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ORIGINAL ARTICLE

Association of the angiotensin II type I receptor gene +1166 A>C polymorphism with hypertension risk: evidence from a meta-analysis of 16474 subjects

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Mounting evidence suggests the potential susceptibility of individuals with a mutation in the angiotensin II type I receptor (*AT1R*) gene to hypertension. One polymorphism, +1166 A>C, has been extensively studied, but the results have often been irreproducible. We therefore aimed to meta-analyze all available case–control studies from the English language literature to explore the association of this polymorphism with hypertension. A total of 22 studies with 24 populations involving 8249 patients and 8225 controls were identified as of 25 February 2010. A random-effects model was performed regardless of the between-study heterogeneity. The study quality was assessed in duplicate. The data were analyzed using RevMan software (version 5.0.23). Overall, the presence of the +1166 C allele significantly conferred an increased risk of hypertension (odds ratio (OR)=1.14; 95% confidence interval, 1.00–1.30; *P*=0.05). Under the assumption of three genetic modes of inheritance, an elevated hypertension risk was observed for each comparison (codominant: AC *vs.* AA, OR=1.10 (*P*=0.20) and CC *vs.* AA, OR=1.21 (*P*=0.36); dominant: OR=1.13 (*P*=0.09); recessive: OR=1.21 (*P*=0.36)). Upon stratification by study design, more obvious associations were observed for the population-based design, whereas there were no changes in direction and only slight changes in magnitude upon stratification by sample size and geographical area. No publication biases were indicated by the fail-safe number. Our study pooled previous findings and showed that the AT1R +1166 C allele conferred an increased risk of hypertension. We suggest that confirmation in a large, well-designed study or from functional aspects of this polymorphism is critical.
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Keywords: AT1R; +1166 A>C polymorphism; meta-analysis

INTRODUCTION

Although genetic signals in the renin–angiotensin system have not ranked the top in all current hypertension genome-wide association studies, its bioactive components such as angiotensinogen still attract special interest in view of their pivotal role in circulatory homoeostasis.[1,2] Mounting evidence indicates that most of the known effects of angiotensin II, the downstream product of angiotensinogen, are mediated via the angiotensin II type I receptor (AT1R), whose antagonists have been shown to be effective anti-hypertensive agents.[3] Moreover, renal AT1R is absolutely required for the development of angiotensin II-dependent hypertension, and the major mechanism of action of renin–angiotensin system inhibitors in hypertension is the attenuation of angiotensin II effects in the kidney.[4] Thus, characterizing the role of AT1R may help elucidate the genetic infrastructure of hypertension.

The human *AT1R* gene consists of five exons and spans over 55 kb on chromosome 3q21-25. Thus far, a great number of polymorphisms have been identified in the *AT1R* gene, and one transversion biallelic polymorphism in particular, +1166 A>C (rs5186), in the 3′ untranslated region has been extensively studied. Functional studies indicate that the expression of the 1166A allele, rather than 1166C, is down-regulated by miRNA155.[5] Further evidence from rodent models shows that the +1166C allele regulates the expression of the *AT1R* gene by weakening the ability of miRNA155.[5]

Dozens of studies have attempted to link the *AT1R* gene +1166A>C polymorphism to hypertension; however, a considerable degree of nonreproducibility has tinged most of these studies. This lack of reproducibility might stem from several causes relating to study design, sample size and study power issues, as well as true variability between populations.[6] In this regard, meta-analysis is an alternative strategy to help establish whether association results are consistent and can be generalized across populations as well as whether findings vary within subgroups.[7] Accordingly, we meta-analyzed all available case–controls studies published in English to

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explore the association of the *AT1R* gene +1166A>C polymorphism with hypertension among 8249 patients and 8225 controls.

METHODS

Publication identification

Three searching engines, including MEDLINE, EMBASE and Web of Science, were employed. The last search was conducted on 25 February 2010. As a prerequisite, all tracked reports were restricted to English language human studies. Keywords used for the search were 'hypertension or blood pressure' and 'angiotensin II type 1 receptor or AGTR1 or AT1R or AT1 or AT2R1' combined with 'gene or variant or allele or genotype'. The search spectrum was also extended to the bibliographies of each eligible study. When studies on the same cases or control subjects had been reported more than once, the most complete study was included. When studies included more than one geographical or ethnic population, each population was considered separately.

