# Association of *ACE I/D, AT1R A1166C, CYP11B2 C344T* polymorphism with essential hypertension in Asia: A meta-analysis

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**ABSTRACT.**

**Aim:** To evaluate the association between *ACE I/D, AT1R A11166C, CYP11B2 C344T* gene polymorphisms and the risk of EH in Asia.

**Materials and Methods:** Related case-control studies were collected, selected and screened; a meta-analysis was conducted to assess the association between polymorphism of target genes and essential hypertension.

**Results:** 41 articles were included. Among them, 17 studies were about *ACE I/D* gene polymorphisms, and 13 studies were about *AT1R A1166C*. Besides, 11 studies were about *CYP11B2 C344T*. The study suggested that *ACE I/D* polymorphism was closely connected with EH risk under all models. After subgroup analysis there was no significant relationship between *AT1R A1166C* under all models in China and no evidence had been found that *CYP11B2 C344T* gene had connection with EH risk in China. Meanwhile was no relationship between *C344T* mutations and EH risk under (CC *vs.* TT) in other countries.

**Conclusion:** The present evidence shows that it is of great guiding significant to identify *ACE I/D* mutation for preventing EH and screening high-risk groups rather than *AT1R A1166C* and *CYP11B2 C344T* polymorphism.

**Keywords:** Essential hypertension; Angiotensin converting enzyme; ACE; Angiotensin Ⅱ type1 receptor; *AT1R*; Aldosterone synthase; CYP11B2; Polymorphism; Meta-analysis

## INTRODUCTION

Among all the diseases that lead to the increase of blood pressure, the essential hypertention (EH) accounts for 90% ~ 95% (Abdalla M, et al., 2016). It is a multifactorial disease which can be attributed to the interaction of genetic heterogeneity and various environmental factors. According to the epidemiological survey (Glorioso N, et al., 2013), 31% ~ 68% of the patients with high blood pressure have a family history. And there are also studies showing that the blood pressure variation caused by heredity account for 30% ~ 50% (Smith CJ, et al., 2016). Since Jeunemaitre (Jeunemaitre X, et al., 1992) first reported the close correlation between the susceptibility genes and high blood pressure in 1992, researches on the susceptibility genes of hypertension have become a heat spot. Candidate genes involved at least 200 kinds (Fowdar JY, et al., 2017), including sympathetic nervous system, endothelial function and signal transduction, of which the polymorphism of renin-angiotensin-aldosterone system also plays an important role in regulating blood pressure. Under physiological conditions the renin makes hemangiotensin convert into angiotensin I, which is further transformed into angiotensin II under the action of angiotensin converting enzyme (ACE) (Gonzalez-Villalobos RA, et al., 2013). The Angiotensin II has a strong contractile effect on blood vessels, and it can also act on angiotensin II type 1 receptor (*AT1R*) stimulating the secretion of aldosterone, which can induce water and sodium retention (Chen K, et al., 2014). Moreover the synthesis of aldosterone needs Aldosterone synthase (*CYP11B2*), a key rate-limiting enzyme in the process (Gu T, et al., 2016). The mechanisms above are involved in the occurrence and maintenance of EH. Therefore if the gene polymorphisms occur in the RAAS system, it can directly affect blood pressure and owing to its importance, a number of molecular epidemiological studies in different countries and regions have been conducted to study the correlation of the polymorphism in RASS systerm and EH over the last ten years, but the results remain inconsistent. This may be due to racial and regional differences, as well as the fact that the sample size is too small to truly reflect relevance. In order to compare different research results more scientifically and objectively, Meta-analysis on this issue is coming to be widely carried out but also generates conflicting results, Gu W, et al., (2011) Wang J, et al., (2016) Zhou T-B, et al., (2011) and most of the documents in the latest Meta-analysis are published in 10 years ago. Besides the content involves a very small number of countries and only focused on one or two gene locus Sun J, et al., (2016), which cannot comprehensively and objectively reflect the influence of RASS system gene polymorphism on EH. Therefore, on this basis, we carry out a meta-analysis including the genotype data from all eligible investigations in the latest years involving more extensive countries and regions in Asia, as well as covering three gene loci affiliated to RASS system to provide a more accurate evaluation of the connection between polymorphisms of *ACE I/D*, *AT1R A1166C*, *CYP11B2 C344T* and EH susceptibility.

### Study selection

Our study followed the Meta-analysis of Observational Studies in Epidemiology guidelines Simonyte S, et al., (2017) and the researches were investigated in the following databases since the establishment of the library to April 2018: the China National Knowledge Infrastructure (CNKI), China Wanfang Database, China Weipu D atabase, Chinese biomedical literature database and PubMed, EMBASE, Cochrane library, Web of Science, Scie Nce direct. The following search words were used: Angiotensin converting enzyme, ACE, Angiotensin II type 1 receptor, *AT1R, A1166C,* aldosterone synthase, *CYP11B2, 344C/T,* and combined together with essential hypert ension, primary hypertension. In addition, we searched the references in detail for further research.

Studies that met the following criteria would be adopted: (1) the literature must be a case–control study pub lished both at home and abroad, with good balance and comparability. (2)Languages were limited to Chinese or English. (3)The research should involve gene polymorphisms of *ACE I/D, AT1R A11166C* or *CYP11B2 344C/T*

and EH. (4) Systolic pressure of EH patients should be greater than 140 mmHg and (or) with diastolic pressure g reater than 90 mmHg. And secondary hypertension should be excluded. (5)Each genotype distribution and indiv idual number in the case and control groups should be listed in the literature, or the corresponding number can b e calculated by the frequency of each genotype given.

