an increased risk of hypertension.[16] However, in these two meta-analyses, the number of the included studies was rather small. In recent years, many new large-sample-size case-control studies have been conducted.[11–14] Therefore, to further assess the relation between *AT1R* gene polymorphism and hypertension, we performed a carefully designed meta-analysis including 56 studies involving 28,952 subjects.

Methods

Selection of studies

We conducted a systematic computerized literature search for studies published before 1 December 2014. We searched the literature in PubMed, EMBASE, ISI Web of Science, Wanfang database in China, and Chinese National Knowledge Infrastructure (CNKI) database with the following search terms: "hypertension" and "angiotensin II type 1 receptor" or "AT1R" and "polymorphism" or "SNP", or "mutation" or "variant", by two independent investigators. The publication date and language were not restricted in the present study. All studies which met to the inclusion criteria were retrieved for further examination and data extraction.

Selection criteria

Studies satisfying the following criteria were included: 1) reported the relation between the *AT1R* genetic polymorphism and susceptibility to hypertension; 2) definition of hypertension as systolic (or diastolic) blood pressure ⩾140 mmHg (or 90 mmHg) or treatment with antihypertensive medication; 3) in a case-control using either a hospital-based or a population-based design; 4) detailed genotype data were provided for the calculation of odds ratio (OR) and 95% confidence interval (95% CI). Studies that focused on juvenile hypertension or secondary forms of hypertension such as pregnancy-induced hypertension were excluded from this study.

Data extraction

Two researchers performed the data extraction independently. The following information from all eligible studies were obtained: first author's last name, year of publication, ethnicity of the population studied, study design, number of subjects in each category, baseline characteristics of the study population, and the number of persons with different genotypes in cases and controls and the genotyping methods.

Statistical analysis

The RevMan 5.0 software was employed for the present meta-analysis. The Hardy–Weinberg equilibrium was estimated by the χ^2-test. We performed analyses under the dominant model (CC+AC vs. AA), recessive model (CC vs. AC+AA), and additive model (C vs. A). We utilized Q-test and I^2 test to examine the heterogeneity between each study. By heterogeneity test, if $I^2 < 50\%$, we select the fixed effect model to merge OR. If $I^2 > 50\%$, we selected the random effect model to merge OR. Sensitivity analysis and publication bias analysis were tested using RevMan 5.0 statistical software. The statistical significance of the pooled OR was determined with the Z test, and a p value of <0.05 was considered significant.

Results

Baseline characteristics

A total of 447 articles concerning the *AT1R* A1166C polymorphism and hypertension were retrieved after first search in PubMed, EMBASE, ISI Web of Science, Wanfang in China, and CNKI databases. As shown in Figure 1, after excluding duplicated publications or those that did not meet the inclusion criteria, we included 56 case-control studies for the final analysis.[11–14,17–68] The characteristics of each study are summarized in Table 1. These 56 studies involved 28,952 subjects (14,708 hypertensive patients and 14,290 healthy control subjects). There were 39 studies carried out in Asian populations,[19–22,24–53,57,58,61,63,65] while 15 studies were performed in Caucasian populations.[11–13,18,23,54–56,59,60,62,64,66–68] Only two studies involved an African population.[17,18]

Meta-analysis

As shown in Table 2. we found the polymorphism (A1166C) of *AT1R* gene was associated with a statistically increased hypertension risk ((AC+CC) vs. AA: OR = 1.44 (95% CI: 1.24–1.66, $p < 0.001$); (AA+AC) vs. CC: OR = 0.61 (95% CI: 0.46–0.81, $p < 0.001$); C allele vs. A allele: OR = 1.35 (95% CI: 1.18–1.55, $p < 0.001$)) in the total population (Figures 2 to 4). In the subgroup analyses, the association was also significant among studies using Asian populations in all genetic models ((AC+CC) vs. AA: OR = 1.41 (95% CI: 1.19–1.66, $p < 0.001$; (AA+AC) vs. CC: OR = 0.50 (95% CI: 0.38–0.65, $p < 0.001$); C allele vs. A allele: OR= 1.40 (95% CI: 1.21–1.63, $p < 0.001$)). However, we only found an association in a dominant model ((AC+CC) vs. AA: OR = 1.37 (95% CI: 0.99–1.89, $p = 0.05$)), but not in a recessive model ((AA+AC) vs. CC: OR = 0.81 (95% CI: 0.53–1.22, $p = 0.32$)) or an additive model (C allele vs. A allele: OR = 1.09 (95% CI: 0.79–1.51, $p = 0.58$)) in