Inclusion and exclusion criteria

Studies satisfying the following criteria were included: (i) evaluation of the *AT1R* gene +1166 A>C polymorphism with hypertension; (ii) retrospective case–control studies using either a hospital-based or a population-based design; (iii) definition of hypertension as systolic (or diastolic) blood pressure $\geqslant$140 mm Hg (or 90 mm Hg) or treatment with antihypertensive medication; (iv) no consanguinity in cases and controls; and (v) sufficient information upon genotype counts of *AT1R* gene +1166 A>C polymorphism between cases and controls for estimating the odds ratio (OR) and its corresponding 95% confidence interval (CI). Studies that focused on juvenile hypertension or secondary forms of hypertension such as pregnancy-induced hypertension were excluded from this study.

Extracted information

Two authors (WN and YQ) of this article independently obtained the following information from all eligible studies: 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. The Hardy–Weinberg equilibrium was congruously tested for each population in both cases and controls. If combinational genotype data were provided in case of minimal variability of mutant alleles, information on the Hardy–Weinberg equilibrium was tracked from the articles. Finally, any encountered discrepancies were adjudicated by a discussion, and a consensus was reached. For the sake of consistency, continuous variables such as age that were expressed as mean ± s.e. were converted to mean ± s.d.

Statistical analysis

The open-source data-mining software, Review Manager (RevMan) (version 5.0.23), available at http://www.cc-ims.net/revman/download, was employed for meta-analysis. The Hardy–Weinberg equilibrium was estimated by the χ^2-test (R software version 2.10 available at http://www.r-project.org). As available evidence did not favor any genetic models of inheritance for the polymorphism under study, we performed analyses under the codominant model (+1166 CC *vs.* +1166 AA and +1166 AC *vs.* +1166 AA), dominant model (+1166 CC+AC *vs.* +1166 AA) and recessive model (+1166 CC *vs.* +1166 AC+AA).

Table 1 The baseline characteristics of all eligible studies

Study	Ethnicity	Study design	Sample size, n (male, %)		Age (year)		BMI (kg m^{-2})		+1166 C frequency (%)	
			Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Wang *et al.*[10]	British	P-B	108	84	—[a]	—	—	—	39.81	28.57
Schmidt *et al.*[11]	German	P-B	278	172	—	—	—	—	27.52	30.81
Liyou *et al.*[12]	Australian	P-B	334	327	—	—	—	—	26.50	22.48
Thomas *et al.*[13]	Chinese	H-B	232 (49.8)	174 (37.6)	47.8 ± 10.1	40.6 ± 9.7	25.8 ± 3.8	23.2 ± 3.6	6.47	6.61
Kato *et al.*[14]	Japanese	H-B	839 (52.2)	631 (58.0)	65.9 ± 11.0	58.9 ± 13.2	23.6 ± 3.0	22.3 ± 2.9	8.58	8.64
Dzida *et al.*[15]	Polish	H-B	250 (44.8)	150 (46.0)	59.1 ± 12.2	43.3 ± 16.9	27.6 ± 5.1	23.3 ± 2.8	28.60	20.00
Jiang *et al.*[16]	Chinese	—	125 (56.0)	103 (52.4)	62.3 ± 10.9	59.6 ± 14.6	23.9 ± 5.2	22.8 ± 3.1	9.20	3.40
Liu *et al.*[17] (Han)	Chinese	H-B	167 (50.9)	72 (62.5)	48.4 ± 8.7	50.0 ± 10.6	26.1 ± 3.1	22.8 ± 2.3	3.29	2.08
Liu *et al.*[17] (Tibetan)	Chinese	H-B	215 (55.8)	115 (51.3)	53.6 ± 12.1	44.1 ± 11.2	23.6 ± 3.5	24.9 ± 3.0	1.86	6.09
Liu *et al.*[17] (Yi)	Chinese	H-B	64 (100)	115 (100)	51.2 ± 11.9	44.3 ± 5.8	24.8 ± 3.5	21.1 ± 2.7	5.47	3.48
Agachan *et al.*[18]	Turkish	H-B	104 (29.4)	81 (40.7)	51.7 ± 9.7	51.6 ± 11.5	27.7 ± 4.5	25.5 ± 3.6	22.60	13.58
Ono *et al.*[19]	Japanese	P-B	1492	2326	—	—	—	—	8.11	5.91
Pamies-Andreu *et al.*[20]	Spain	H-B	41 (51.2)	61 (60.7)	39.4 ± 8.8	35.9 ± 10.4	27.6 ± 3.7	27.5 ± 3.6	34.15	30.33
Tsai *et al.*[21]	Taiwanese	H-B	408 (56.1)	286 (52.8)	61.4 ± 14.1	53.1 ± 15.2	26.1 ± 2.0	23.6 ± 5.0	3.80	2.80
Stankovic *et al.*[22]	Serbian	H-B	100 (49.0)	198 (47.5)	Males: 48.4 ± 15.8; females: 56.2 ± 10.7	Males: 48.6 ± 11.9; females: 55.7 ± 12.3	Males: 27.7 ± 3.0; females: 26.6 ± 3.3	Males: 25.0 ± 2.6; females: 23.5 ± 4.2	28.00	26.26
Sugimoto *et al.*[23]	Japanese	P-B	576 (38.5)	631 (33.8)	62.6 ± 8.6	58.1 ± 8.5	24.1 ± 3.1	23.3 ± 3.3	8.68	7.69
Barbalic *et al.*[24]	Croatian	P-B	95 (51.3)	115 (52.8)	35.3 ± 5.3	34.8 ± 5.3	27.5 ± 4.7	25.2 ± 3.9	32.11	30.43
Freitas *et al.*[25]	Brazilian	P-B	82 (40.2)	78 (39.7)	49.3 ± 18.6	36.3 ± 12.5	26.1 ± 3.4	24.6 ± 3.7	25.61	16.67
Born *et al.*[26]	Netherland	P-B	221	139	—	—	—	—	15.38	17.63
Bautista *et al.*[27]	Colombia	P-B	255 (32.8)	231 (32.7)	52.2 (51.4, 53.7)[b]	52.1 (51.0, 53.2)[b]	27.7 (27.2, 28.3)[b]	26.6 (26.0, 27.2)[b]	6.47	5.41
Niu *et al.*[28]	Chinese	P-B	1089 (58.4)	926 (42.2)	50.6 ± 6.6	53.0 ± 7.5	26.3 ± 3.7	24.4 ± 3.0	20.57	17.71
Jiang *et al.*[29]	Chinese	P-B	220 (51.8)	235 (55.7)	62.2 ± 6.1	61.1 ± 7.7	24.37 ± 2.69	23.34 ± 2.60	4.32	4.89
Niu *et al.*[30]	Chinese	H-B	444 (53.6)	465 (51.6)	47.8 ± 7.6	48.6 ± 8.0	26.7 ± 3.4	24.7 ± 2.4	17.23	24.52
Nie *et al.*[31]	Chinese	H-B	510 (65.7)	510 (65.7)	53.8 ± 10.2	53.5 ± 10.4	24.6 ± 2.8	23.0 ± 2.8	6.47	5.88