Studies with the following characteristics would be excluded: (1) the literature was not associated with *AC E I/D, AT1R A11166C* or *CYP11B2* 344C/T polymorphism and EH; (2) it was not a case–control study; (3) The case group did not exclude the secondary hypertension; (4) The data of genotype frequency and allele frequency in the literature were incomplete or unclear.

If the information provided in this article was not comprehensive and uncertain, contact the original author by phone, email and other means to obtain relevant information. We used the 9 - star Newcastle - Ottawa scale t o evaluate the quality of the studies. Han Y, et al., (2017) It includes three aspects: study object selection, group comparability and exposure factor measurement. In brief, a maximum of 9 points was assigned to each study: 4 for selection, 2 for comparability, and 3 for outcomes. A final score of >6 was regarded as high quality. Organiz e each article that are included in and extract relevant data: The first author's name, years of publication, country and region, genotype frequencies in the observation group and control group. Minimum number of abortions, H ardy–Weinberg equilibrium and Quality score of case-control study were showed in Figure 1.

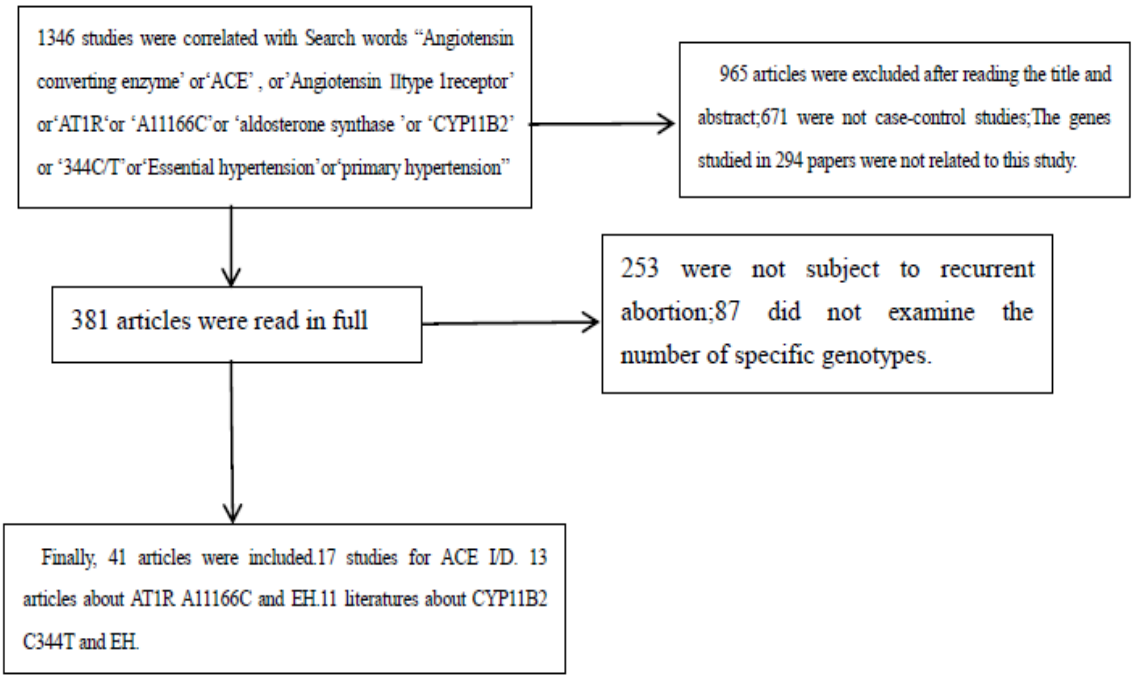



**Figure 1.** Article screening flowchart.

## Statistical analysis

All the data were analyzed by Stata 12.0 software and the related charts were drawn below. Based on the o dds ratio (OR) with a corresponding 95% confidence interval (CI), we counted the pooled odds to analyze the ef fect on the association. While crossing these studies, Q test and $I^2$ were used to test the heterogeneity of the incl uded literature firstly. When $I^2$>50%, it was proved that heterogeneity exists between the studies, the random eff ect model was used, and if not, the fixed effect model was used instead. In order to Search for the sources of het erogeneity, we mainly conducted subgroup analysis on the nations. In order to evaluate the stability of the combi ned results, a sensitivity analysis was conducted for the meta-analysis results after each removal of a case-contro l study. The Begg funnel plot was used as a criterion for assessing publication bias.

# RESULTS

## Characteristics of the included studies

Overall, a total of 41 out of 1346 articles were selected for the final meta-analysis (Gong HT, et al., Vamsi UM, et al., (2016)) Among the included articles, 17 studies reported the association between *ACE I/D* gene mutation and EH with 2816 cases and 3727 controls involving 5 countries.13 articles demonstrated the relationship between *AT1R A11166C* and EH with 2869 cases and 3063 controls touching on 5 countries.11 studies described the connection between *CYP11B2 C344T* and EH with 4476 cases and 4237 controls concerning 3 countries. The baseline characteristics of the studies related to mutation of *ACE I/D, AT1R A11166C* and CYP11B2*C344T* are respectively shown in Tables 1, 2 and 3. All of the 41 articles were published before Jan. 2018. In addition, 16 manuscripts were published in English, and 21 manuscripts were published in Chinese.

**Table 1.** Characteristics of studies on the association between *ACE I/D, AT1R A1166C, CYP11B2 C344T* gene polymorphisms and EH risk.

