Angiotensin-Converting Enzyme Insertion/Deletion Polymorphism Contributes High Risk for Chronic Kidney Disease in Asian Male with Hypertension–A Meta-Regression Analysis of 98 Observational Studies

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Abstract

**Background:** Associations between angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphisms and chronic kidney disease (CKD) have been extensively studied, with most studies reporting that individuals with the D allele have a higher risk. Although some factors, such as ethnicity, may moderate the association between ACE I/D polymorphisms and CKD risk, gender-dependent effects on the CKD risk remain controversial.

**Objectives:** This study investigated the gender-dependent effects of ACE I/D polymorphisms on CKD risk.

**Data sources:** PubMed, the Cochrane library, and EMBASE were searched for studies published before January 2013.

**Study eligibility criteria, participants, and interventions:** Cross-sectional surveys and case–control studies analyzing ACE I/D polymorphisms and CKD were included. They were required to match the following criteria: age >18 years, absence of rare diseases, and Asian or Caucasian ethnicity.

**Study appraisal and synthesis methods:** The effect of carrying the D allele on CKD risk was assessed by meta-analysis and meta-regression using random-effects models.

**Results:** Ethnicity [odds ratio (OR): 1.24; 95% confidence interval (CI): 1.08–1.42] and hypertension (OR: 1.55; 95% CI: 1.04–2.32) had significant moderate effects on the association between ACE I/D polymorphisms and CKD risk, but they were not significant in the diabetic nephropathy subgroup. Males had higher OR for the association between ACE I/D polymorphisms and CKD risk than females in Asians but not Caucasians, regardless of adjustment for hypertension (p<0.05). In subgroup analyses, this result was significant in the nondiabetic nephropathy group. Compared with the I allele, the D allele had the highest risk (OR: 3.75; 95% CI: 1.84–7.65) for CKD in hypertensive Asian males.

**Conclusions and implications of key findings:** The ACE I/D polymorphisms may incur the highest risk for increasing CKD in hypertensive Asian males.

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Introduction

The prevalence of chronic kidney disease (CKD) is approximately 10% in several countries [1–3]. CKD patients have high risk for cardiovascular disease and death [4]. Genetic factors, including ethnicity [5] and family history of disease [6,7], play a key role in CKD pathogenesis. Thus, it is desirable to identify candidate genes and evaluate their effects.

The renin-angiotensin system (RAS) regulates blood pressure and electrolyte balance [8]. Owing to the key role of angiotensin-converting enzyme (ACE) in RAS, ACE polymorphisms have frequently been investigated. One of the most important ACE polymorphisms is a 207-bp insertion/deletion in intron 16 (ACE
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I/D, and a previous study revealed a significant effect of this polymorphism on ACE gene expression [9]. Most studies have found that carriers of the D allele had a higher risk of CKD or end-stage renal disease (ESRD) than those of the I allele [10–12].

Because previous studies have found that gender and the DD genotype had an additive effect on blood ACE levels [13], we hypothesized that gender differences affect the relative risk of ACE I/D polymorphisms for CKD. Numerous studies of CKD or ESRD have reported appreciable, but not significant, gender-dependent effects of ACE I/D polymorphisms [14–19], but the populations used in these studies were of different ethnicities. Studies of Caucasian subjects have indicated additive effects of the D allele in females [14–16], but studies of Asian subjects have shown different results [17–19]. Although many previous meta-analysis studies investigating ACE I/D polymorphisms and CKD have been reported, but no studies have considered moderate effects of gender in our knowledge [10–12,20–22]. This study focused on general population without genetic abnormality or rare disorder, and we wanted to compare the risk of CKD in people with major allele (I allele) or minor allele (D allele) on ACE I/D. In addition, gender-dependent effects of ACE I/D polymorphisms on CKD risk was investigated.

Methods

Search Methods and Criteria for Considering Studies

The PRISMA 2009 Checklist was reported in Table S1. This study focused on the general population without genetic predisposing factors, and aimed to compare CKD risk between individuals carrying the major (I) and minor (D) alleles of ACE I/D. To identify relevant studies, English-language articles in MEDLINE, Cochrane Library and EMBASE were searched using relevant text words and medical subject headings that included all spellings of ACE I/D and CKD (the detailed search strategy is shown in Table S2). All articles published from the dates of inception of these medical databases to January 2013 were included. We manually scanned the reference lists of identified...
Table 1. Characteristics of published studies included in this meta-analysis.

