Association between angiotensin converting enzyme gene polymorphism and essential hypertension: A systematic review and meta-analysis

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Abstract
Background: The current meta-analytic study explored the relation between ACE gene insertion/deletion (I/D), and the risk of EH by reviewing relevant trials so as to determine the association between Angiotensin Converting Enzyme (ACE) gene polymorphism and essential hypertension (EH) susceptibility.

Methods: Relevant studies published before May 2019 were collected from the PubMed, Cochrane, Embase, CNKI, VAFUN, and VIP databases.

Results: Fifty-seven studies involving a total of 32,862 patients were included. These studies found that ACE gene D allele was associated with higher EH susceptibility in allelic model, homozygote model, dominant model, and regressive model, and that Asian population with ACE gene D allele showed a higher EH susceptibility in all these models. Moreover, ACE gene D allele was found closely related to a higher EH susceptibility in the subgroups of HWE, NO HWE, Caucasian population, and Mixed population, with the majority being males in allelic model, homozygote model, and regressive model and the majority being females in allelic model.

Conclusion: ACE gene D allele is associated with an overall higher EH susceptibility, which is confirmed in the subgroup analysis of Asian population, HWE, NO HWE, Caucasian population, and Mixed population.

Keywords
Angiotensin converting enzyme, gene polymorphism, essential hypertension, meta-analysis

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Introduction
Essential hypertension (EH), abbreviated as hypertension, is a common and frequently-occurring disease mainly manifested by elevated blood pressure, and it remains one of the principal causes of death in cardiovascular diseases. With the acceleration of population aging and the growing number of obese people, the prevalence rate of EH shows an increasing trend in both developed and developing countries. Hypertension is a disease prominently featured by family clustering. The incidence rate of hypertension in children whose parents both suffer from the health problem can be as high as 46%, and about 60% of hypertensive patients can be asked about family history.1-3

Key gene dominant inheritance and polygene associated inheritance are the two main modes of inheritance of hypertension. In the genetic phenotype of hypertension, occurrence, height, and other factors related to blood pressure complications, such as obesity, are also hereditary, and the incidence of elevated blood pressure can be hereditary. Candidate genes for hypertension include renin–angiotensin system (RAS) genes, sodium system related genes, signal transduction pathway related genes, and endothelin system genes. Angiotensin converting enzyme (ACE) is an important enzyme in the RAS system. The relationship between this gene polymorphism and the genetic

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heterogeneity of hypertension has been extensively researched by scholars around the world.\textsuperscript{4,5}

The relation between ACE gene polymorphism and essential hypertension research is currently a research hot spot, and most research results include ACE gene polymorphism and the pathogenesis of EH. Besides, there is a certain relationship between the risk factors of cardiovascular diseases. Therefore, whether the ACE gene I/D polymorphism can be employed as a clinical and subclinical marker for the prognosis observation, diagnosis, and treatment of essential hypertension still needs further research. This meta-analysis was performed with all available literature to obtain updated evidence about the association between ACE gene insertion/deletion (I/D) and EH susceptibility.

Materials and methods

Searching strategy

To identify studies on the association between ACE gene insertion/deletion (I/D) and the risk of EH, relevant studies published before May 2019 were retrieved from the Cochrane, Pubmed, Embase, CNKI, V ANFUN, and VIP databases. The references of all the identified articles were also retrieved to identify additional related studies. The search terms were as follows: polymorphism, variant, genotype, gene, angiotensin converting enzyme, ACE, hypertension, essential hypertension, and EH. These terms were searched in combination with “AND” or “OR.” The literature review was performed independently by two investigators, with a third resolving any disputes as needed.

Following the PICOS (Participants, Interventions, Comparisons, Outcomes, and Study Design) principle, the key search terms included (P) patients with EH; (I) detection of ACE gene polymorphism; (C/O) comparison of ACE gene polymorphism between the EH group and the control group; (S) case-control trial or cohort study.

Study selection criteria

Included studies met the following criteria: (1) case-control studies or cohort studies; (2) the subjects in the case group were patients with EH; (3) the subjects in the control group were healthy controls or patients without EH; (4) the research factors were ACE gene insertion/deletion (I/D); and (4) articles were written in English or Chinese.