**Characteristics of studies between *ACE I/D* and EH risk**

| The first author | Publication date | Country/city | Total of cases II ID DD I D | Total of controls II ID DD I D | HWE inspection | Quality score |
|---|---|---|---|---|---|---|
| Gong H, et al. | 2011 | Beijing, China | 160<br>58 46 56 202 198 | 192<br>74 94 24 242 142 | 0.053 | 9 |
| Wang B, et al. | 2014 | Heilongjiang. China | 486<br>167 181 138 515 457 | 457<br>159 227 71 545 369 | <0.05 | 5 |
| Simonyte S, et al. | 2017 | Lithuanian | 269<br>59 149 61 267 271 | 430<br>123 205 102 451 409 | 0.077 | 9 |
| Singh KhD, et al. | 2014 | India | 211<br>40 88 83 168 254 | 211<br>51 93 67 195 227 | 0.059 | 8 |
| Xue T, et al. | 2015 | Heilongjiang. China | 64<br>18 25 21 62 68 | 43<br>19 19 5 57 29 | 0.083 | 7 |
| Dong N [19] | 2011 | Qinghai, China | 116<br>45 50 21 140 92 | 97<br>57 24 16 138 56 | 0.28 | 7 |
| Guo S, et al. [20] | 2010 | Xinjiang, China | 220<br>48 76 96 172 268 | 220<br>61 107 52 229 211 | 0.057 | 7 |
| Fu Y, et al. | 2013 | Hainan, China | 38<br>17 13 8 47 29 | 63<br>34 21 8 89 37 | 0.089 | 6 |
| Zhang C, et al. | 2007 | Neimenggu, China | 98<br>43 37 18 123 73 | 108<br>45 35 28 125 91 | 0.057 | 8 |
| Jia S | 2010 | Neimenggu, China | 68<br>27 30 11 84 52 | 67<br>26 34 7 86 48 | 0.586 | 8 |
| Hu R, et al. | 2007 | Neimenggu.China | 98<br>43 37 18 123 73 | 108<br>45 35 28 125 91 | 0.057 | 6 |
| Han X, et al. | 2010 | Hebei.China | 220<br>67 97 56 231 209 | 1004<br>403 388 213 1194 814 | 0.085 | 7 |
| Li D, et al. | 2012 | Shandong, China | 235<br>64 116 55 244 226 | 240<br>92 118 30 302 178 | 0.862 | 7 |
| Fang J, et al. | 2007 | Gansu, China | 115<br>22 72 21 116 114 | 102<br>21 57 24 99 105 | 0.084 | 7 |
| Akra-Ismail M, et al. | 2010 | Lebanese | 115<br>13 52 50 78 152 | 77<br>10 40 27 60 94 | 0.925 | 9 |
| Nakhjavani M, et al. | 2007 | Iran | 82<br>22 33 27 77 87 | 87<br>25 51 11 101 73 | 0.082 | 9 |
| He Q, et al. | 2013 | Zhejiang, China | 221<br>73 97 51 243 199 | 221<br>87 95 39 269 173 | 0.092 | 7 |

**Characteristics of studies between *AT1R A1166C* and EH risk**

| The first author | Publication date | Country/city | Total of cases AA AC CC A C | Total of controls AA AC CC A C | HWE inspection | Quality score |
|---|---|---|---|---|---|---|
| Luo J | 2010 | Hunan, China | 100<br>66 31 3 163 37 | 100<br>85 14 1 184 16 | 0.779 | 9 |
| Zheng F, etal. | 2014 | Beijing, China | 101<br>85 15 1 185 17 | 100<br>88 12 0 188 12 | 0.713 | 9 |
| Ding Y, et al. | 2008 | Xinjiang. China | 201<br>157 43 1 357 45 | 220<br>179 41 0 399 41 | 0.281 | 8 |
| Zhong Z, et al. | 2016 | Guizhou. China | 75<br>65 9 1 139 11 | 78<br>76 2 0 154 2 | 0.31 | 8 |
| Chen L | 2012 | Ningxia. China | 147<br>129 17 1 275 19 | 112<br>105 7 0 217 7 | 0.598 | 7 |
| Li N, et al. | 2005 | Xinjiang, China | 198<br>153 44 1 350 46 | 130<br>99 31 0 229 31 | 0.247 | 6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Simonyte S, et al. | 2017 | Lithuanian | 271<br>146 106 19 311 144 | 425<br>208 184 33 600 250 | 0.968 | 9 |
| Dhanachandra Singh KH, et al. | 2014 | India | 211<br>88 84 39 260 162 | 211<br>85 83 43 253 169 | 0.021 | 7 |
| Yang CH, et al. | 2015 | Taiwan, China | 313<br>287 25 1 599 27 | 130<br>115 14 1 244 16 | 0.567 | 8 |
| Tong J, et al. | 2017 | Hebei. China | 312<br>278 33 1 589 35 | 623<br>580 42 1 1202 44 | 0.984 | 8 |
| Shahin DS, et al. | 2014 | Jordan | 108<br>67 37 4 171 45 | 102<br>64 32 6 160 44 | 0.688 | 8 |
| Guo S, et al. | 2010 | Xinjiang, China | 221<br>173 47 1 393 49 | 220<br>179 41 0 399 41 | 0.242 | 7 |
| Kooffreh ME, et al. | 2013 | Nigeria | 611<br>605 7 1 1217 9 | 612<br>606 6 0 1218 6 | 0.012 | 9 |