| First author & year | Ethnicity | Study design | CKD type | Kidney function of case | Definition of case |
|---------------------|-----------|--------------|----------|-------------------------|--------------------|
| Shaikh, 2012 [27]   | Caucasian | CC           | DN       | non-ESRD                | UAE >300 mg/day |
| Rahimi, 2012 [28]   | Caucasian | CS           | DN       | non-ESRD                | ACR >30 mg/g |
| El-Baz, 2012 [29]   | Caucasian | CS           | DN       | non-ESRD                | ACR >30 mg/g |
| Zsom(1), 2011 [30]  | Caucasian | CC           | non-DN   | non-ESRD                | biopsy, ultrasound diagnosed & eGFR <60 ml/min/1.73 m² |
| Zsom(2), 2011 [30]  | Caucasian | CC           | DN       | non-ESRD                | proteinuria & eGFR <60 ml/min/1.73 m² |
| Al-Harbi, 2011 [31] | Caucasian | CC           | DN       | non-ESRD                | no description |
| Jung, 2011 [32]     | Asian     | CC           | GN       | non-ESRD                | biopsy diagnosed |
| Ali, 2011 [33]      | Asian     | CC           | Comb     | ESRD                    | doctor diagnosed |
| Huang, 2010 [34]    | Asian     | CC           | GN       | ESRD                    | biopsy diagnosed |
| Jayapalan, 2010 [35]| Asian     | CS           | DN       | non-ESRD                | ACR >30 mg/g or RRT |
| Mansoor, 2010 [14]  | Caucasian | CS           | DN       | non-ESRD                | albuminuria or RRT |
| Naresh, 2009 [36]   | Asian     | CC           | DN       | non-ESRD                | no description |
| Ezzidi, 2009 [37]   | Caucasian | CS           | DN       | non-ESRD                | ACR >30 mg/g or eGFR <90 ml/min/1.73 m² |
| Nikzamir, 2009 [38] | Caucasian | CS           | DN       | non-ESRD                | UAE >30 mg/day |
| Anbazhagah, 2009 [39]| Asian     | CC           | Comb     | ESRD                    | RRT |
| Ahluwalia, 2009 [40]| Asian     | CC           | DN       | non-ESRD                | UAE >200 μg/min, ACR >300 mg/g or RRT |
| Palomo-Piñón, 2009 [16]| Caucasian | CS           | DN       | non-ESRD                | ACR >30 mg/g |
| Möllsten, 2008 [41] | Caucasian | CS           | DN       | non-ESRD                | ACR >20 mg/g |
| Ergolu, 2008 [42]   | Caucasian | CC           | DN       | non-ESRD                | 30 mg/day < UAE < 300 mg/day |
| Afra, 2008 [43]     | Caucasian | CS           | DN       | non-ESRD                | UAE >30 mg/day |
| Tripathi, 2008 [44] | Asian     | CC           | non-DN   | ESRD                    | Ccr < 15 mL/min/1.73 m² & ultrasound diagnosedor CT |
| Movva, 2007 [45]    | Asian     | CC           | DN       | ESRD                    | SCR >1.5 mg/dL and UAE >30 mg/day |
| Uddin, 2007 [46]    | Asian     | CC           | DN       | ESRD                    | proteinuria |
| Buraczynska, 2006 [47]| Caucasian | CC           | Comb     | ESRD                    | RRT |
| So, 2006 [48]       | Asian     | CS           | DN       | non-ESRD                | ACR >30 mg/g |
| Shestakova, 2006 [49]| Caucasian | CC           | DN       | non-ESRD                | ACR >300 mg/g |
| Ng, 2006 [50]       | Caucasian | CS           | DN       | non-ESRD                | urinalyses positive, ACR >250 mg/g (men) or >355 mg/g (women) |
| Prasad, 2006 [51]   | Asian     | CC           | DN       | non-ESRD                | SCR >3 mg/dl & ACR >200 mg/g |
| Degirmenci, 2005 [52]| Caucasian | CS           | DN       | ESRD                    | UAE >30 mg/day |
| van der Sman-de Beer, 2005 [53]| Caucasian | CC           | Comb     | non-ESRD                | RRT |
| Park, 2005 [18]     | Asian     | CC           | DN       | ESRD                    | RRT |
| Canani, 2005 [54]   | Caucasian | CS           | DN       | non-ESRD                | UAE >20 μg/min |
| Fabris, 2005 [55]   | Caucasian | CC           | HN       | non-ESRD                | SCR >1.5 mg/dL |
| Lau, 2004 [56]      | Asian     | CC           | GN       | ESRD                    | biopsy diagnosed |
| Suzuki, 2004 [57]   | Asian     | CC           | GN       | non-ESRD                | biopsy diagnosed |
| Stratta, 2004 [58]  | Caucasian | CC           | GN       | non-ESRD                | biopsy diagnosed |
| Lochynska, 2003 [59]| Caucasian | CC           | GN       | non-ESRD                | biopsy diagnosed |
| Papp, 2003 [60]     | Caucasian | CC           | GN       | ESRD                    | RRT |
| Aucella, 2003 [61]  | Caucasian | CC           | Comb     | non-ESRD                | RRT |
| Okuno, 2003 [62]    | Asian     | CS           | DN       | non-ESRD                | UAE >10 μg/min |
| Ortiz, 2003 [63]    | Caucasian | CC           | non-DN   | non-ESRD                | Ccr < 50 mL/min/1.73 m² |
| Hadjadj, 2003 [15]  | Caucasian | CC           | DN       | non-ESRD                | urinary albumin concentration >20 mg/L |
| Wang, 2003 [64]     | Asian     | CC           | Comb     | ESRD                    | RRT |
| Dixit, 2002 [65]    | Caucasian | CC           | GN       | ESRD                    | biopsy diagnosed |
| Lee(1), 2002 [26]   | Asian     | CS           | non-DN   | non-ESRD                | UAE >20 μg/min or ACR >20 mg/g |
| Lee(2), 2002 [26]   | Asian     | CS           | DN       | non-ESRD                | UAE >20 μg/min or ACR >20 mg/g |
Table 1. Cont.

| First author & year | Ethnicity | Study design | CKD type | Kidney function of case | Definition of case |
|---------------------|-----------|--------------|----------|------------------------|-------------------|
| Losito, 2002 [66]  | Caucasian | CC           | Comb     | ESRD                   | RRT               |
| Yoon, 2002 [67]    | Asian     | CC           | GN       | non-ESRD               | biopsy diagnosed  |
| Fradin, 2002 [68]  | Caucasian | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Drouet, 2002 [69]  | Caucasian | CC           | GN       | non-ESRD               | biopsy diagnosed  |
| Nicrod, 2002 [70]  | Caucasian | CC           | Comb     | non-ESRD               | RRT               |
| Araz, 2001 [71]    | Caucasian | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Azar, 2001 [72]    | Caucasian | CC           | DN       | non-ESRD               | UAE >30 mg/day    |
| Lovati, 2001 [73]  | Caucasian | CC           | Comb     | ESRD                   | RRT               |
| Wang, 2001 [74]    | Caucasian | CS           | Comb     | non-ESRD               | UAE >30 mg/day    |
| Taniwaki, 2001 [75]| Asian     | CC           | DN       | non-ESRD               | proteinuria >500 mg/dL |
| Hadijdi, 2001 [77]| Caucasian | CS           | DN       | non-ESRD               | urinary albumin concentration >20 mg/L |
| Wu, 2000 [78]      | Asian     | CC           | DN       | non-ESRD               | no description    |
| Hsieh, 2000 [79]   | Asian     | CC           | DN       | non-ESRD               | proteinuria >500 mg/dL |
| van Ittersum, 2000 [80]| Caucasian | CS         | DN       | non-ESRD               | UAE >30 mg/day    |
| Tomino, 1999 [19]  | Asian     | CS           | DN       | non-ESRD               | UAE >20 µg/min or ACR >30 mg/g |
| Solini, 1999 [81]  | Caucasian | CS           | DN       | non-ESRD               | Albuminuria       |
| De Cosmo, 1999 [82]| Caucasian | CC           | DN       | non-ESRD               | UAE >30 mg/day    |
| Miura, 1999 [83]   | Asian     | CS           | DN       | non-ESRD               | UAE >10 µg/min    |
| Kuramoto, 1999 [84]| Asian     | CS           | DN       | non-ESRD               | UAE >15 µg/min    |
| Huang, 1998 [85]   | Caucasian | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Walder, 1998 [86]  | Caucasian | CC           | DN       | non-ESRD               | UAE >30 mg/day    |
| Freire, 1998 [87]  | Caucasian | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Grzeszczak, 1998 [88]| Caucasian | CS       | DN       | non-ESRD               | ACR >1.9 mg/mol (men) or >2.8 mg/mol (women) |
| Young, 1998 [89]   | Asian     | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Pirno, 1998 [90]   | Caucasian | CS           | DN       | non-ESRD               | UAE >20 µg/min    |
| Fernández-Llama, 1998 [91]| Caucasian | CS | HN      | non-ESRD               | UAE >20 µg/min    |
| Frost, 1998 [92]   | Caucasian | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Pei, 1997 [93]     | Caucasian | CS           | GN       | non-ESRD               | biopsy diagnosed  |
| Manre, 1997 [94]   | Caucasian | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Barnas, 1997 [95]  | Caucasian | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Ringel, 1997 [96]  | Caucasian | CC           | DN       | non-ESRD               | UAE >30 mg/day    |
| Schmidt, 1997 [97] | Caucasian | CS           | DN       | non-ESRD               | UAE >30 mg/day    |
| Kawada, 1997 [98]  | Asian     | CC           | Comb     | ESRD                   | RRT               |
| Karia, 1997 [99]   | Asian     | CS           | DN       | non-ESRD               | UAE >15 µg/min    |
| Nakajima, 1996 [17]| Asian     | CS           | DN       | non-ESRD               | ACR >30 mg/g      |
| Chowdhury, 1996 [100]| Caucasian | CS     | DN      | non-ESRD               | Albuminuria       |
| McLaughlin, 1996 [101]| Caucasian | CC     | Comb     | non-ESRD               | RRT or doctor diagnosed |
| Oh, 1996 [102]     | Asian     | CS           | DN       | non-ESRD               | UAE >20 µg/min    |
| Schmidt, 1996 [103]| Caucasian | CC           | Comb     | ESRD                   | RRT               |
| Doi, 1996 [104]    | Asian     | CS           | DN       | non-ESRD               | ACR >30 mg/g      |
| Ohno, 1996 [105]   | Asian     | CS           | DN       | non-ESRD               | ACR >10 mg/g      |
| Mizuiri, 1995 [106]| Asian     | CN           | DN       | non-ESRD               | UAE >20 µg/min or RRT |
| Yoriko, 1995 [107] | Asian     | CN           | GN       | non-ESRD               | biopsy diagnosed  |
| Fujisawa, 1995 [108]| Asian     | CS           | DN       | non-ESRD               | Albuminuria or RRT|
| Panagiotopoulo, 1995 [109]| Caucasian | CS | DN      | non-ESRD               | UAE >20 µg/min    |
| Tarnow, 1995 [110] | Caucasian | CC           | DN       | non-ESRD               | UAE >300 mg/day or biopsy diagnosed |
trials and review articles to avoid missing any other relevant studies [10–12,20–22].