Studies were excluded for meeting the following criteria: (1) repeated articles or results; (2) clear data errors; (3) case reports, case-control studies, theoretical research, conference reports, systematic reviews, meta-analyses, or other forms of research or comment that were not designed in a randomized controlled manner; (4) irrelevant outcomes; and (5) lack of a comparable control group.

Two investigators independently determined whether studies met the inclusion criteria, with a third resolving any disputes as needed.

Data extraction and quality assessment

Two categories of information were extracted from each included study: basic information and primary study outcomes. Basic information relevant to this meta-analysis was as follows: author names, year of publication, country, ethnicity, sample size, age, polymorphism, and genotyping method. Primary clinical outcomes relevant to this analysis were genotype frequencies (ACE gene insertion/deletion (I/D)) in the EH group and control groups. The data extraction was performed independently by two investigators, with a third resolving any disputes as needed.

Statistical analysis

STATA v12.0 (TX, USA) was used for all statistical analyses. Heterogeneity in the study results was assessed using chi-squared and $I^2$ tests, and appropriate analysis models (fixed-effect or random-effect) were determined. A chi-squared $p < 0.05$ and an $I^2 > 50\%$ indicated high heterogeneity, and thus a random-effects model was used. A chi-squared $p > 0.05$ and an $I^2 \leq 50\%$ indicated acceptable heterogeneity, and thus a fixed-effects model was used instead. Egger’s test and Begg’s test were performed to determine publication bias. On condition that the Hady Weinberg equilibrium (HWE) genetic balance test was neither provided in the original text nor performed in the control group, Stata v12.0 was used to obtain corresponding results (p value). Five commonly used gene models were selected for this meta-analysis: allelic model (D vs I), homozygote model (DD vs II), heterozygote model (DI vs II), dominant model (DD + DI vs II), and regressive model (DD vs DI + II). All the indexes and statistics were analyzed by OR and 95%CI.

Overview of included studies

A total of 877 articles were screened in the initial key word search, of which 786 were excluded after title/abstract review. The remaining 91 articles were subject to a complete full-text assessment, and as a result, 34 articles were excluded due to the following reasons: (1) theoretical research (11); (2) without clinical outcomes (18); (3) repeated articles (2); and (4) lack of a control group (3). We ultimately identified 57 studies\textsuperscript{6–62} that met the inclusion criteria of the current meta-analysis, which incorporated a total of 16,298 EH patients in the EH group and 16,564 healthy controls or patients without EH in the
control group. Study selection is outlined in Figure 1. Table 1 summarizes the basic information of each study, including author names, year of publication, country, ethnicity, sample size, age, polymorphism, and genotyping method.

**Meta-analysis of ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility**

All the included studies reported the association between ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility. In view of the significant heterogeneity between studies (chi-squared \( p < 0.05 \) and \( I^2 > 50% \)), a random-effects model was established to analyze the five gene models in all the subgroup analyses except for allelic model in the subgroup of Caucasian (D vs I) (chi-squared \( p > 0.05 \) and \( I^2 < 50\% \)).

The results suggested that ACE gene D allele was associated with a higher EH susceptibility as compared with ACE gene I allele, as evidenced by the following statistics: allelic model (D vs I) (OR: 2.273, 95%CI: 2.068–2.499); homozygote model (DD vs II) (OR: 1.472, 95%CI: 1.247–1.739); dominant model (DD + DI vs II) (OR: 1.178, 95%CI: 1.053–1.319); and regressive model (DD vs DI + II) (OR: 1.422, 95%CI: 1.240–1.630).