**Characteristics of studies between *CYP11B2 C344T* and EH risk**

| The first author | Publication date | Country/city | Total of cases<br>CC CT TT C T | Total of controls<br>CC CT TT C T | HWE inspection | Quality score |
|---|---|---|---|---|---|---|
| Luo J | 2010 | Hunan, China | 100<br>17 40 43 74 126 | 100<br>18 36 46 72 128 | 0.156 | 7 |
| Tao X | 2010 | Neimenggu, China | 925<br>139 368 418 646 1204 | 1199<br>134 495 570 763 1635 | 0.000 | 8 |
| Mi D | 2011 | Neimenggu, China | 201<br>24 85 92 133 269 | 202<br>22 93 87 137 267 | 0.524 | 7 |
| Li J | 2008 | Xinjiang, China | 233<br>36 107 90 179 287 | 252<br>42 109 101 193 311 | 0.581 | 6 |
| Hlubocká Z, et al. | 2009 | Czech | 213<br>23 122 68 168 258 | 156<br>35 81 40 151 161 | 0.653 | 9 |
| Rajan S, et al. | 2010 | India | 406<br>43 185 178 271 541 | 424<br>56 226 142 338 510 | 0.62 | 7 |
| Zhang H, et al. | 2017 | Heilongjiang, China | 1023<br>482 454 87 1418 628 | 956<br>462 420 74 1348 568 | 0.168 | 9 |
| Sia SK, et al. | 2012 | Taiwan, China | 514<br>37 209 268 283 745 | 192<br>16 85 91 117 267 | 0.666 | 9 |
| Vamsi UM, et al. | 2016 | India | 279<br>47 130 102 224 334 | 200<br>26 116 58 168 232 | 0.611 | 7 |
| Wang B, et al. | 2014 | Heilongjiang, China | 486<br>66 228 192 360 612 | 457<br>76 200 181 352 562 | 0.897 | 8 |
| Hu R, et al. | 2007 | Neimenggu, China | 96<br>45 42 9 132 60 | 99<br>37 53 9 127 71 | 0.859 | 6 |

## Results of the overall meta-analysis

## Meta-analysis of *ACE I/D* polymorphism and EH risk

17 articles were related to I/D and the risk of EH. The results showed that the polymorphism of *ACE I/D* gene was significantly correlated with the risk of EH under dominant model (DD+ID *vs.* II; OR 1.289, 95% CI 1.154 4-1.439), recessive model (DD *vs.* II+ID); OR 1.367, 95% CI 1.213, 1.541), heterozygote model (ID *vs.* II; OR 1. 213, 95% CI 1.078-1.364), homozygote model (DD *vs.* II; OR 1.478, 95% CI 1.288-1.695), and additive model (D *vs.* I; OR 1.260, 95% CI 1.169-1.359). (Table 2)

**Table 2.** Meta-analysis of ACE I/D polymorphism and EH risk.

| Variables | $I^2$ | Model | OR 95%CL | p | z |
|---|---|---|---|---|---|
| DD *vs.* II | 35.8% | FEM | 1.478 1.288 1.695 | <0.05 | 5.58 |
| ID *vs.* II | 30.5% | FEM | 1.213 1.078 1.364 | <0.05 | 3.21 |
| (DD + ID) *vs.* II | 0.2% | FEM | 1.289 1.154 1.439 | <0.05 | 4.50 |
| DD *vs.* (II + ID) | 58.8% | REM | 1.367 1.213 1.541 | <0.05 | 5.12 |
| D *vs.* I | 32.3% | FEM | 1.260 1.169 1.359 | <0.05 | 6.00 |

## Test for heterogeneity

In the heterogeneity test for the I/D genotypes of each model, $I^2$ of recessive group (DD *vs.* (II + ID)) were >50%, indicating that the included studies have heterogeneity. Sub-group analysis was needed to explore the source of heterogeneity.

## Sub-group analysis

Of the 17 articles included, one of the articles conducted by Wang was judged to be of low quality and high heterogeneity in accordance with the standard, and therefore, to prevent errors in data analysis, this article was r ejected. After it was eliminated, meta-analysis was conducted again, and the results showed that besides other m odels, the recessive model (DD *vs.* II + ID) was also had relationship with EH susceptivity [OR=1.265, 95% CI= (1.111, 1.440)]. The results were shown in Table 3.

**Table 3.** Meta-analysis of (DD vs. II + ID) gene polymorphism and EH risk without Wang.

| Variables | $I^2$ | Model | OR 95% CL | p | z |
|---|---|---|---|---|---|
| DD *vs.* (II + ID) | 49.2% | FEM | 1.265 1.111 1.440 | <0.05 | 3.55 |

## Meta-analysis of *AT1R A1166C* polymorphism and EH risk

13 articles were associated with *A1166C* and the EH emotivity. The results showed that the polymorphism of *AT1R A1166C* gene was not significantly associated with EH riskunder dominant model (CC+AC *vs.* AA; O R 1.132, 95% CI 0.978-1.310), recessive model (CC *vs.* AA+AC; OR0.993, 95% CI 0.715-1.379), heterozygote model (AC *vs.* AA; OR1.134, 95% CI 0.975-1.318) homozygote model (CC *vs.* AA; OR 0.984, 95% CI 0.698-1. 387), and heterozygote model (AC *vs.* AA; OR 1.134, 95% CI 0.975-1.318) (p>0.05).The results were shown in Table 4.

**Table 4.** Results of *AT1R A1166C* polymorphism and EH risk.

| | $I^2$ | Model | OR 95% CL | p | z |
|---|---|---|---|---|---|
| CC *vs.* AA | 0.0% | FEM | 0.984 0.698 1.387 | 0.926 | 0.09 |
| AC *vs.* AA | 42.4% | FEM | 1.134 0.975 1.318 | 0.104 | 1.63 |
| CC+AC *vs.* AA | 50.0% | FEM | 1.132 0.978 1.310 | 0.096 | 1.66 |
| CC *vs.* AA+AC | 0.0% | FEM | 0.993 0.715 1.379 | 0.966 | 0.04 |
| C *vs.* A | 54.2% | REM | 1.093 0.966 1.238 | 0.159 | 1.41 |

## Test for heterogeneity

In the heterogeneity test for the *AT1R A1166C* genotypes of each model, $I^2$ of additive model (C *vs.* A) were> 50%, indicating that the included studies have heterogeneity. Sub group analysis was needed to explore the sour ce of heterogeneity.