All related studies assessing the association between ACE I/D polymorphisms and CKD risk were considered for inclusion. The criteria for inclusion of a study were as follows: (1) cross-sectional surveys or case–control studies; (2) CKD defined according to the criteria for inclusion of a study were as follows: (1) cross-sectional surveys or case–control studies; (2) CKD defined according to the population age >18 years; (3) control group with normal kidney function; (4) study population >18 years; (5) Asian or Caucasian ethnicity of the populations, and (6) articles providing detailed distribution of ACE genotypes. Studies investigating the relationships between genetic polymorphisms and other kidney diseases (lupus nephritis, polycystic kidney disease, endemic nephropathy, or reflux nephropathy) were excluded.

Data Extraction and Quality Assessment

Two reviewers (Chin Lin and Sui-Lung Su) independently extracted the data and assessed risk of bias. We recorded the first author’s name, year of publication, ethnicity of the study population, kidney function of the cases, definition of the case group and its population characteristics (mean age, proportion of male subjects, body mass index, diabetes mellitus prevalence, hypertension prevalence, and ACE I/D genotype distribution). Ethnicity of the study population was categorized by study area. Subjects in the Arabian peninsula were classified as Caucasian because Arabs were the main race, and subjects in other regions of Asia (excluding Russia) were classified as Asian. Diabetes mellitus and hypertension were defined as plasma glucose level of >126 mg/dL and systolic blood pressure of >140 mmHg. If the article did not report the prevalence of diabetes mellitus and hypertension or the definition did not match, we assumed a normal distribution of plasma glucose level and systolic blood pressure for calculation.

Estimating moderate effects is difficult in meta-analysis using case–control studies. Researchers prefer that studies provide stratified data or matching data, but previous studies have seldom reported these. Fortunately, the characteristics of case groups may be used to estimate moderate effects under the following two conditions: (1) outcomes were rare events, (2) the major independent variable and moderators were independent events.

For example, when the major independent variable is exposure, with values “yes” or “no,” and the moderator is gender, with values “male” or “female,” the variables $p_1, p_2, p_3,$ and $p_4$ are the outcome prevalence of women without exposure, men without exposure, women with exposure, and men with exposure. The variable $p_5$ is the proportion of individuals with exposure in the whole population; $p_6$ is the proportion of men in the population without exposure; and $p_7$ is the proportion of men in the population with exposure.

When researchers wish to conduct a case–control study, they must survey the exposure proportion in the case and control groups to estimate the odds ratio (OR). The exposure proportions using a stratified view and ORs are as follows:

**Table 1.** Cont.

| First author & year | Ethnicity | Study design | CKD type | Kidney function of case | Definition of case |
|---------------------|-----------|--------------|----------|-------------------------|-------------------|
| Schmidt, 1995 [111]| Caucasian | CC           | GN       | non-ESRD                | biopsy diagnosed   |
| Yoshida, 1995 [112]| Asian     | CC           | GN       | non-ESRD                | biopsy diagnosed   |
| Dudley, 1995 [113] | Caucasian | CC           | DN       | non-ESRD                | patients with urine in top tertile of the median UAE |
| Harden, 1995 [114] | Caucasian | CC           | GN       | non-ESRD                | biopsy diagnosed   |
| Doria, 1995 [115]  | Caucasian | CC           | DN       | non-ESRD                | UAE >30 μg/min     |
| Marre, 1994 [116]  | Caucasian | CS           | DN       | non-ESRD                | UAE >30 mg/day     |
| Powrie, 1994 [117] | Caucasian | CS           | DN       | non-ESRD                | ACR >3 mg/mmol     |

CC: case control study; CS: cross-sectional survey; DN: diabetic nephropathy; non-DN: non diabetic nephropathy; GN: glomerulonephritis; HN: hypertensive nephropathy; Comb: combined; ESRD: end stage renal disease; non-ESRD: not only ESRD patients; UAE: urinary albumin excretion rate; ACR: Albumin creatinine ratio; eGFR: estimated glomerular filtration rate; CCr: creatinine clearance; RRT: renal replacement therapy; CT: computed tomography; SCR: serum creatinine.