Abbreviations: BMI, body mass index; H-B, hospital-based; P-B, population-based.
[a]Information not available.
[b]Data are expressed as mean (95% confidence interval).
Age and BMI are expressed as mean ± s.d. unless otherwise indicated.

Generally, the fixed-effects model was employed in the absence of between-study heterogeneity (on the basis of the Cochran's Q statistic and I^2 statistic); otherwise, the random-effects model was used.[8] However, in this meta-analysis, we used only the random-effects model to combine the individual effect-size estimates. We used this model mainly because within a fixed-effects model, only sampling error contributes to the differences between the observed effect-size estimates across individual studies.[9] In contrast, there are two sources of variance coexisting in a random-effects model: the sample error and the between-study heterogeneity. Considering the ubiquitous nature of heterogeneity between studies, it is appropriate to utilize the random-effects model.

In addition, stratified analyses were conducted to seek more narrowly drawn subsets of the studies by removing an individual study each time or studies with similar features such as deviations from Hardy–Weinberg equilibrium to assess their separate influences.

Finally, we assessed publication bias using the fail-safe number (N_{fs}) with the significance set at 0.05 for each meta-comparison. Specifically, if the calculated N_{fs} value was smaller than the number of observed studies, then the meta-analysis results might run the risk of having publication bias. We calculated the $N_{fs0.05}$ according to the formula $N_{fs0.05}=(\sum Z/1.64)^2-k$, where k is the number of included articles.

RESULTS

Baseline characteristics

Following an extensive search, a total of 22 studies were collected based on our inclusion/exclusion criteria.[10–31] If more than one geographical or ethnic group was included in the same study, then data from different populations were extracted.[17] Therefore, 24 populations totaling 8249 patients with hypertension and 8225 controls were finally identified: thirteen populations were from Asia,[13,14,16,17,19,21,23,28–31] eight from Europe,[10,11,15,18,20,22,24,26] two from Latin America[25,27] and one from Australia.[12] With regard to the study design, 11 of these studies were population based,[10–12,19,23–29] and 12 employed a hospital-based design.[13–15,17,18,20–22,30,31]

The baseline characteristics of all eligible studies are summarized in Table 1. The frequencies of the *AT1R* gene +1166 C allele in patients ranged widely, from 6.47 to 39.81%, and similarly, the frequency in controls varied from 2.08 to 30.81%. Except for one Chinese population in patients[28] and one Japanese population in controls,[19] no deviations from Hardy–Weinberg equilibrium were observed in the genotype distributions of either cases or controls at the significance level of 0.05.