## Sub-group analysis

Of the 13 articles included, 9 studies were from China, of which 3 were carried out in the Han nationality a nd 6 were from national minorities. And we conducted subgroup analysis on C *vs.* A genotype and EH risk acco rding to the population of ethnic groups. The $I^2$ of (C *vs.* A) in Chinese Han nationality and minorities were <50 %, indicating that ethnic differences had an impact on heterogeneity. And there is no significantly associated wit h EH risk under additive (C *vs.* A） model in Chinese people (p>0.05). The results were shown in Figure 2.

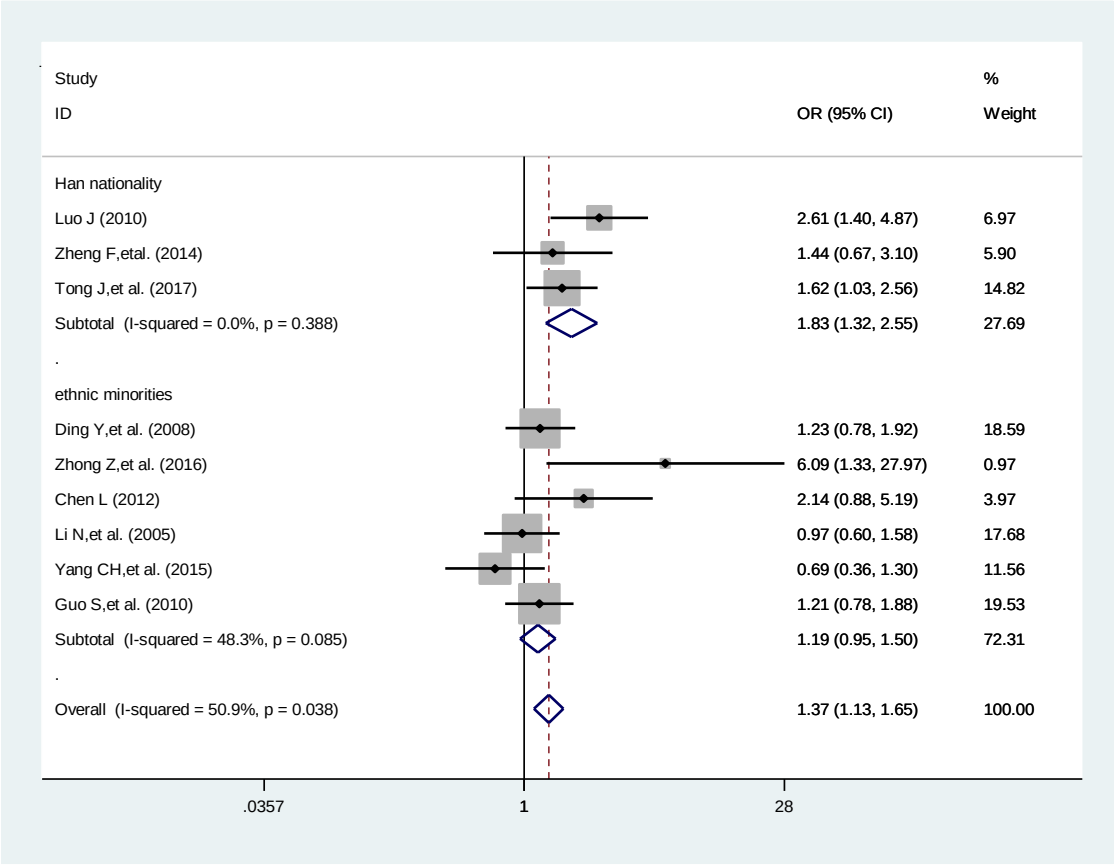



**Figure 2**. Results of *AT1R A1166C* mutation and EH risk in subgroup analysis

## Meta-analysis of *CYP11B2 C344T* polymorphism and EH risk

The contents of the 11 articles involved *C344T* and EH risk.The results elucidated that the polymorphism o f *CYP11B2 C344T* gene was not significantly associated with EH risk under additive model (C *vs.* T; OR 1.204, 95% CI1.044-1.390, p=0.011<0.05), dominant model (CC+TC *vs.* TT), heterozygote model (CT *vs.* TT); OR1.0 75, 95% CI 0.874 -1.322) and homozygote model (CC *vs.* TT; OR1.343, 95% CI 0.966-1.867). (p>0.05), except for recessive model (CC *vs.* TT+TC; OR 1.290, 95% CI 0.956-1.740) and homozygote model (CC *vs.* TT).The r esults were shown in Table 5.