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$$E_1 = \frac{p_3 p_5 (1-p_7)}{p_1 (1-p_3)(1-p_6) + p_3 p_5 (1-p_7)}$$

$$E_2 = \frac{p_4 p_5 p_7}{p_2 (1-p_3)p_6 + p_4 p_5 p_7}$$

$$E_3 = \frac{(1-p_3)p_5 (1-p_7)}{(1-p_1)(1-p_3)(1-p_6) + (1-p_3)p_5 (1-p_7)}$$

$$E_4 = \frac{(1-p_4)p_5 p_7}{(1-p_2)(1-p_3)p_6 + (1-p_4)p_5 p_7}$$

OR in women: $OR_{women} = \frac{E_3 (1-E_1)}{E_1 (1-E_3)}$

OR in men: $OR_{men} = \frac{E_2 (1-E_4)}{E_4 (1-E_2)}$

Crude OR (simple combined):

$$OR_{crude} = \frac{((1-k_1)E_1 + k_1 E_2)((1-k_2)(1-E_3) + k_2(1-E_4))}{((1-k_1)E_3 + k_1 E_4)((1-k_2)(1-E_1) + k_1(1-E_2))}$$

$k_1$ = proportion of males in the case group.

$k_2$ = proportion of males in the control group.

Two factors ($k_1$ and $k_2$) may affect the crude OR. However, when $p_1, p_2, p_3,$ and $p_4$ are very rare and there is no association between the major independent variable and the moderator ($p_6 = p_7$),

$$E_3 = \lim_{p_1 \to 0} \lim_{p_3 \to 0} \frac{(1-p_3)p_5 (1-p_7)}{(1-p_1)(1-p_3)(1-p_6) + (1-p_3)p_5 (1-p_7)} = p_5$$

$$E_4 = \lim_{p_2 \to 0} \lim_{p_4 \to 0} \frac{(1-p_2)p_4 p_7}{(1-p_2)(1-p_3)p_6 + (1-p_4)p_5 p_7} = p_5$$
### Table 2. Quality score and description of studies’ population in included studies.