The subgroup analysis also indicated that the Asian population with ACE gene D allele was associated with a higher EH susceptibility as compared with those with ACE gene I allele, as demonstrated by the following data: allelic model (D vs I) (OR: 2.199, 95%CI: 1.991–2.430); homozygote model (DD vs II) (OR: 1.545, 95%CI: 1.314–1.817); dominant model (DD + DI vs II) (OR: 1.189, 95%CI: 1.066–1.326); regressive model (DD vs DI + II) (OR: 1.488, 95%CI: 1.298–1.706). Moreover, ACE gene D allele was associated with a higher EH susceptibility in the subgroup of HWE, as evidenced by the statistics below: allelic model (D vs I) (OR: 2.158, 95%CI: 1.976–2.356); homozygote model (DD vs II) (OR: 1.394, 95%CI: 1.182–1.644); regressive model (DD vs DI + II) (OR: 1.372, 95%CI: 1.193–1.578). ACE gene D allele was associated with a higher EH susceptibility in the subgroup of NO HWE, as shown by the following results: allelic model (D vs I) (OR: 3.158, 95%CI: 1.948–5.121); regressive model (DD vs DI + II) (OR: 1.782, 95%CI: 1.070–2.967). The Caucasian population with ACE gene D allele were associated with a higher EH susceptibility, as demonstrated by the following statistics: allelic model (D vs I) (OR: 2.448, 95%CI: 2.0212.965). The Mixed population with ACE gene D allele was associated with a higher EH susceptibility as suggested by the data below: allelic model (D vs I) (OR: 2.516, 95%CI: 1.289–4.911). All these results were shown in Figures 2 and 3 and Table 2.

**Meta-analysis of ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility in males**

Eight studies involving a total of 7124 EH patients in the EH group and 6967 healthy controls or patients without EH in the control group reported the association between ACE gene insertion/deletion (I/D) polymorphism and EH susceptibility in males. Studies that were significantly heterogeneous (chi-squared \( p < 0.05 \) and \( I^2 > 50\% \)) were analyzed using a random-effects...
Table 1. The basic characteristics description of included studies.