**Table 5.** Results of *CYP11B2 C344T* polymorphism and EH risk

| Variables | $I^2$ | Model | OR 95% CL | p-value | z |
|---|---|---|---|---|---|
| CT *vs.* TT | 19.9% | FEM | 0.915 0.827 1.013 | 0.087 | 1.71 |
| CC *vs.* TT | 51.0% | REM | 0.978 0.923 1.037 | 0.464 | 0.73 |
| (CC+TC) *vs.* TT | 32.5% | FEM | 0.926 0.842 1.019 | 0.115 | 1.58 |
| CC *vs.* (TT+TC) | 55.8% | REM | 0.995 0.924 1.072 | 0.895 | 0.13 |
| C *vs.* T | 50.0% | FEM | 0.961 0.902 1.024 | 0.220 | 1.23 |

## Test for heterogeneity

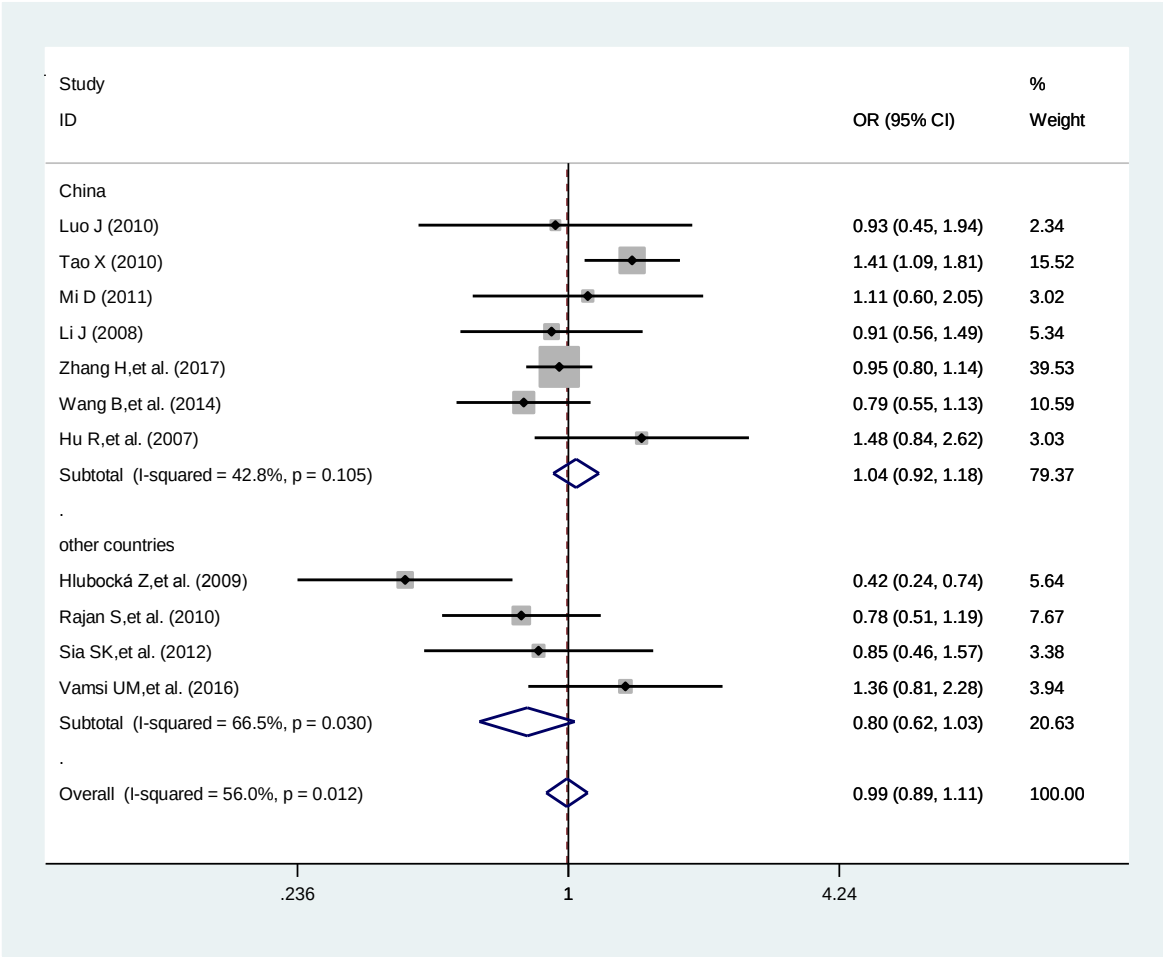
In the heterogeneity test for the *C344T* genotypes of each model, $I^2$ of recessive group (CC *vs.* TT+TC) and homozygote group (CC *vs.* TT) were>50%, indicating that the studies included have heterogeneity. Subgroup analysis was needed to explore the source of heterogeneity.

## Sub-group analysis

Of the 11 articles included, 7 were from China and 4 was from other countries.Therefore, the subgroup analysis of recessive model (CC *vs.* TT+TC) and homozygote model (CC *vs.* TT)were conducted according to the source of the countries.The meta-analysis of 7 Chinese articles showed that $I^2$ of the two models were both <50%, indicating that different countries had an impact on heterogeneity.And the subgroup analysis showed that there was no significant association between *C344T* mutation and EH risk under (CC*vs.* TT+TC) [OR=1.0421 95%CI=（0.923, 1.177）] and (CC *vs.* TT) [OR=1.069, 95%CI=（0.909, 1.256）]in China (p>0.05).There was no relationship between *C344T* mutation and EH risk under (CC *vs.* TT) [OR=0.87，95%CI=（0.51, 1.09）] in other countries.The results were shown in Table 6 and Figure 3.