Genetic association

As shown in Figure 1, the presence of the +1166 C allele is significantly associated with a 14% increased risk of hypertension as compared with the +1166 A allele when pooling all eligible studies in the meta-analysis (OR=1.14; 95% CI, 1.00–1.30; P=0.05). Except for an analysis of two Chinese populations[17,30] that significantly favored a protective role for the +1166 C allele, most of the remaining studies supported the reverse trend. After excluding these two populations, the +1166 A>C allelic association was strikingly potentiated (OR=1.21; 95% CI, 1.10–1.33; $P<0.0001$).

As no specific inherited model was confirmed based on the studies examined, we conducted analyses with codominant, dominant and recessive models. Overall, under the codominant model, those individuals with the +1166 AC (Figure 2, OR=1.10; 95% CI, 0.95–1.27; P=0.20) or CC (Figure 3, OR=1.21; 95% CI, 0.80–1.84; P=0.36) genotypes were associated with an elevated, albeit nonsignificant, risk for hypertension as compared with carriers homogeneous for the +1166 A allele. Under the dominant and recessive models, similar

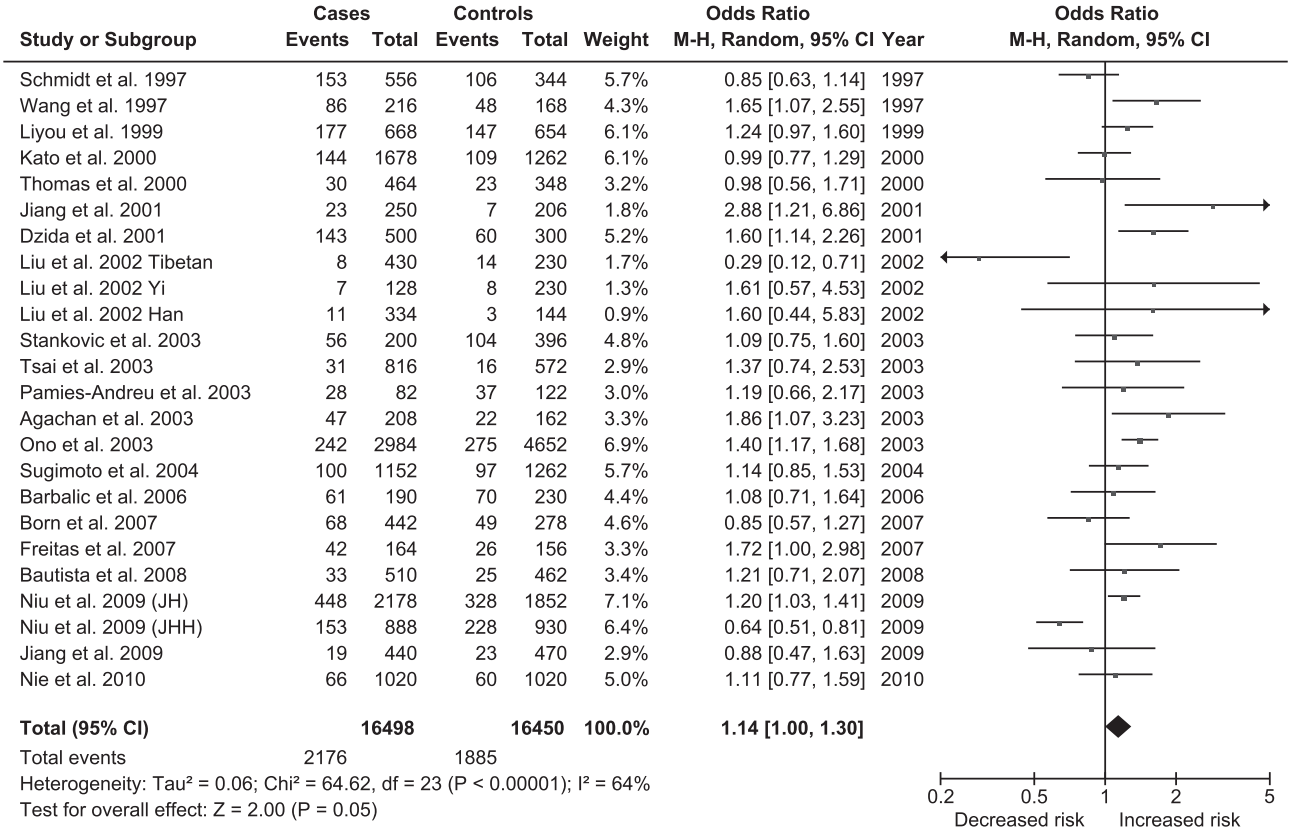

Figure 1 Comparison of the angiotensin II type I receptor (*AT1R*) gene +1166 C allele *vs.* the +1166 A allele under the random-effects model.

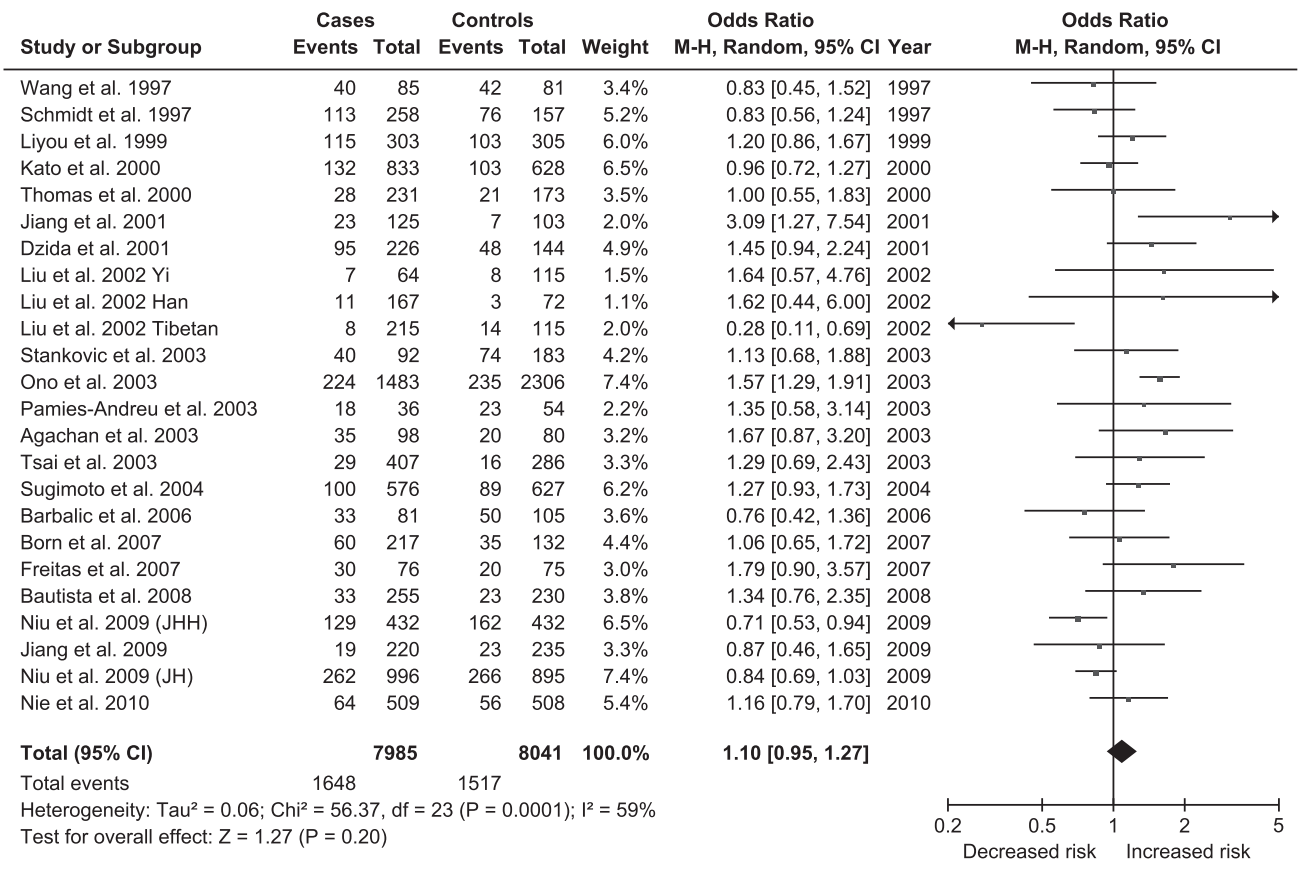

Figure 2 Comparison of the angiotensin II type I receptor (*AT1R*) gene +1166 AC genotype *vs.* the +1166 AA genotype under the random-effects and codominant models.

directions of association were obtained with an increased risk of 13% (95% CI, 0.98–1.30; P=0.09) and 21% (95% CI, 0.80–1.84; P=0.36), respectively, for hypertension (data not shown).