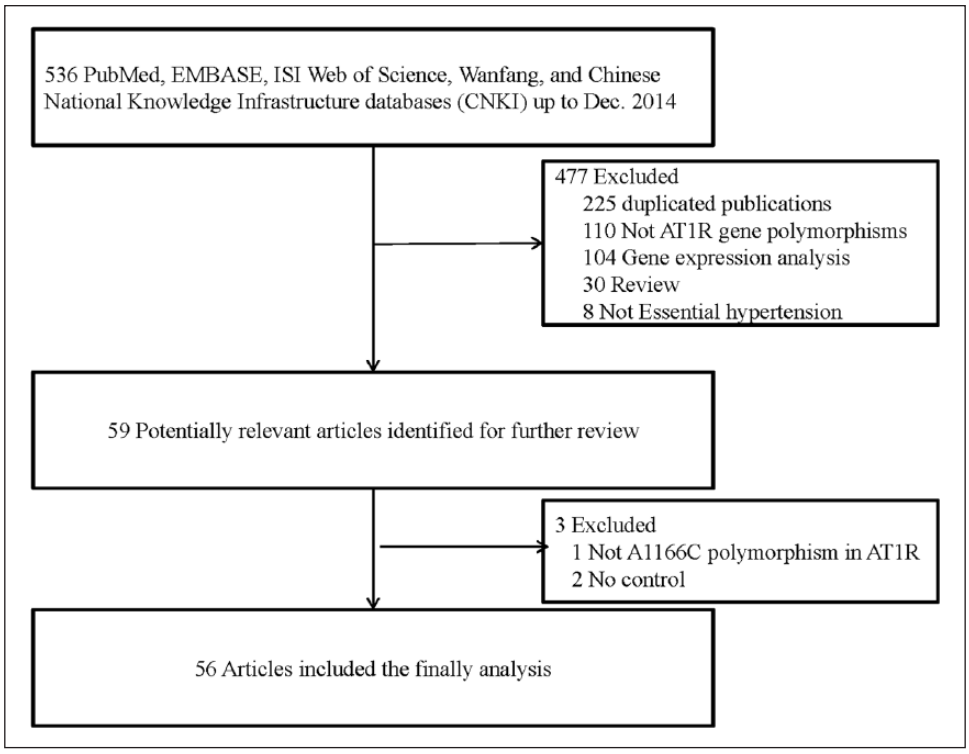

Figure 1. Flow diagram of study identification.

Caucasian populations. We did not found any association in African populations ((AC+CC) vs. AA: OR = 2.53 (95% CI: 0.66–9.70, $p = 0.18$); C allele vs. A allele: OR = 2.16 (95% CI: 0.93–5.01, $p = 0.18$)).

Publication bias

The publication bias test of the literature was conducted using a funnel plot and Egger's test. Symmetrical funnel plots were obtained in the SNP tested in all of the models, which displayed no publication bias (Figure 5). Egger's test further confirmed the absence of publication bias in this meta-analysis (all $p > 0.05$, data not shown).

Sensitivity analysis

We removed one single study from the overall pooled analysis each time to check the influence of the removed data set to the overall ORs. The pooled ORs and 95% CIs were not significantly altered when any part of the study was omitted, which indicated that any single study had little impact on the overall ORs and the results of this meta-analysis were stable.

Discussion

The present study aimed to explore the association of the *AT1R* gene A1166C polymorphism with hypertension among a total of 28,952 subjects via a meta-analysis. We demonstrated that the AT1R gene 1166C allele carriers have higher risk for hypertension in Asian and Caucasian population, but not in African population.

Meta-analysis is a powerful tool for summarizing results from different studies by producing a single evaluation of the major effect. Genetic association studies have a tendency to lack the power to detect a statistically significant association with complex diseases, especially studies with small sample sizes. To achieve a satisfactory power, meta-analysis of multiple studies clearly has a role in offering an association study with such potentials. In the present study, we collected 56 case-control studies involving 28,952 subjects in this meta-analysis to clarify the relation between *AT1R* genetic polymorphism and hypertension. We found a significant association between C allele and the increased risk of essential hypertension. In the stratified analysis, we divided these studies into different subgroups by race of the participants. Significant association between hypertension and the A1166C polymorphism was observed in both Asian and Caucasian populations, but not in African populations. Our results were in line with a previous meta-analysis in a Chinese population. However, the mechanism responsible for the association of hypertension risk with A1166C polymorphism remains unclear. A1166C polymorphism is in a non-coding region of AT1R gene, and therefore the amino acid sequence of the AT1 receptor is not altered. The lack

Table 1. Characteristics of participants.