| Study            | Country | Ethnicity | No. of patients | Age          | Genotype of EH group | Genotype of Control group |
|------------------|---------|-----------|-----------------|--------------|-----------------------|--------------------------|
|                  |         |           |                 |              | EH group | Control group | Control group | II | ID | DD | II | ID | DD |
| Yi et al.⁸       | China   | Asian     | 198             | 50           | 42        | 67           | 95           | 36 | 34 | 69 | 28 |
| Yi et al.⁹       | China   | Asian     | 120             | 53           | 41        | 22           | 74           | 24 | 26 | 50 | 26 |
| Fan et al.⁹      | China   | Asian     | 921             | 311          | 427       | 183          | 333          | 454 | 164|
| Fan et al.⁹      | China   | Asian     | 285             | 113          | 126       | 46           | 113          | 156 | 40 |
| Wang Xiaoyun¹⁰   | China   | Asian     | 81              | 38           | 9         | 34           | 18           | 7  | 5  |
| Yuan Fengxian¹¹  | China   | Asian     | 69              | 15           | 30        | 24           | 39           | 45  | 14 |
| Xu Xiangjun¹⁸    | China   | Asian     | 28              | 12           | 11        | 5            | 10           | 13  | 6  |
| Tian Lihong¹⁹    | China   | Asian     | 56              | 12           | 20        | 24           | 11           | 21  | 8  |
| Dong-Ming et al.¹²| China  | Asian     | 146             | 58           | 57        | 31           | 50           | 40  | 18 |
| Liful²⁰         | China   | Asian     | 158             | 60           | 69        | 28           | 130          | 153 | 54 |
| Shi Zhilin¹¹     | China   | Asian     | 128             | 47           | 67        | 14           | 62           | 78  | 10 |
| Lv Dongxia¹²     | China   | Asian     | 102             | 44           | 42        | 16           | 42           | 46  | 19 |
| Lii et al.²³     | China   | Asian     | 100             | 13           | 43        | 44           | 21           | 50  | 29 |
| Zheng et al.²⁴  | China   | Asian     | 115             | 24           | 51        | 40           | 33           | 45  | 18 |
| He Fengrong²⁵    | China   | Asian     | 209             | 77           | 111       | 21           | 124          | 134 | 45 |
| He Fengrong²⁵    | China   | Asian     | 189             | 78           | 87        | 24           | 124          | 134 | 45 |
| Yun Meling²⁶     | China   | Asian     | 106             | 59           | 30        | 17           | 39           | 43  | 15 |
| Liang Rirong²⁷   | China   | Asian     | 64              | 60           | 18        | 16           | 56           | 50  | 16 |
| Song Xin et al.²⁸| China   | Asian     | 91              | 28           | 43        | 20           | 54           | 41  | 14 |
| Jiang et al.²⁹   | China   | Asian     | 220             | 83           | 108       | 29           | 110          | 112 | 13 |
| Qi Xiaohua²⁹     | China   | Asian     | 100             | 39           | 41        | 20           | 32           | 54  | 14 |
| Zhao Yan²⁰      | China   | Asian     | 200             | 62           | 14        | 24           | 89           | 86  | 10 |
| Niu et al.³⁰     | China   | Asian     | 1089            | 62           | 14        | 24           | 300          | 451 | 175|
| Zhou Bao³¹       | China   | Asian     | 112             | 31           | 36        | 45           | 38           | 44  | 21 |
| Gao Bingfang³²   | China   | Asian     | 78              | 21           | 43        | 14           | 25           | 33  | 4  |
| Dong et al.³³    | China   | Asian     | 120             | 51           | 43        | 26           | 94           | 13  | 3  |