After excluding the two aforementioned Chinese populations,[17,30] the associations of the genotypes +1166 AC, +1166 CC, +1166 AC+CC, and +1166 CC with hypertension were positively strengthened with a 16 (P=0.03), 40 (P=0.07), 19 (P=0.001) and 38% (P=0.09) increased hypertension risk, respectively (data not shown).

Stratified analyses

As the genotype distributions of the +1166 A>C polymorphism deviated from Hardy–Weinberg proportions in two populations,[19,28] we separated the effect of those two populations by pooling the others and found that the overall allelic and genotypic associations were slightly weakened in the same directions of association (data not shown).

After stratification by study design, more obvious associations were found for the population-based design (Table 2). For example, presence of the +1166 C allele significantly conferred an 18% increased risk for hypertension as compared with the +1166 A allele (OR=1.18; 95% CI, 1.05–1.33; P=0.007). No significance was linked to the pooled results of hospital-based studies for both allelic and genotypic associations.

In the stratified analyses by sample size with a cutoff of 500 subjects, which has proven to be an effective way to handle persistent heterogeneity, the magnitude of association was stronger among populations with small sample sizes than among large sample sizes, reflecting a lack of statistical power (Table 2). In addition, under the assumption of a homogeneous comparison (+1166 CC *vs.* +1166 AA) in the codominant model and the recessive model, the +1166 CC genotype carriers had a nonsignificant reduced risk of hypertension compared with the other genotype carriers.

In subgroup analyses by geographical area, the magnitude of both allelic and genotypic associations was even stronger among populations from Europe and Latin America than from Asia (Table 2). For example, with regard to comparison of the +1166 C allele *vs.* +1166 A allele, there was an 8 (P=0.39), 19 (P=0.11) and 44% (P=0.06) increased risk of hypertension for populations from Asia, Europe and Latin America, respectively.

Finally, after excluding studies deviating from Hardy–Weinberg equilibrium,[19,28] there were no material changes in direction and only slight changes in magnitude for each association upon stratification by study design, sample size and geographical area (data not shown).

Publication bias

To assess the publication bias, we calculated the fail-safe number (N_{fs}) at the significance level of 0.05 for each comparison. The $N_{fs0.05}$ values for all the contrasts were greater than the number of studies included in this meta-analysis.

DISCUSSION

This study aimed to explore the association of the *AT1R* gene +1166A>C polymorphism with hypertension among a total of 16500 subjects via a meta-analysis. Notably, expanding upon previous findings, we demonstrated that the presence of the *AT1R* gene +1166