Authors	Year	Country	Ethnicity	Case	Control	H-WE	Genotyping methods	Genotype						Allele			
								Case			Control			Case		Control	
								AA	AC	CC	AA	AC	CC	A	C	A	C
Bayramoglu et al.[11]	2014	Turkey	Caucasian	142	108	Yes	PCR-RFLP	137	5	0	94	14	0	279	5	202	14
Chandra et al.[12]	2014	India	Caucasian	250	250	Yes	PCR-RFLP	101	144	35	155	83	12	346	214	393	107
Shahin et al.[13]	2014	Jordanian	Caucasian	108	102	Yes	PCR-RFLP	67	37	4	64	32	6	171	45	160	44
Kooffreh et al.[14]	2013	Nigeria	West Africa	612	612	Yes	PCR-RFLP	605	7	0	606	6	0	1217	7	1218	6
Mehri et al.[17]	2012	Tunisia	North Africa	142	191	Yes	PCR-RFLP	17	63	62	74	82	35	97	187	230	152
Saab et al.[18]	2011	Lebanon	Caucasian	124	146	Yes	PCR-RFLP	31	64	29	83	52	11	126	122	218	74
Guo et al.[19]	2010	China	Asian	220	220	Yes	PCR	173	47	0	179	41	0	393	47	399	41
Nie et al.[20]	2009	China	Asian	510	510	Yes	PCR-RFLP	445	64	1	452	56	2	954	66	960	60
Li et al.[21]	2009	China	Asian	296	198	Yes	PCR-RFLP	226	70	0	147	51	0	522	70	345	51
Jiang et al.[22]	2009	China	Asian	220	235	Yes	PCR-RFLP	201	19	0	212	23	0	421	19	447	23
Bautista et al.[23]	2008	USA	Caucasian	256	257	Yes	PCR-RFLP	223	33	0	233	23	1	479	33	489	25
Liu et al.[24]	2003	China	Asian	446	302	Yes	PCR-RFLP	420	26	0	277	25	0	866	26	579	25
Ding et al.[25]	2008	China	Asian	200	220	Yes	PCR-RFLP	157	43	0	179	41	0	357	43	399	41
Niu et al.[26]	2009	China	Asian	1089	926	Yes	PCR-RFLP	734	262	93	629	266	31	1730	448	1524	328
Fan et al.[27]	1998	China	Asian	51	74	Yes	PCR-RFLP	41	10	0	68	6	0	92	10	142	6
Fang et al.[28]	2003	China	Asian	104	154	Yes	PCR-RFLP	83	18	3	139	14	1	184	24	292	16
Fang et al.[29]	2007	China	Asian	468	233	Yes	PCR-RFLP	411	53	4	198	34	1	565	61	430	36
Guo et al.[30]	2007	China	Asian	290	291	Yes	PCR-RFLP	255	35	0	237	53	1	545	35	527	55
Han and Li[31]	2000	China	Asian	95	80	Yes	PCR-RFLP	85	10	0	72	8	0	180	10	152	8
He et al.[32]	2007	China	Asian	148	125	Yes	PCR-RFLP	114	34	0	109	16	0	262	34	234	16
Jiang et al.[33]	2001	China	Asian	125	103	Yes	PCR-RFLP	102	23	0	96	7	0	227	23	199	7
Lin et al.[34]	2000	China	Asian	116	86	Yes	PCR-RFLP	95	21	0	81	5	0	211	21	167	5
Li et al.[35]	2007	China	Asian	104	98	Yes	PCR-RFLP	83	20	1	82	16	0	186	22	180	16
Li et al.[36]	2008	China	Asian	321	203	Yes	PCR-RFLP	246	73	2	153	50	0	565	77	356	50
Liu et al.[37]	2001	China	Asian	68	186	Yes	PCR-RFLP	63	4	1	171	15	0	130	6	357	15
Peng et al.[38]	2006	China	Asian	68	84	Yes	PCR-RFLP	53	13	2	75	8	1	119	17	158	10
Xiang et al.[39]	1998	China	Asian	48	67	Yes	PCR-RFLP	43	4	1	64	3	0	90	6	131	3
Xie et al.[40]	2008	China	Asian	55	80	Yes	PCR-RFLP	45	10	0	76	4	0	100	10	156	4
Xu et al.[41]	2002	China	Asian	83	64	Yes	PCR-RFLP	48	32	3	43	19	2	128	38	105	23