**Table 6.** Results of *CYP11B2 C344T* mutation and EH risk in subgroup analysis.

| Variables | $I^2$ | Model | OR 95% CL | p-value |
|---|---|---|---|---|
| CC *vs.* (TT+TC)in China | 42.86% | FEM | 1.042 0.923 1.177 | 0.105 |
| CC *vs.* (TT+TC)in other countries | 66.5% | REM | 0.80 0.62 1.03 | 0.03 |
| CC *vs.* TT in China | 19.2% | FEM | 1.069 0.909 1.256 | 0.422 |
| CC *vs.* TT in other countries | 42.4% | FEM | 0.67 0.51 0.88 | 0.157 |



## Sub-group analysis of homozygote group (CC *vs.* TT)

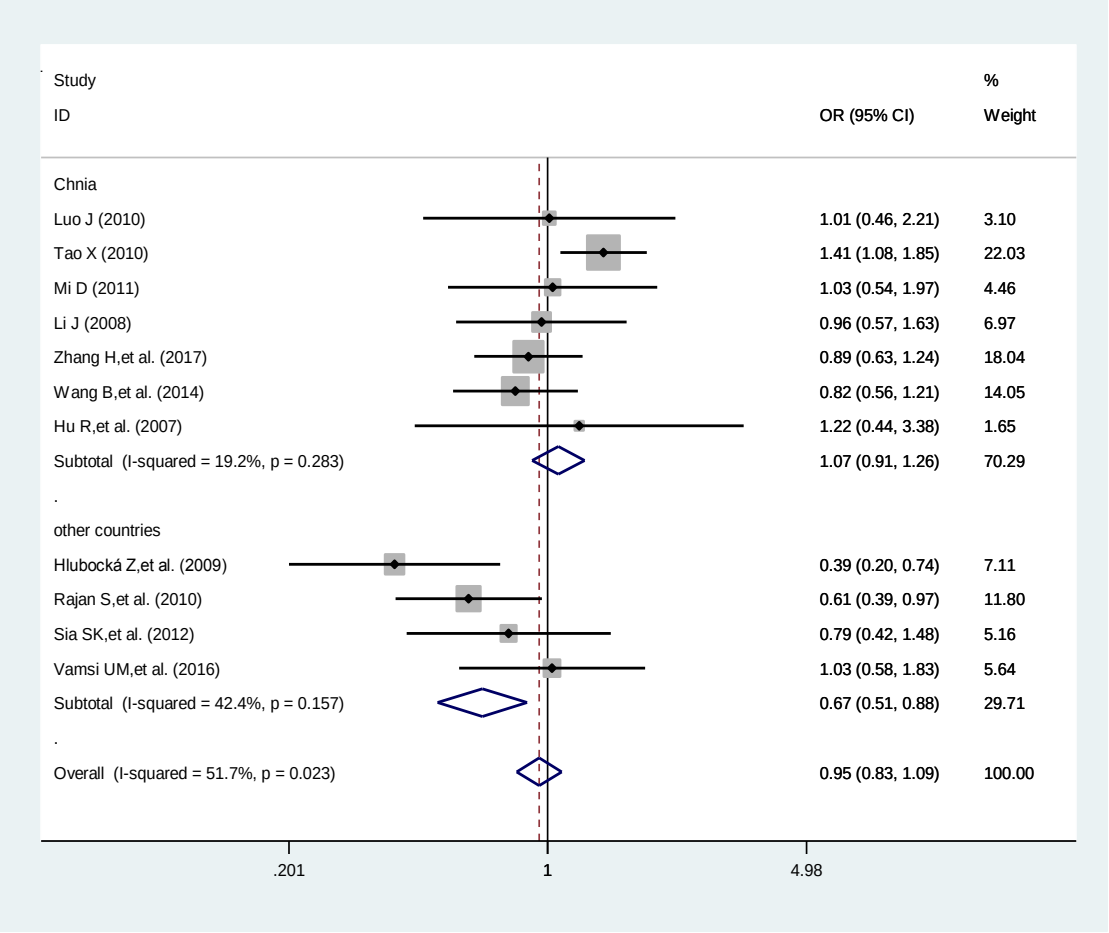



**Figure 3.** Results of *CYP11B2 C344T* mutation and EH risk in subgroup analysis.

## Publication bias evaluation

We analyzed the publication bias of articles on the relationship between *ACE I/D, AT1R A1166C, C344T* a nd EH risk. The two groups of gene funnel plot analysis showed asymmetry, indicating the possibility of publica tion bias. The results were shown in Figure 4.

## Discussion

Among all the the gene polymorphisms associated with RASS system, mutation of *ACE I/D, AT1R* A11166C, *CYP11B2 C344T* are paid intensive attention at home and abroad.Insertions and deletions of Alu sequence are the most common mutation in ACE gene, namely I/D which can affect the expression of ACE gene so as to participate in the regulation of blood pressure Singh A, et al., (2018). At present, researches show that I/D polymorphisms are more than 50%.Besides, *A1166C*, as the closest gene polymorphism to *AT1R*, situates at the 5' end of 3'untranlated region which will not impact the open reading frame and functional change, but involve in regulating transcription and translation and affect the role of *AT1R* in turn Wang HB, et al., (2015).Transcriptional regulatory zone -334T/C, one of the four major genetic variants of *CYP11B2* is the most studied, which can influence the binding of *CYP11B2* gene promoter and sf-1 factor, influencing the synthesis and secretion of aldosterone synthase mRNA and aldosterone Munshi A, et al., (2010).