| First author & year | Quality score | Age (years) | Male (%) | BMI (kg/m²) | DM (%) | HT (%) | Case group | Control group |
|----------------------|---------------|-------------|----------|-------------|--------|--------|------------|---------------|
| Shaikh, 2012 [27]    | 7             | 58          | 54       | 27          | 100    | 86     | 18         | 98            |
| Rahimi, 2012 [28]    | 7             | 56          | 40       | 27          | 100    | 63     | 19         | 66            |
| El-Baz, 2012 [29]    | 6             | 59          | 53       | 39          | 100    | 4      | 39         | 88            |
| Zsom(1), 2011 [30]   | 4             | 64          | 55       | 39          | 100    | 45     | 19         | 40            |
| Zsom(2), 2011 [30]   | 4             | 70          | 61       | 20          | 100    | 60     | 20         | 60            |
| Al-Harbi, 2011 [31]  | 4             | 58          | 48       | 30          | 100    | 86     | 12         | 39            |
| Jung, 2011 [32]      | 7             | 34          | 57       | 61          | 100    | 22     | 14         | 40            |
| Ali, 2011 [33]       | 5             | 55          | 55       | 25          | 16     | 41     | 47         | 125           |
| Huang, 2010 [34]     | 3             | 40          | 50       | 54          | 10     | 10     | 9          | 88            |
| Jayapalan, 2010 [35] | 7             | 60          | 38       | 20          | 100    | 20     | 27         | 45            |
| Mansoor, 2010 [14]   | 6             | 53          | 31       | 27          | 100    | 29     | 27         | 45            |
| Naresh, 2009 [36]    | 5             | 54          | 33       | 29          | 100    | 45     | 11         | 11            |
| Ezzidi, 2009 [37]    | 7             | 60          | 46       | 28          | 100    | 50     | 88         | 260           |
| Nikzamir, 2009 [38]  | 5             | 59          | 56       | 26          | 100    | 54     | 31         | 84            |
| Anbazhagan, 2009 [39]| 7             | 49          | 73       | 20          | 100    | 27     | 33         | 58            |
| Ahluwalia, 2009 [40] | 7             | 58          | 66       | 24          | 100    | 44     | 11         | 74            |
| Palomo-Piñón, 2009 [16]| 7          | 60          | 48       | 27          | 100    | 26     | 87         | 105           |
| Möllsten, 2008 [41]  | 7             | 47          | 49       | 25          | 100    | 52     | 25         | 69            |
| Ergulu, 2008 [42]    | 7             | 58          | 41       | 29          | 100    | 38     | 13         | 17            |
| Afra, 2008 [43]      | 7             | 62          | 43       | 29          | 100    | 68     | 9          | 41            |
| Tripathi, 2008 [44]  | 6             | 36          | 88       | 0           | 100    | 69     | 53         | 72            |
| Movva, 2007 [45]     | 6             | 57          | 70       | 100         | 100    | 47     | 89         | 39            |
| Uddin, 2007 [46]     | 4             | 51          | 54       | 100         | 100    | 78     | 12         | 22            |
| Buraczynska, 2006 [47]| 8             | 51          | 56       | 19          | 100    | 78     | 174        | 228           |
| So, 2006 [48]        | 6             | 100         |          |             |        |        | 407        | 364           |
| Shestakova, 2006 [49] | 6            | 26          | 48       | 23          | 100    | 26     | 15         | 35            |
| Ng, 2006 [50]        | 7             | 61          | 61       | 32          | 100    | 48     | 47         | 148           |
| Prasad, 2006 [51]    | 7             | 57          | 33       | 100         | 100    | 63     | 67         | 74            |
| Degirmenci, 2005 [52] | 4            | 5           | 54       | 100         | 100    | 4      | 25         | 12            |
| van der Sman-de Beer, 2005 [53]| 6  | 59 | 61 | 26 | 17 | 65 | 110 | 227 | 116 | 112 | 235 | 125 |
| Park, 2005 [18]      | 5             | 60          | 58       | 23          | 100    | 83     | 27         | 49            |
| Canani, 2005 [54]    | 6             | 100         |          |             |        |        | 407        | 364           |
| Fabris, 2005 [55]    | 7             | 60          | 78       | 26          | 100    | 100    | 13        | 32            |
| Lau, 2004 [56]       | 5             | 43          | 48       | 53          | 100    | 48     | 17         | 47            |
| Suzuki, 2004 [57]    | 5             | 36          | 56       | 42          | 100    | 56     | 21         | 111           |
| Stratta, 2004 [58]   | 5             | 50          | 67       | 39          | 100    | 50     | 44         | 29            |
| Lochynska, 2003 [59] | 5             | 42          | 74       | 0           | 100    | 100    | 13        | 32            |
| Papp, 2003 [60]      | 4             | 49          | 46       | 65          | 100    | 65     | 11         | 25            |
| Aucella, 2003 [61]   | 5             | 62          | 54       | 16          | 100    | 58     | 57         | 201           |
| Okuno, 2003 [62]     | 7             | 78          | 50       | 20          | 100    | 31     | 1         | 8             |
| Ortiz, 2003 [63]     | 6             | 56          | 59       | 22          | 100    | 100    | 9         | 71            |
| Hadjadj, 2003 [15]   | 9             | 66          | 73       | 29          | 100    | 72     | 552        | 1468          |
| Wang, 2003 [64]      | 5             | 55          | 51       | 23          | 100    | 66     | 106        | 104           |
| Dixit, 2002 [65]     | 7             | 24          | 55       | 0           | 100    | 12     | 26         | 9             |
| Lee(1), 2002 [26]    | 8             | 0           |          |             |        |        | 20         | 45            |
| Lee(2), 2002 [26]    | 8             | 0           |          |             |        |        | 20         | 45            |
| Losito, 2002 [66]    | 6             | 67          | 61       | 25          | 100    | 50     | 27         | 81            |
| Yoon, 2002 [67]      | 5             | 35          | 56       | 0           | 100    | 35     | 44         | 116           |
| First author & year | Quality score | Age (years) | Male (%) | BMI (kg/m²) | DM (%) | HT (%) | Case group | Control group |
|---------------------|---------------|-------------|----------|-------------|--------|--------|------------|---------------|
| Fradin, 2002 [68]  | 7             | 57          | 53       | 32          | 100    | 33     | II         | ID DD         |
| Drouet, 2002 [69]  | 6             | 44          | 77       |             |        |        | II         | ID DD         |
| Nicod, 2002 [70]   | 5             | 54          | 57       | 25          |        |        | II         | ID DD         |
| Araz, 2001 [71]    | 7             | 56          | 41       | 28          | 100    | 63     | II         | ID DD         |
| Azar, 2001 [72]    | 6             | 23          | 46       |             |        |        | II         | ID DD         |
| Lovati, 2001 [73]  | 7             | 54          | 57       | 25          | 12     | 51     | II         | ID DD         |
| Wang, 2001 [74]    | 8             |             |          |             |        |        | II         | ID DD         |
| Taniwaki, 2001 [75]| 7             | 61          | 59       | 23          | 100    | 54     | II         | ID DD         |
| Viswanathan, 2001 [76] | 7         | 57          | 66       | 26          | 100    | 64     | II         | ID DD         |
| Hadjadi, 2001 [77] | 7             | 40          | 59       | 23          | 100    | 53     | II         | ID DD         |
| Wu, 2000 [78]      | 3             | 60          | 55       |             |        |        | II         | ID DD         |
| Hsieh, 2000 [79]   | 5             | 61          | 49       | 23          | 100    | 60     | II         | ID DD         |
| van Ittersum, 2000 [80] | 6           | 55          | 59       |             | 100    | 80     | II         | ID DD         |
| Tomino, 1999 [19]  | 7             | 61          | 63       |             | 100    | 312    | II         | ID DD         |
| Solini, 1999 [81]  | 8             | 60          | 58       | 30          | 100    | 61     | II         | ID DD         |
| De Cosmo, 1999 [82] | 7            | 43          | 61       |             | 100    | 42     | II         | ID DD         |
| Miura, 1999 [83]   | 7             | 36          | 34       |             | 100    | 21     | II         | ID DD         |
| Kuramoto, 1999 [84] | 7             | 58          | 61       | 23          | 100    | 56     | II         | ID DD         |
| Huang, 1998 [85]   | 6             |             |          |             | 100    | 4      | II         | ID DD         |
| Walder, 1998 [86]  | 7             | 42          | 71       |             | 100    | 86     | II         | ID DD         |
| Freire, 1998 [87]  | 6             | 28          | 48       |             | 100    | 17     | II         | ID DD         |
| Grzeszczak, 1998 [88] | 7          | 62          | 29       |             | 100    | 68     | II         | ID DD         |
| Young, 1998 [89]   | 7             | 56          | 34       | 25          | 100    | 73     | II         | ID DD         |
| Penno, 1998 [90]   | 5             |             |          |             | 100    | 15     | II         | ID DD         |
| Fernández-Llama, 1998 [91] | 5       | 0           | 100      | 1           | 6      | 7      | II         | ID DD         |
| Frost, 1998 [92]   | 5             |             |          |             | 100    | 10     | II         | ID DD         |
| Pei, 1997 [93]     | 6             | 49          | 68       |             |        |        | II         | ID DD         |
| Marre, 1997 [94]   | 8             | 43          | 57       | 24          | 100    | 57     | II         | ID DD         |
| Barnas, 1997 [95]  | 6             | 47          | 70       |             | 100    | 48     | II         | ID DD         |
| Ringel, 1997 [96]  | 8             | 51          | 54       | 26          | 100    | 43     | II         | ID DD         |
| Schmidt, 1997 [97] | 7             | 65          | 51       | 29          | 100    | 74     | II         | ID DD         |
| Kawada, 1997 [98]  | 5             | 59          | 62       |             | 100    | 22     | II         | ID DD         |
| Kario, 1997 [99]   | 6             | 72          | 41       | 25          | 0      | 100    | II         | ID DD         |
| Nakajima, 1996 [17] | 6           | 56          | 64       |             | 100    | 37     | II         | ID DD         |
| Chowdhury, 1996 [100] | 6          | 39          | 55       |             | 100    | 97     | II         | ID DD         |
| McLaughlin, 1996 [101] | 4         | 42          | 57       |             | 100    | 22     | II         | ID DD         |
| Oh, 1996 [102]     | 6             | 35          | 42       | 19          | 100    | 62     | II         | ID DD         |
| Schmidt, 1996 [103] | 5            | 55          | 58       |             | 100    | 63     | II         | ID DD         |
| Doi, 1996 [104]    | 7             | 62          | 51       | 22          | 100    | 55     | II         | ID DD         |
| Ohno, 1996 [105]   | 7             | 61          | 53       | 23          | 100    | 56     | II         | ID DD         |
| Mizuiri, 1995 [106] | 6             | 54          |          |             | 100    | 90     | II         | ID DD         |
| Yoroika, 1995 [107] | 5            | 33          | 44       |             | 100    | 90     | II         | ID DD         |
| Fujisawa, 1995 [108] | 4           |             |          |             | 100    | 24     | II         | ID DD         |
| Panagiotopoulos, 1995 [109] | 5       | 62          | 66       |             | 100    | 16     | II         | ID DD         |
| Tarnow, 1995 [110] | 8             | 41          | 61       | 24          | 100    | 68     | II         | ID DD         |
| Schmidt, 1995 [111] | 6            | 45          | 75       |             | 100    | 59     | II         | ID DD         |
| Yoshida, 1995 [112] | 7            | 39          | 64       |             | 100    | 15     | II         | ID DD         |
| Dudley, 1995 [113] | 7             | 53          | 67       | 29          | 100    | 58     | II         | ID DD         |
gender-dependent effects, we investigated the interaction between moderate effects [10–12]. To assess the effect of ethnicity on ethnicity because most previous studies have found significant tested by meta-regression. In multivariable analyses, we adjusted factors: (1) selection of study population, (2) comparability between the case and control groups, and (3) the exposure assessed. Each study received a score between 0 and 9. We investigated the relationship between the quality of studies and the estimation of risk. This report displays results from the allele type model, unless calculate the association between genetic polymorphism and CKD risk for each study by odds ratios (ORs) with 95% confidence intervals (CIs).