Table 1. (Continued)

Authors	Year	Country	Ethnicity	Case	Control	H-WE	Genotyping methods	Genotype						Allele			
								Case			Control			Case		Control	
								AA	AC	CC	AA	AC	CC	A	C	A	C
Zhang et al.[42]	2006	China	Asian	100	40	Yes	PCR-RFLP	85	11	4	38	2	0	181	19	78	2
Yu et al.[43]	1999	China	Asian	137	63	Yes	PCR-RFLP	106	29	2	57	6	0	241	33	120	6
Yuan et al.[44]	2007	China	Asian	679	616	Yes	PCR-RFLP	590	88	1	505	110	1	1268	90	1120	112
Zhang et al.[45]	2005	China	Asian	213	200	Yes	PCR-RFLP	164	47	2	148	50	2	375	51	346	54
Zhang et al.[46]	2007	China	Asian	126	143	Yes	PCR-RFLP	92	34	0	107	36	0	218	34	250	36
Zhang et al.[47]	2001	China	Asian	87	55	Yes	PCR-RFLP	70	14	3	51	4	0	154	20	106	4
Zhong and Ha[48]	2000	China	Asian	112	70	Yes	PCR-RFLP	85	26	1	65	5	0	196	28	135	5
Lu et al.[49]	2005	China	Asian	206	86	Yes	PCR-RFLP	180	24	2	82	4	0	384	28	168	4
Shi et al.[50]	2004	China	Asian	45	40	Yes	PCR-RFLP	19	26	0	20	20	0	64	26	60	20
Zhao et al.[51]	2006	China	Asian	64	61	Yes	PCR-RFLP	27	35	2	47	13	1	89	39	107	15
Yang et al.[52]	2006	China	Asian	328	571	Yes	PCR-RFLP	253	75	0	510	61	0	581	75	1081	61
Pan et al.[53]	2010	China	Asian	246	285	Yes	PCR-RFLP	151	77	18	255	26	4	379	113	536	34
Wang et al.[54]	1997	British	Caucasian	108	84	Yes	PCR-RFLP	45	40	23	39	42	3	130	86	120	48
Schmidt et al.[55]	1997	German	Caucasian	278	172	Yes	PCR-RFLP	145	113	20	81	76	15	403	153	238	106
Liyou et al.[56]	1999	Australian	Caucasian	334	327	Yes	PCR-RFLP	188	115	31	202	103	22	491	177	507	147
Thomas et al.[57]	2000	China	Asian	232	174	Yes	PCR-RFLP	203	28	1	152	21	1	434	30	325	23
Kato et al.[58]	2000	Japan	Asian	839	631	Yes	PCR-RFLP	701	132	6	525	103	3	1534	144	1153	109
Dzida et al.[59]	2001	Poland	Caucasian	250	150	Yes	PCR-RFLP	131	95	24	96	48	6	357	143	240	60
Agachan et al.[60]	2003	Turkey	Caucasian	104	81	Yes	PCR-RFLP	63	35	6	60	20	1	161	47	140	22
Ono et al.[61]	2003	Japan	Asian	1492	2326	Yes	PCR-RFLP	1259	224	9	2071	235	20	2742	242	4377	275
Pamies-Andreu et al.[62]	2003	Spain	Caucasian	41	61	Yes	PCR-RFLP	18	18	5	31	23	7	54	28	85	37
Tsai et al.[63]	2003	China	Asian	408	286	Yes	PCR-RFLP	378	29	1	270	16	0	785	31	556	16
Stankovic et al.[64]	2003	Serb	Caucasian	100	198	Yes	PCR-RFLP	52	40	8	109	74	15	144	56	292	104
Sugimoto et al.[65]	2004	Japan	Asian	576	631	Yes	PCR-RFLP	476	100	0	538	89	4	1052	100	1165	97
Barbalić et al.[66]	2006	Croatian	Caucasian	95	115	Yes	PCR-RFLP	48	33	14	55	50	10	129	61	160	70
Freitas et al.[67]	2007	Brazil	Caucasian	82	78	Yes	PCR-RFLP	46	30	6	55	20	3	122	42	130	184
Born et al.[68]	2006	Netherlands	Caucasian	221	139	Yes	PCR-RFLP	157	60	4	97	35	7	374	68	229	49

Table 2. Meta-analysis of A1166C polymorphism of the AT1R gene and hypertension.