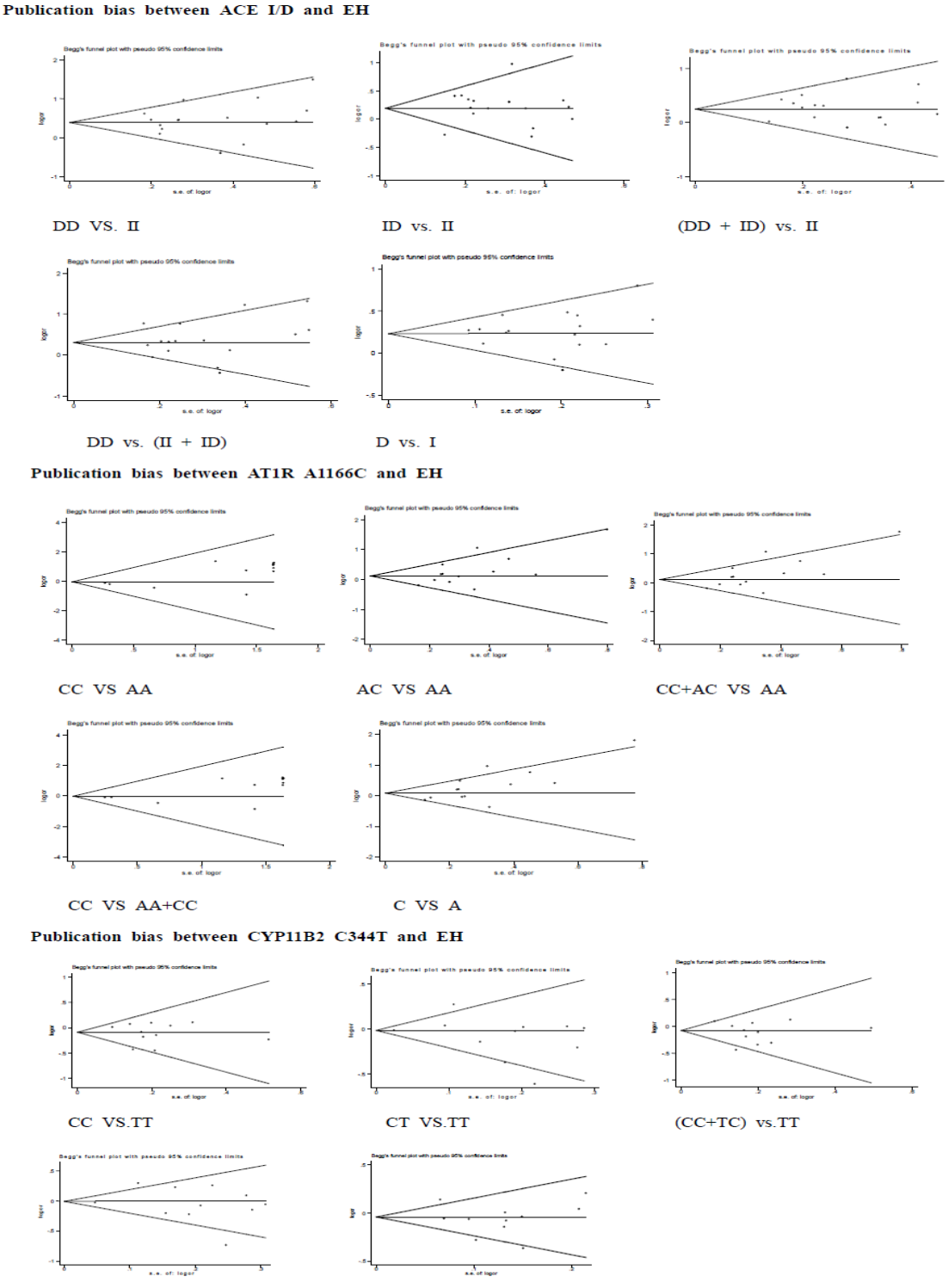



**Figure 4.** The publication bias of articles on the relationship between *ACE I/D*, *AT1R A1166C*, *CYP11B2 C344T* and EH risk was s hown in the Funnel figure.

The results of the studies on the correlation between gene polymorphism above and EH are not consistent. In our current meta-analysis, a total of 41 studies (17 studies for the *ACE I/D* polymorphism, 13 studies for the *A1166C* polymorphism and 11 studies for the *C344T* polymorphism) are accepted to review the relationship between ACE, *AT1R* as well as *CYP11B2* gene polymorphism and EH risk. The results show that the presence of the ACE gene I/D mutation is related to the susceptibility to EH under all models, which is consistent with Wang's research results Wang ZG, et al., (2010). For *A1166C*, 13 articles are associated with *A1166C* and the EH risk. The results show that the polymorphism of *A1166C* gene has no connection with EH risk under dominant model (CC+AC *vs.* AA), recessive model (CC *vs.* AA+AC, heterozygote model (AC *vs.* AA) homozygote model (CC *vs.* AA) and heterozygote model (AC *vs.* AA).Besides, we also find that ethnic differences have an impact on heterogeneity.$I^2$ of (C *vs.* A) is changed from greater than 50% to less than 50% when the minority is not considered in subgroup analysis**.** And there is no significantly association between *A1166C* mutation and EH risk under additive model (C *vs.* A) in China. When it comes to *C344T*, 11 articles showed that there is no relationship with EH risk in the polymorphism of *CYP11B2 C344T* under additive model (C *vs.* T), dominant model (CC+TC *vs.* TT), recessive model (CC *vs.* TT+TC), heterozygote model (CT *vs.* TT) and homozygote model (CC *vs.* TT) ($p>0.05$). Moreover, besides above models, no significantly relationship has been found between *CYP11B2 C344T* mutation and EH in Chinese people when compared with other countries under recessive model (CC *vs.* TT+TC)and homozygote model (CC *vs.* TT) ($p>0.05$).'Our finding is different from Li WX's results Li WX, et al., (2014) The length and quality of the included literature may be the result of different results.

## CONCLUSION

In a nutshell, to identify *ACE I/D* mutation has certain clinical significance for the prevention of EH and th ere is not enough evidence to suggest that gene polymorphism of *AT1R A1166C, CYP11B2 C344T* are associate d with EH.

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## CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

## DISCLOSURE

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

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