| Gong Hongmei³⁴   | China   | Asian     | 200             | 58           | 46        | 56           | 74           | 94  | 24 |
| Yao Bingfu³⁵     | China   | Asian     | 125             | 42           | 50        | 33           | 34           | 48  | 28 |
| Lin Huazhong³⁶   | China   | Asian     | 1380            | 534          | 621       | 225          | 346          | 421 | 121|
| Xue et al.³⁶     | China   | Asian     | 110             | 28           | 44        | 38           | 19           | 19  | 5  |
| Study                        | Country | Ethnicity | No. of patients | Age | Genotype of EH group | Genotype of control group |
|-----------------------------|---------|-----------|-----------------|-----|----------------------|--------------------------|
|                             | EH group | Control group | EH group | Control group | II | ID | DD | II | ID | DD |
| Lai Yanxian et al. | China | Asian | 108 | 102 | —— | —— | 27 | 50 | 27 | 42 | 47 | 13 |
| Fan et al. | China | Asian | 3630 | 826 | —— | —— | 1286 | 1689 | 626 | 268 | 392 | 158 |
| Jhawat | India | Asian | 510 | 279 | —— | —— | 154 | 250 | 106 | 60 | 140 | 70 |
| Bin | China | Asian | 486 | 457 | 62.65 | 62.67 | 167 | 181 | 138 | 159 | 227 | 71 |
| Liu Longmei et al. | China | Asian | 50 | 50 | 52.1 | 52.1 | 13 | 16 | 21 | 20 | 18 | 12 |
| Krishnan et al. | India | Mixed | 280 | 220 | 43.6 | 42.7 | 59 | 68 | 81 | 118 | 58 | 44 |
| Aziz et al. | Algeria | Caucasian | 75 | 70 | 48.1 | 43.1 | 25 | 40 | 10 | 43 | 25 | 2 |
| Abbas S et al. | India | Mixed | 138 | 116 | 41.29 | 40.03 | 37 | 83 | 18 | 12 | 70 | 34 |
| Heidari F et al. | Malaysia | Asian | 72 | 72 | 47.22 | 46.92 | 4 | 25 | 43 | 18 | 35 | 19 |
| Raj et al. | India | Asian | 109 | 99 | —— | —— | 21 | 34 | 49 | 21 | 34 | 44 |
| Srivastava et al. | India | Mixed | 222 | 252 | 51.6 | 49.7 | 42 | 106 | 74 | 16 | 98 | 138 |
| Gupta et al. | India | Mixed | 106 | 110 | 53.9 | 51.96 | 27 | 49 | 30 | 33 | 50 | 27 |
| Das et al. | India | Mixed | 35 | 35 | —— | —— | 12 | 4 | 19 | 14 | 18 | 3 |
| Ramachandran et al. | Malaysia | Asian | 65 | 70 | 58.48 | 46.2 | 24 | 34 | 7 | 40 | 28 | 2 |
| Dall’omo et al. | Italy | Caucasian | 79 | 16 | 48 | 47 | 7 | 36 | 36 | 2 | 8 | 6 |
| Zapolska-Downar et al. | Poland | Caucasian | 40 | 40 | 24.1 | 24.7 | 6 | 26 | 8 | 13 | 17 | 10 |
| Fu et al. | Japan | Asian | 275 | 441 | 61.7 | 64.9 | 117 | 113 | 45 | 195 | 194 | 52 |
| Demirel et al. | Italy | Caucasian | 129 | 129 | 45 | 35.6 | 23 | 63 | 43 | 20 | 51 | 38 |
| Stankovic et al. | Yugoslavia | Caucasian | 105 | 210 | —— | —— | 31 | 85 | 59 | 34 | 115 | 61 |
| Lari et al. | Bangladesh | Asian | 44 | 59 | 47.3 | 43.5 | 5 | 17 | 22 | 19 | 26 | 14 |
| Gesang et al. | China | Asian | 103 | 123 | 49 | 47 | 29 | 47 | 27 | 48 | 60 | 15 |
| Fu Y et al. | China | Asian | 235 | 510 | 60.9 | 64.7 | 5 | 68 | 162 | 20 | 158 | 332 |
| Higaki et al. | Japan | Asian | 1200 | 3814 | 65.9 | 57.7 | 525 | 529 | 191 | 1638 | 1708 | 468 |
| Bedir et al. | Turkey | Caucasian | 165 | 143 | 49.8 | 58.9 | 23 | 77 | 65 | 19 | 82 | 42 |
| Sugiyama et al. | Japan | Asian | 711 | 532 | 63.8 | 55.3 | 290 | 322 | 99 | 200 | 247 | 85 |
| Mondorf et al. | Germany | Caucasian | 121 | 125 | 46.42 | 47.3 | 31 | 55 | 35 | 19 | 66 | 40 |
| Maeda et al. | Japan | Asian | 41 | 34 | 59.3 | 61.1 | 13 | 14 | 14 | 16 | 9 | 9 |
| Vassilikioti et al. | Greece | Caucasian | 98 | 84 | —— | —— | 23 | 45 | 30 | 15 | 40 | 29 |
| Magiouchi et al. | Japan | Asian | 84 | 84 | 48 | 48 | 40 | 29 | 15 | 28 | 39 | 17 |
| Ishigami et al. | Japan | Asian | 87 | 95 | 59.3 | 57.4 | 44 | 26 | 17 | 35 | 43 | 17 |
model, while the rest studies were analyzed using a fixed-effects model (chi-squared $p > 0.05$ and $I^2 < 50\%$).