Genetic model	Sample size		Test of association			Test for heterogeneity	
	Case	Control	OR	95% CI	*p*	*p*	I^2
Total							
(AC+CC) vs. AA	14,708	14,290	1.44	1.24–1.66	<0.001	<0.001	78%
(AA+AC) vs. CC	14,708	14,290	0.61	0.46–0.81	<0.001	0.005	40%
C vs. A	29,166	28,738	1.35	1.18–1.55	<0.001	<0.001	81%
Caucasian							
(AC+CC) vs. AA	2385	2184	1.37	0.99–1.89	0.05	<0.001	83%
(AA+AC) vs. CC	2385	2184	0.81	0.53–1.22	0.32	0.01	53%
C vs. A	4830	4526	1.09	0.79–1.51	0.58	<0.001	89%
Asian							
(AC+CC) vs. AA	11,461	11,219	1.41	1.19–1.66	<0.001	<0.001	75%
(AA+AC) vs. CC	11,461	11,219	0.50	0.38–0.65	<0.001	0.57	0%
C vs. A	22,612	22,438	1.40	1.21–1.63	<0.001	<0.001	73%
African							
(AC+CC) vs. AA	754	803	2.53	0.66–9.70	0.18	<0.001	78%
(AA+AC) vs. CC	–	–	–	–	–	–	–
C vs. A	1508	1606	2.16	0.93–5.01	0.07	0.12	60%

OR: odds ratio, CI: confidence interval.