**Statistical Analysis**

Variables are presented as means, proportions, or numbers as appropriate. Our meta-analysis examined the association between ACE I/D polymorphisms and CKD risk for each study by odds ratios (ORs) with 95% confidence intervals (CIs).

The $\chi^2$ statistic estimated by the DerSimonian–Laird method was used for the assessment of heterogeneity, and a random-effects model based on the Mantel–Haenszel method was applied. Allele type, genotype, and dominant/recessive models were used to calculate the association between genetic polymorphism and CKD risk. This report displays results from the allele type model, unless estimates using a different model were obviously different. Egger’s regression was used to test symmetry of pooled results. Prespecified subgroup analyses included the causes of CKD.

A moderate effect was defined as ratio between ORs in a stratified analysis. For example, if OR for the association between ACE I/D polymorphisms and CKD risk is 6 in the Asian group and 5 in the Caucasian group, the moderate effect of ethnicity will be $6/5 = 2$. Possible moderators (ethnicity, age, gender, body mass index, diabetes mellitus, and hypertension) and study characteristic (quality score, study design, and kidney functions of cases) were tested by meta-regression. In multivariable analyses, we adjusted ethnicity because most previous studies have found significant moderate effects [10–12]. To assess the effect of ethnicity on gender-dependent effects, we investigated the interaction between gender and ethnicity. The interaction between other moderators and gender were also tested.

This study considered a p-value of <0.05 as significant for all analyses. Statistical analyses were carried out with R, version 2.15.0, using the “metafor” [24] and “meta” [25] packages.

**Results**

**Screening Process**

Our search strategy returned 501 papers (the identification process is shown in Figure 1). We excluded 249 papers after a preliminary search of titles and abstracts. An additional 129 papers were excluded after full-text articles were assessed, leaving 123 articles that matched our criteria. Of these, 15 used duplicate databases, 9 lacked detailed data, and 1 likely reported wrong data. In 98 of the studies finally included [14–19,26–117], 2 (Zsom et al. [30] and Lee et al. [26]) reported results of stratification, but studies by Zsom et al. [30] used a single control group. Accordingly, 99 populations were included in this meta-analysis, and their detailed data are shown in Tables 1 and 2.

**Preliminary Pooled Analyses**

Our meta-analysis showed that a significantly increased CKD risk was associated with the D allele compared with the I allele in each subgroup. Figure 2 shows that D allele carriers had an OR of 1.21 for risk of all-cause CKD compared with I allele carriers, and that these ORs were dissimilar in different ethnicities ($p=0.002$). OR for CKD in Asian individuals carrying the D allele compared with those carrying the I allele was 1.40 (95% CI: 1.23–1.59), and in Caucasian individuals was 1.12 (95% CI: 1.04–1.21). A summary of the other results is shown in Table 3 and are very similar to those in Figure 2. In the allele type, genotype, and dominant/recessive models, individuals carrying the D allele showed higher CKD risk, and ORs were higher in Asians than in Caucasians. The heterogeneities were higher in Asian populations than in Caucasian populations in each subgroup.

**Identifying Moderators of the Association between ACE I/ D Polymorphisms and CKD Risk**

Table 4 shows the assessment results of moderate effect on all-cause CKD using the allele type model. Compared with I allele carriers, D allele carriers had a higher OR for CKD risk in Asians than in Caucasians (OR of moderate effect: 1.24; 95% CI: 1.08–1.42). Hypertension also was a moderator (OR of moderate effect: 1.55; 95% CI: 1.04–2.32) and still had a significant moderate effect after adjusting ethnicity (OR of moderate effect: 1.57; 95% CI: 1.07–2.31). No additional moderators were significant after adjustment for ethnicity and hypertension (data not shown). In

| First author & year | Quality score | Age (years) | Male (%) | BMI (kg/m²) | DM (%) | HT (%) | Case group | Control group |
|---------------------|--------------|-------------|----------|-------------|--------|--------|-------------|---------------|
| Harden, 1995 [114]  | 5            | 35          |          |             |        |        | II 19      | ID 41         |
| Donre, 1994 [115]   | 5            | 29          |          |             |        |        | DD 10      | II 35         |
| Marre, 1994 [116]   | 6            | 39          | 60       | 23          | 100    |        | DD 24      | II 35         |
| Powrie, 1994 [117]  | 6            | 35          | 50       | 20          | 100    |        | DD 24      | II 37         |

Quality score: result of quality assessed in each study (detailed data were shown in supplementary file); Age: mean age; Male: probability of male; BMI: mean body mass index; DM: prevalence of diabetes mellitus; HT: prevalence of hypertension; II: number of II genotype carries; ID: number of ID genotype carries; DD: number of DD genotype carries.

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$$OR_{crude} = \frac{((1-k_1)E_1+k_1E_2)(1-p_s)}{p_s((1-k_1)(1-E_1)+k_1(1-E_2))}$$

If moderate effects are present ($OR_{women} \neq OR_{men}$), the proportion of males in the case group ($k_1$) is the only factor that can affect the crude OR. In addition, the relationship between $k_1$ and log of odds ratio approximate the first order polynomial when above assumption were proper. We may accordingly use the characteristics of the case group to estimate the moderate effects in this study under the above assumptions.

Risk of bias was assessed by the following procedures suggested by the Newcastle–Ottawa Quality Assessment Scale [23] (shown in Table S3). This tool assesses studies with a focus on the following factors: (1) selection of study population, (2) comparability between the case and control groups, and (3) the exposure assessed. Each study received a score between 0 and 9. We investigated the relationship between the quality of studies and the estimation of risk.
In subgroup analyses of diabetic nephropathy, study design (OR for moderate effect: 1.21; 95% CI: 1.02–1.42) and body mass index (OR of moderate effect: 0.84; 95% CI: 0.70–1.00) had significant moderate effects on ACE I/D polymorphisms and diabetic nephropathy. After adjustment for ethnicity, the moderate effects of study design (OR of moderate effect: 1.19; 95% CI: 1.01–1.41) was still significant but that of body mass index (OR for moderate effect: 0.91; 95% CI: 0.73–1.13) was not (data not shown). The results of the nondiabetic nephropathy subgroup were similar to those for all-cause CKD, with ethnicity (OR of moderate effect: 1.69; 95% CI: 1.07–2.68) and hypertension (OR of moderate effect: 2.42; 95% CI: 1.19–4.93) the only two significant moderators in multivariable analyses (data not shown).