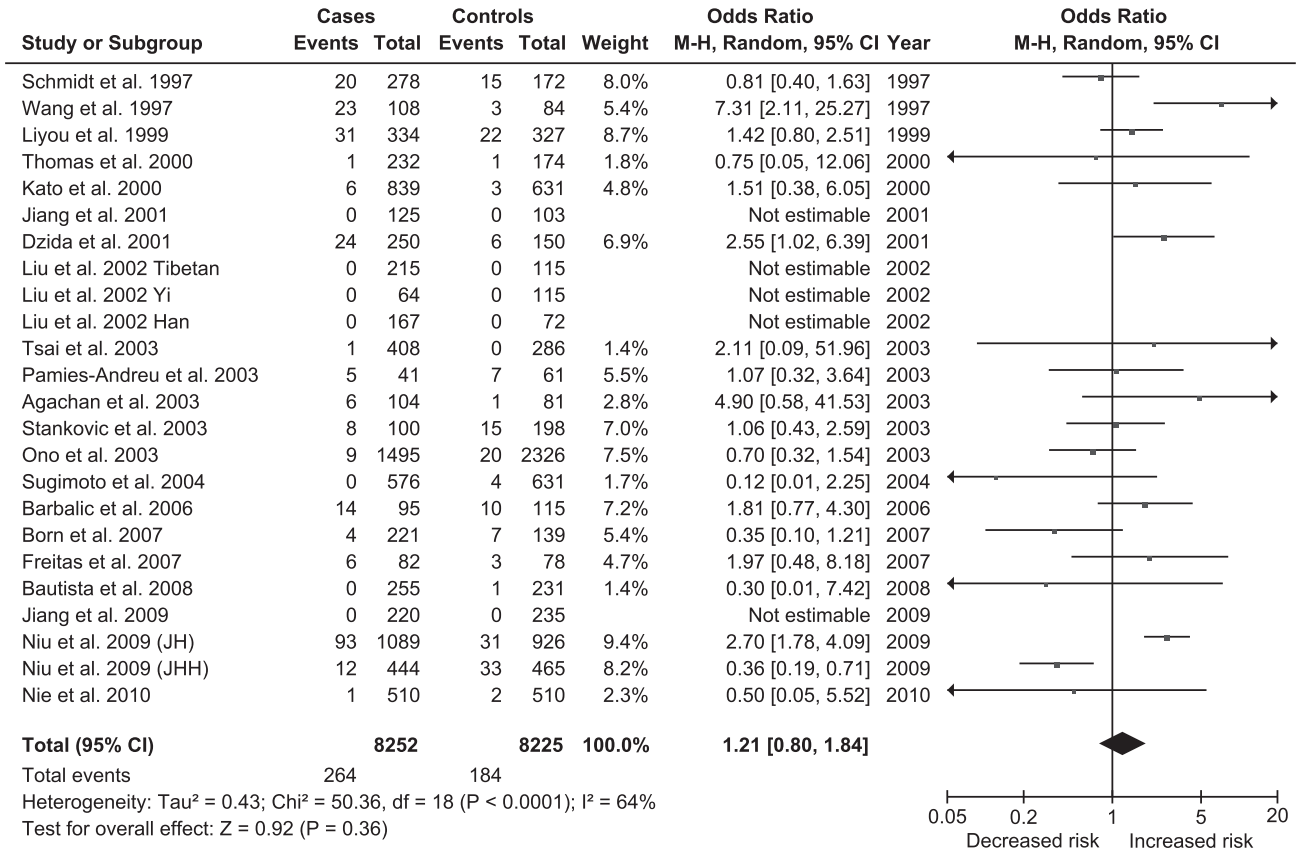

Figure 3 Comparison of the angiotensin II type I receptor (*AT1R*) gene +1166 CC genotype *vs.* the +1166 AA genotype under the random-effects and codominant models.

C allele is associated with an increased risk of hypertension; this finding is in agreement with a recent meta-analysis conducted only in a Chinese population showing that the variant genotype +1166 AC/CC significantly conferred a 48% increased risk of developing essential hypertension.[32] In addition, our subgroup analyses indicate that studies in a population-based design, with a small sample size or from European and Latin American geographical areas had more obvious associations as compared with those in a hospital-based design, with a large sample size or from Asian ancestry. The lack of confounding from Hardy–Weinberg deviation and publication bias supports the robustness of this meta-study.

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. It is suggested that to generate robust data, a much larger sample involving >1000 subjects in each group might be required, and often, it depends on the prevalence of the polymorphism under study.[33] For most genetic association studies, such a large sample size is usually an unrealistic goal. To achieve a satisfactory power, meta-analysis of multiple studies clearly has a role in offering an association study with such potentials.[34]

As stated by Lohmueller *et al.*,[35] except for false negatives (underpowered studies) and false positives (spurious findings), true variability across different populations can account for in the inconsistency of findings across studies. This statement might be true for the present meta-analysis because we observed a wide divergence of the +1166 C allele among different ethnic populations, even within the same ethnicity. For example, frequencies of the +1166 C allele in two Chinese populations[28,30] were remarkably higher than that in other Chinese populations (Table 1), suggesting a possible role of either ethnic differences or environmental differences in genetic profiles. In addition, we noted obvious differences in the effect of the +1166 C allele between the Asian group and the other ethnic groups. Except for the discrepant genetic composition between these ethnic populations, anthropometric characteristics, environmental factors and lifestyle backgrounds might account for these differences. These differences are exemplified by body mass index, a reflection of general obesity, in that its average levels were relatively lower ($-2\,kg\,m^{-2}$) among Asians than among Europeans and Latin Americans (Table 1). Furthermore, as simulated by a recent data-mining investigation, differences in allele frequency can result in a reversal of allelic effects in which a protective allele becomes a risk factor in replication studies;[36] this seems to be a possible explanation for divergent results between the two Chinese populations[17,30] and most of the other populations. It is thus reasonable to speculate that, if involved, the *AT1R* gene +1166 A>C polymorphism may have pleiotropic effects on the etiology of hypertension among different races or ethnic groups; this is also reflected by the different magnitudes of +1166 A>C association with hypertension when stratified by geographical area in this meta-analysis.