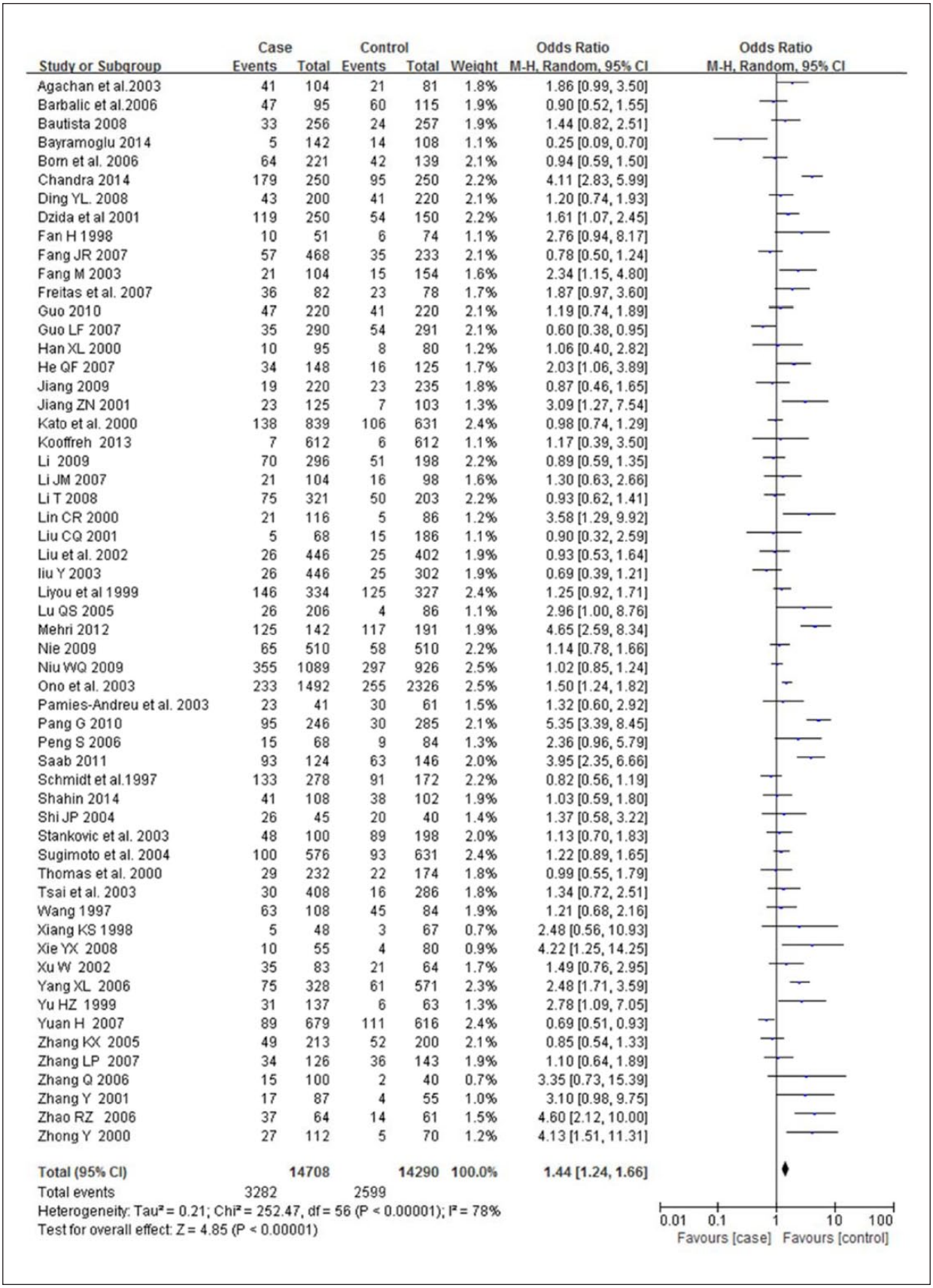

Figure 2. Forest plot of hypertension associated with *AT1R* genetic polymorphism in a dominant model ((AC+CC) vs. AA). The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