Estimated Gender-dependent Effects

Table 5 shows the interaction of ethnicity and gender. We found no significant interactions between the other variables and gender. Coefficients of interaction were significant for hypertension (p before adjustment for hypertension = 0.015; p after adjustment for hypertension = 0.003). No other moderators were significant when added to the final model. A proportion of 32.8% of heterogeneity (crude $\tau^2 = 0.100$; after adjustment, $\tau^2 = 0.068$) was caused by different ethnicity, gender probability, and prevalence of hypertension in the study population, and p of Egger’s regression test was not significant (p = 0.217). Figure 3 shows OR of ACE I/D polymorphisms and CKD risk in different combination of ethnicity, gender, and hypertension status based on Model 2 in Table 5. A gender-dependent effect analysis showed the strongest association between the ACE I/D polymorphisms and CKD risk in Asian males with hypertension (OR: 3.75; 95% CI: 1.84–7.65) or without (OR: 2.42; 95% CI: 1.19–4.93). Interaction of ethnicity and gender was borderline significant (p = 0.056) in the diabetic nephropathy subgroup, but was significant (p = 0.030) in the nondiabetic nephropathy subgroup. Although the result of symmetry assessment was significant in nondiabetic nephropathy subgroup (p of Egger’s regression test = 0.032), it was noteworthy that 78.3% of heterogeneity (crude $\tau^2=0.166$; after adjustment, $\tau^2=0.036$) were caused by ethnicity, gender, and hypertension.

The symmetry of final models was shown in Figure 4. Funnel plots presented the association between residual and standard error based on results of Table 5, and each point represents a study. Egger’s regression test indicated no evidence of publication bias among studies included into the final model this meta-analysis and diabetic nephropathy subgroup. The model in nondiabetic nephropathy subgroup was asymmetric, and it might be due to the study reported by Jung et al. [32]. We did sensitivity analyses leaving the article out (data not shown). The result of symmetry assessment was not significant (p of Egger’s regression test = 0.245), and the coefficients in this model were still significant (p of interaction effect of ethnicity and gender = 0.002; p of moderate effect of hypertension <0.001). In addition, the $\tau^2$ was 0 in this sensitivity model.
Discussion

This study showed that CKD risk was higher in D allele carriers than in I allele carriers, and there was no strong evidence that analyses using different model assumptions might produce dissimilar results. Heterogeneity was higher in the Asian population than in the Caucasian population. Interaction between ACE I/D polymorphisms and hypertension exerted an additive effect on CKD risk. A gender-dependent effect of ACE I/D polymorphisms on CKD risk was clearly apparent in Asians but not in Caucasians.

The DD genotype showed higher gene expression and serum ACE levels than the ID genotype, followed by the II genotype [9,118]. High blood ACE levels may increase blood angiotensin II levels [8], and individuals with higher angiotensin II levels may have a higher CKD risk [119,120]. Previous studies showed that the association between ACE I/D polymorphisms and CKD risk might not be dominant or recessive [8,9,118]. Previous meta-analysis studies showed the supported results, they reported that DD genotype had higher risk of CKD than ID genotype, followed by the II genotype. We also observed the apparent linear association between numbers of D allele and odds ratios compared

Table 3. Odds ratio of ACE I/D and all-cause CKD, diabetic nephropathy, non-diabetic nephropathy using assumption of allele type, genotype, dominant and recessive model.

| Model          | Ethnicity | All-cause CKD | Diabetic nephropathy | Non-diabetic nephropathy |
|----------------|-----------|---------------|----------------------|-------------------------|
|                |           | n  | OR   | 95% CI | $\chi^2$ | n  | OR   | 95% CI | $\chi^2$ | n  | OR   | 95% CI | $\chi^2$ |
| Allele type (D vs. I) | All studies | 99  | 1.21 (1.13, 1.29) | 0.076 | 65  | 1.23 (1.14, 1.33) | 0.063 | 22  | 1.29 (1.06, 1.56) | 0.166 |
|                | Asian     | 38  | 1.40 (1.23, 1.59) | 0.118 | 24  | 1.36 (1.18, 1.56) | 0.070 | 10  | 1.59 (1.17, 2.17) | 0.212 |
|                | Caucasian | 61  | 1.12 (1.04, 1.21) | 0.053 | 41  | 1.17 (1.06, 1.29) | 0.064 | 12  | 1.08 (0.91, 1.29) | 0.054 |
| Genotype-1 (DD vs. II) | All studies | 99  | 1.44 (1.26, 1.64) | 0.277 | 65  | 1.48 (1.26, 1.74) | 0.249 | 22  | 1.67 (1.16, 2.41) | 0.556 |
|                | Asian     | 38  | 1.87 (1.46, 2.38) | 0.377 | 24  | 1.66 (1.27, 2.18) | 0.230 | 10  | 2.77 (1.62, 4.75) | 0.567 |
|                | Caucasian | 61  | 1.25 (1.07, 1.46) | 0.224 | 41  | 1.39 (1.14, 1.71) | 0.275 | 12  | 1.11 (0.77, 1.60) | 0.211 |
| Genotype-2 (ID vs. II) | All studies | 99  | 1.20 (1.10, 1.32) | 0.098 | 65  | 1.26 (1.13, 1.40) | 0.082 | 22  | 1.17 (0.92, 1.49) | 0.206 |
|                | Asian     | 38  | 1.34 (1.14, 1.57) | 0.152 | 24  | 1.31 (1.09, 1.57) | 0.088 | 10  | 1.43 (0.99, 2.05) | 0.259 |
|                | Caucasian | 61  | 1.13 (1.02, 1.25) | 0.062 | 41  | 1.23 (1.07, 1.42) | 0.084 | 12  | 0.91 (0.74, 1.13) | 0.570 |
| Dominant (DD+ID vs. II) | All studies | 99  | 1.28 (1.16, 1.41) | 0.132 | 65  | 1.33 (1.19, 1.50) | 0.110 | 22  | 1.30 (1.00, 1.69) | 0.271 |
|                | Asian     | 38  | 1.48 (1.25, 1.74) | 0.180 | 24  | 1.42 (1.19, 1.70) | 0.095 | 10  | 1.66 (1.12, 2.45) | 0.317 |
|                | Caucasian | 61  | 1.17 (1.05, 1.31) | 0.100 | 41  | 1.28 (1.10, 1.49) | 0.130 | 12  | 1.01 (0.80, 1.27) | 0.031 |
| Recessive (DD vs. ID+II) | All studies | 99  | 1.27 (1.15, 1.39) | 0.090 | 65  | 1.26 (1.13, 1.42) | 0.112 | 22  | 1.53 (1.18, 1.99) | 0.262 |
|                | Asian     | 38  | 1.56 (1.28, 1.90) | 0.227 | 24  | 1.42 (1.12, 1.79) | 0.169 | 10  | 2.22 (1.42, 3.48) | 0.369 |
|                | Caucasian | 61  | 1.16 (1.04, 1.28) | 0.090 | 41  | 1.21 (1.06, 1.37) | 0.097 | 12  | 1.20 (0.92, 1.57) | 0.118 |