The results demonstrated that ACE gene D allele was associated with a higher EH susceptibility in males, as evidenced by the following statistics: allelic model (D vs I) (OR: 1.834, 95%CI: 1.688–1.993); homozygote model (DD vs II) (OR: 1.260, 95%CI: 1.076–1.477); regressive model (DD vs DI + II) (OR: 1.286, 95%CI: 1.117–1.480). All these results were presented in Figure 4 and Table 3.
Table 2. Meta-analysis of ACE gene insertion/deletion (I/D) polymorphisms and EH susceptibility.

| Gene type  | Race      | N (case/control) | OR (95% CI)       | p*  | p | p# | p Value |
|------------|-----------|------------------|-------------------|-----|---|----|---------|
| DD vs II + ID | Overall | 16,298/16,564   | 1.422 (1.240, 1.630) | 0  | 75.30% | 0 | 0.005 | 0.004 |
| DD vs II + ID | Mixed   | 781/733         | 1.274 (0.470, 3.458) | 0  | 93.60% | 0.634 | 0.624 | 0.477 |
| DD vs II + ID | Caucasian| 856/876       | 1.185 (0.831, 1.689) | 0.011 | 59.70% | 0.349 | 0.297 | 0.331 |
| DD vs II + ID | Asian   | 14,661/14,955  | 1.488 (1.296, 1.706) | 0  | 69.50% | 0 | 0.008 | 0.001 |
| DD vs II + ID | HWE     | 15,021/15,507  | 1.372 (1.193, 1.578) | 0  | 74.00% | 0 | 0.008 | 0.010 |
| DD vs II + ID | NO HWE  | 1277/1057      | 1.782 (1.070, 2.967) | 0  | 79.90% | 0.026 | 0.404 | 0.578 |
| DD+ID vs II | Overall | 16,298/16,564  | 1.178 (1.053, 1.319) | 0  | 73.20% | 0.004 | 0.021 | 0.024 |
| DD+ID vs II | Mixed   | 781/733         | 0.850 (0.311, 2.322) | 0  | 92.50% | 0.752 | 0.327 | 0.274 |
| DD+ID vs II | Caucasian| 856/876       | 1.219 (0.773, 1.922) | 0.001 | 68.20% | 0.394 | 0.940 | 0.205 |
| DD+ID vs II | Asian   | 14,661/14,955  | 1.189 (1.066, 1.326) | 0  | 68.20% | 0.002 | 0.004 | 0.003 |
| DD+ID vs II | HWE     | 15,021/15,507  | 1.109 (0.999, 1.231) | 0  | 64.40% | 0.053 | 0.018 | 0.031 |
| DD+ID vs II | NO HWE  | 1277/1057      | 1.527 (0.904, 2.578) | 0  | 86.30% | 0.114 | 0.835 | 0.638 |
| DD vs II | Overall | 16,298/16,564  | 1.472 (1.247, 1.739) | 0  | 77.20% | 0 | 0.005 | 0.008 |
| DD vs II | Mixed   | 781/733         | 1.010 (0.242, 4.212) | 0  | 94.70% | 0.989 | 1.000 | 0.750 |
| DD vs II | Caucasian| 856/876       | 1.268 (0.756, 2.127) | 0.005 | 63.90% | 0.368 | 0.211 | 0.053 |
| DD vs II | Asian   | 14,661/14,955  | 1.545 (1.314, 1.817) | 0  | 71.70% | 0 | 0.003 | 0.001 |
| DD vs II | HWE     | 15,021/15,507  | 1.394 (1.182, 1.644) | 0  | 73.90% | 0 | 0.006 | 0.011 |
| DD vs II | NO HWE  | 1277/1057      | 1.920 (0.955, 3.861) | 0  | 85.10% | 0.067 | 0.835 | 0.813 |
| ID vs II | Overall | 16,298/16,564  | 1.037 (0.935, 1.150) | 0  | 61.60% | 0.495 | 0.170 | 0.169 |
| ID vs II | Mixed   | 781/733         | 0.699 (0.297, 1.644) | 0  | 87.10% | 0.411 | 0.624 | 0.154 |
| ID vs II | Caucasian| 856/876       | 1.142 (0.744, 1.755) | 0.010 | 60.10% | 0.544 | 0.144 | 0.217 |
| ID vs II | Asian   | 14,661/14,955  | 1.039 (0.939, 1.150) | 0  | 56.00% | 0.459 | 0.083 | 0.074 |
| ID vs II | HWE     | 15,021/15,507  | 0.993 (0.901, 1.094) | 0  | 51.70% | 0.881 | 0.103 | 0.231 |
| ID vs II | NO HWE  | 1277/1057      | 1.272 (0.786, 2.059) | 0  | 80.10% | 0.327 | 0.404 | 0.669 |
| D vs I | Overall | 16,298/16,564  | 2.273 (2.068, 2.499) | 0  | 80.40% | 0 | 0 | 0 |
| D vs I | Mixed   | 781/733         | 2.516 (1.893, 4.911) | 0  | 92.60% | 0.007 | 0.624 | 0.935 |
| D vs I | Caucasian| 856/876       | 2.448 (2.021, 2.965) | 0.172 | 30.80% | 0 | 0.095 | 0.105 |
| D vs I | Asian   | 14,661/14,955  | 2.199 (1.991, 2.430) | 0  | 79.60% | 0 | 0 | 0 |
| D vs I | HWE     | 15,021/15,507  | 2.158 (1.976, 2.356) | 0  | 74.40% | 0 | 0 | 0 |
| D vs I | NO HWE  | 1277/1057      | 3.158 (1.948, 5.121) | 0  | 91.00% | 0 | 0.532 | 0.228 |

*p value of Heterogeneity chi-squared.

#p value of Pooled statistic.
The results showed that ACE gene D allele was associated with a higher EH susceptibility in females, as evidenced by the following statistics: allelic model (D vs I) (OR: 1.840, 95%CI: 1.582-2.141).

All these results were presented in Figure 5 and Table 4.