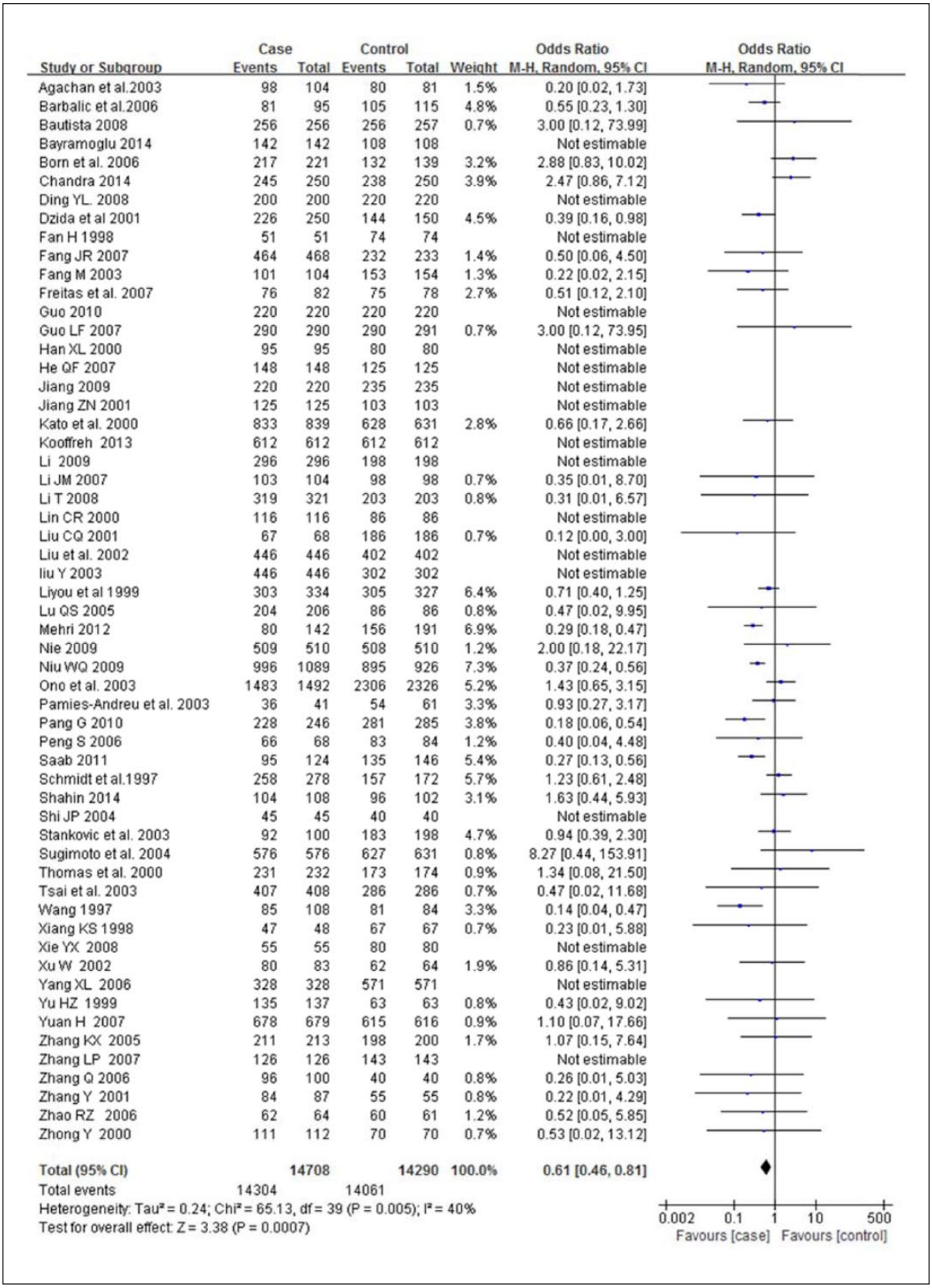

Figure 3. Forest plot of hypertension associated with *AT1R* genetic polymorphism in a recessive model ((AA+AC) vs. CC). The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