Nevertheless, we could not rule out the possibility of a modest effect of the +1166 A>C polymorphism in predisposition to hypertension. In this study involving about 16500 subjects, the sample size was adequately powerful ($>85\%$) to detect differences between cases and controls under the conditions of a type I error probability of 0.05 for a two-sided test and the OR of 1.14 for the pooled association of +1166 C (Figure 1). Moreover, it is conceivable that the +1166 A>C polymorphism might be linked to a causal variant or may interact

Table 2 Stratified analyses by study design, sample size and geographical area respectively for both allelic and genotypic associations of AT1R gene +1166 A>C polymorphisms with hypertension among all eligible studies

	Study design		*Sample size (cutoff: 500)*		*Geographical area*		
Comparisons	*Population-based*	*Hospital-based*	*Large (n ⩾ 500)*	*Small (n < 500)*	*Asia*	*Europe*	*Latin America*
C *vs.* A	1.18; 1.05–1.33; 0.007	1.08; 0.84–1.37; 0.56	1.10; 0.91–1.33; 0.34	1.19; 0.98–1.44; 0.08	1.08; 0.90–1.30; 0.39	1.19; 0.96–1.48; 0.11	1.44; 0.98–2.11; 0.06
AC *vs.* AA	1.09; 0.90–1.32; 0.38	1.06; 0.85–1.32; 0.62	1.08; 0.87–1.34; 0.47	1.12; 0.91–1.37; 0.30	1.08; 0.88–1.32; 0.49	1.10; 0.89–1.35; 0.39	1.51; 0.97–2.33; 0.07
CC *vs.* AA	1.28; 0.76–2.17; 0.35	1.18; 0.58–2.40; 0.66	0.95; 0.46–1.97; 0.89	1.46; 0.86–2.48; 0.16	0.94; 0.47–1.89; 0.87	1.61; 0.78–3.31; 0.20	1.45; 0.26–8.14; 0.67
CC+AC *vs.* AA	1.15; 1.00–1.33; 0.06	1.08; 0.84–1.38; 0.56	1.09; 0.90–1.34; 0.38	1.16; 0.95–1.43; 0.15	1.08; 0.89–1.32; 0.42	1.18; 0.97–1.45; 0.10	1.27; 0.62–2.60; 0.52
CC *vs.* AC+AA	1.29; 0.75–2.21; 0.35	1.10; 0.59–2.07; 0.76	0.96; 0.47–1.97; 0.90	1.43; 0.86–2.39; 0.17	0.95; 0.48–1.89; 0.88	1.37; 0.69–2.72; 0.36	1.36; 0.31–5.93; 0.68

Abbreviations: CI, confidence interval; OR, odds ratio.
Data are expressed as OR, 95% CI and *P*-values.

with other genes or polymorphisms within or near the *AT1R* gene to produce the final disease phenotype, such as elevated blood pressure. Therefore, a large, well-performed study must be conducted to confirm or refute our results.

In this meta-analysis, study design was identified as a potential source of between-study heterogeneity by stratified analyses for the +1166 A>C polymorphism. Indeed, the magnitude of associations was potentiated among population-based studies under both allelic and genotypic models (Table 2). In hospital-based studies, poor comparability between cases and controls might confound the true association in light of a regional specialty for the disease under study and the differential hospitalization rates between cases and controls.[37] As most of our studies recruited subjects from only one hospital, the hospital controls may have a narrower socioeconomic profile. In contrast, controls drawn from the general population might be representative of the true population of those without the disease.[38] In this respect, the results from the population-based studies might hold water.

This meta-analysis should be interpreted within the context of its limitations. First, this meta-analysis only focused on papers published in the English language. Second, the cross-sectional nature of our included studies precludes comments on causality. Third, we cannot retrieve information from all of these original publications on various confounding factors such as dietary salt consumption, which are regarded as effective modulators for the development of hypertension and should be considered in the analyses. Finally, in this study, we only focused on the *AT1R* gene +1166 A>C polymorphism and did not evaluate other polymorphisms in the *AT1R* gene or other targeted genes such as endothelial nitric oxide synthase,[39] leading to the possibility that the potential role of the +1166 A>C polymorphism is diluted or masked by other gene–gene or gene–environment interactions.

To summarize, our study expands upon previous findings on hypertension by showing that the presence of *AT1R* gene +1166 C allele is associated with an increased risk of hypertension. Additional longitudinal studies examining gene–gene or gene–environment interactions, as well as studies seeking to provide biological or clinical validations of our results, are warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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