**Discussion**

It is generally believed that EH is caused by the interaction between multi-gene heredity and environment, while the true cause of the disease remains unclear. As the most common epidemic disease in modern times, EH seriously endangers human health and can further lead to coronary atherosclerosis. EH is acknowledged as one of the major risk factors for death and serious diseases, including heart disease, stroke, heart failure, and kidney failure. EH is closely related to multiple factors, and statistics from studies at home and abroad shows that the influence of genetic factors on blood pressure accounts for 30%–50% of all their effects on the pathogenesis of EH.1–3
The renin-angiotensin system (RAS) has significant functions in blood pressure regulation, electrolyte balance, vascular tension, and cardiovascular remodeling. As a membrane binding enzyme, ACE is located in vascular endothelial cells and widely distributed in the body. ACE is a key enzyme of RAS, and it can catalyze angiotensin I into angiotensin II, a strong vasoconstrictor, and slow down inactive shock peptide vasodilation. Given the role of RAS in blood pressure regulation, the ACE gene may be a candidate gene for treating EH.37–39

The gene-encoding ACE is an important candidate gene for cardiovascular disease, and its 16 intron insertion/deletion (I/D) polymorphism in the non-coding region can cause the presence or absence of a 287 bp DNA fragment. Studies on high-accutase and Japanese populations demonstrated that ACE insertion/deletion polymorphism accounts for 50% of the variation in plasma ACE levels. Ang II is a powerful vasoconstrictor converted from Ang I by ACE, and it affects the structures of the arterial wall and induces arteriosclerosis by promoting cell growth or extracellular matrix synthesis. ACE inactivates bradykinin and leads to the proliferation of vascular smooth muscle cells.4–6

In the present study, we found that ACE gene D allele was associated with a higher EH susceptibility in allelic model, homozygote model, dominant model, and regressive model. The Asian population with ACE gene D allele was related to a higher EH susceptibility in allelic model, homozygote model, dominant model, and regressive model. Moreover, ACE gene D allele was found associated with a higher EH susceptibility in the subgroups of HWE, NO HWE, Caucasian population, and Mixed population. In addition, ACE gene D allele was associated with a higher EH susceptibility in males in allelic model, homozygote model, and regressive model as well as a higher EH susceptibility in females in allelic model.

It should be noted that there were certain limitations in the present analysis, which inevitably precluded more in-depth analyses. First, only articles written in English and Chinese were included. Second, the exclusion/inclusion criteria and the severity of EH differed in various individual studies. Third, environmental factors such as smoking, high-fat diet, antioxidant intake, use of certain lipid-lowering drugs, or hormone varied among the patients. Fourth, only pooled data were analyzed due to the unavailability of individual patient data.

**Figure 5.** Forest plot of studies evaluating the relationship between ACE I/D polymorphism and EH risk in females based on dominant model.
Conclusion

Our results indicate that ACE gene D allele is associated with an overall higher EH susceptibility in Asian population, HWE, NO HWE, Caucasian population, and Mixed population in both males and females.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 4. Meta-analysis of ACE gene insertion/deletion (I/D) polymorphisms and EH susceptibility in female.

| Gene type     | N (case/control) | OR (95%CI) | \(p^*\) | \(\rho\) | \(p^#\) | \(p\) Value | Begg | Egger |
|---------------|------------------|------------|--------|--------|--------|-------------|-------|-------|
| DD vs II + ID | 7124/6967        | 1.206 (0.909, 1.599) | 0.004  | 64.60% | 0.194  | 0.118 0.04  |       |       |
| DD + ID vs II | 7124/6967        | 0.974 (0.872, 1.087) | 0.133  | 35.60% | 0.634  | 0.076 0.033 |       |       |
| DD vs II      | 7124/6967        | 1.264 (0.903, 1.770) | 0.002  | 67.20% | 0.173  | 0.251 0.033 |       |       |
| ID vs II      | 7124/6967        | 0.953 (0.847, 1.073) | 0.749  | 0.00%  | 0.427  | 0.175 0.047 |       |       |
| D vs I        | 7124/6967        | 1.840 (1.582,2.141) | 0.026  | 54.00% | 0      | 0.016 0.017 |       |       |

\(p^*\) value of Heterogeneity chi-squared.
\(p^#\) value of Pooled statistic.
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