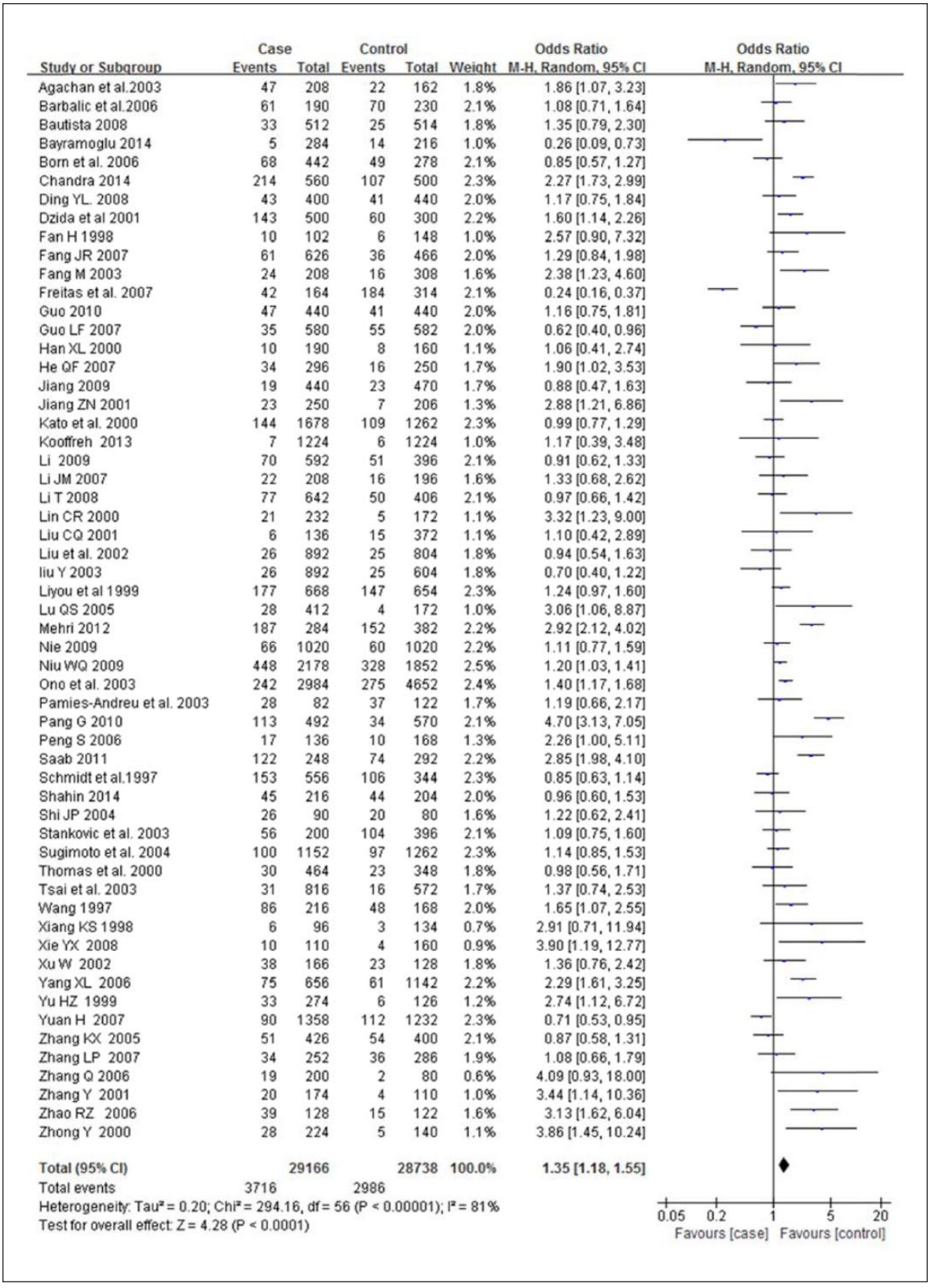

Figure 4. Forest plot of hypertension associated with *AT1R* genetic polymorphism in an additive model (C vs. A). The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

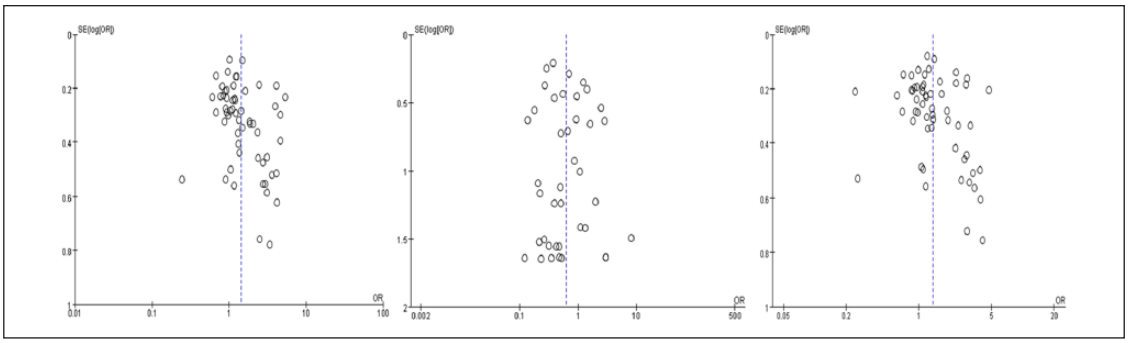

Figure 5. Funnel plot for publication bias test. Each circle denotes an independent study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line stands for mean effect size. A: dominant model; B: recessive model; C: additive model.

of a functional role of the A1166C polymorphism makes this SNP somewhat unappealing as a "true" influence of hypertension susceptibility. However, the A1166C polymorphism might affect mRNA stability and transcription, or alternatively be in linkage disequilibrium with other functional polymorphisms. Therefore, the functional study of this variant was expected in the future.

Furthermore, we did not find the publication bias. Sensitivity analysis also showed that omission of any single study did not have significant impact on the combined ORs. This made the results of this meta-study more reliable to some extent. However, we found significant heterogeneity among all the included studies. This heterogeneity may result from study design of included studies. Two kinds control sources-hospital-based controls and population-based controls were used in the studies. The hospital-based controls might have selection biases and might not be representative of the general population. In addition, three races including Asian, Caucasian, and African populations were involved in the present study. This fact may be another source of heterogeneity.

There were also some limitations in this meta-analysis. Firstly, some clinical factors such as age, sex may affect the hypertension risk. In the present study, we did not adjust these confounders. Determining whether or not these factors influence the results of this meta-analysis would need further investigation. Secondly, this meta-analysis only focused on papers published in the English and Chinese language. Thirdly, the cross-sectional nature of our included studies precludes comments on causality. Finally, in this study, we only focused on the AT1R gene A1166 C polymorphism and did not evaluate other polymorphisms in the AT1R gene, leading to the possibility that the potential role of the A1166 C polymorphism is diluted or masked by other gene–gene or gene–environment interactions.

Conclusion

In conclusion, this meta-analysis clarified the association of A1166C polymorphism in *AT1R* gene of the risk of hypertension. The presence of *AT1R* gene 1166C allele is associated with an increased risk of hypertension in Asian and Caucasian populations.

Conflict of interest

The authors declare that there are no conflicts of interest.

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