Table 4. Moderator effects of allele type model (D vs. I) on all-cause CKD.

| Moderator | Unadjusted | Adjusted |
|-----------|------------|----------|
|           | n  | OR   | 95% CI |           | n  | OR   | 95% CI |
| Ethnicity (Caucasian is ref.) | 99  | 1.24* | (1.08, 1.42) |           |     |       |        |
| Study design (CS is ref.) | 99  | 1.05  | (0.92, 1.20) | 1.03  | (0.90, 1.18) |
| Quality score (per 1 score) | 99  | 0.98  | (0.93, 1.04) | 0.99  | (0.94, 1.05) |
| Kidney function of case (non-ESRD is ref.) | 99  | 1.03  | (0.87, 1.23) | 0.97  | (0.81, 1.16) |
| Age (per 10 years) | 88  | 1.02  | (0.95, 1.09) | 1.01  | (0.95, 1.08) |
| Male (per 100%) | 84  | 1.48  | (0.72, 3.01) | 1.63  | (0.81, 3.28) |
| BMI (per 5 kg/m²) | 45  | 0.86  | (0.73, 1.03) | 0.95  | (0.78, 1.16) |
| DM (per 100%) | 81  | 0.96  | (0.78, 1.18) | 0.99  | (0.81, 1.22) |
| Hypertension (per 100%) | 68  | 1.55* | (1.04, 2.32) | 1.57* | (1.07, 2.31) |

Depend variable: log odds ratio of ACE I/D and all-cause CKD using allele type model.
n: number of studies; OR: odds ratio for moderate effect; 95% CI: 95% confidence interval.
CS: cross-sectional study; non-ESRD: not only ESRD patients; Age: mean age; Male: probability of male; BMI: mean body mass index; DM: prevalence of diabetes mellitus; Hypertension: prevalence of hypertension.
* p < 0.05.
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the II genotype in genotype analyses [10–12,20–22]. The assumption of the allele type model in this association might be more reasonable, and it may thus be true that individuals carrying the D allele have a higher CKD risk.

Hypertension in some patients is due to a dysfunction of RAS such as abnormal secretion of renin, causing increased blood angiotensin I levels [121]. D allele carriers had higher ACE levels than I allele carriers [118], leading to more efficient conversion of angiotensin I to angiotensin II, resulting in CKD [119,120]. The mechanism may be an additive effect of hypertension and the D allele. An additive effect was significant in the nondiabetic group but not in the diabetic nephropathy subgroups. The blood levels of advanced glycation end products (AGE) diabetic patients may be high, possibly causing blood pressure increases [122].

**Table 5.** Three way interaction of Asian, male and ACE D allele on all-cause CKD, diabetic nephropathy and non-diabetic nephropathy.

|                      | All-cause CKD | Diabetic nephropathy | Non-diabetic nephropathy |
|----------------------|---------------|-----------------------|--------------------------|
|                      | Model 1       | Model 2               |                          |
| Intercept            | 0.297         | 0.275                 | 0.115                    | 0.291 | 0.369 | -0.213 | 0.746 |
| Race (Caucasian is ref.) | -0.697 | 0.391                 | -0.853*                  | 0.402 | 0.569 | -1.080 | 0.816 |
| Male (per 100%)      | -0.312        | 0.476                 | -0.470                   | 0.501 | 0.691 | -0.349 | 1.050 |
| Race × Male          | 1.662*        | 0.686                 | 2.094*                   | 0.715 | 1.082 | 2.666* | 1.231 |
| Hypertension (per 100%) | 0.437*       | 0.192                 | 0.229                    | 0.294 | 0.857* | 0.245  |
| t²                   | 0.075         | 0.068                 | 0.081                    | 0.036* |
| Egger’s test         | p = 0.097     | p = 0.217             | p = 0.385                | p = 0.032 |

Dependent variable: log odds ratio of ACE I/D and CKD using allele type model.

β: coefficients in meta-regression; se: standard error of β.

Model 1: Hypertension was not included in independent variables.

Model 2: Hypertension was included in independent variables.

Egger’s test: p-value of Egger’s regression test.

*: p < 0.05.

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Accordingly, we hypothesize that the probability of hypertension because of a dysfunction of RAS was higher in the nondiabetic nephropathy subgroup than in the diabetic nephropathy subgroup. Thus, the interaction between ACE I/D polymorphisms and hypertension was significant only in the nondiabetic nephropathy subgroup. This hypothesis may require further studies for confirmation.

We found a significant gender-dependent effect of ACE I/D polymorphisms on CKD risk in Asians. In previous studies in Asians, the ORs of the additive effect on the DD genotype of males were 2.94 and 1.41 in Japanese [17] and Koreans [18], respectively. Another study in Japan also reported a positive additive effect of the DD genotype of males [19]. Studies of Caucasians reported contrary results, with an interaction OR of 0.42 in Pakistan [14]. Another two studies in France [15] and Mexico [16] also showed an additive effect between the DD genotype and female gender but not male gender. Although the interaction tests in these studies were not significant, we could observe dissimilar gender-dependent effect in different ethnicity. Previous studies have also reported a different gender-dependent effect.

Figure 4. Funnel plot of three way interaction model in each subgroup. The model in nondiabetic nephropathy subgroup was asymmetric. The triangle in that plot was study reported by Jung et al. [32], and the p value of the student residual was less 0.05. After excluding this study, the p value of Egger’s regression test was not significant (p = 0.245) and the moderate effect of interaction and hypertension were more significantly (p of interaction: 0.0304→0.0023; p of hypertension: 0.0005→<0.0001).

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The effect of ACE I/D polymorphisms on blood ACE levels in Asians and Caucasians. In a study conducted in China [13], differences in blood ACE levels between DD genotype and other genotypes among men were significantly greater than those in women. On the other hand, a study conducted in Germany [123] reported the opposite result. Androgens may play a key role in this additive effect. A study has shown that in intact male rats and ovariectomized female rats that received testosterone for 5 weeks, the androgen may have contributed to the decrease in pressure natriuresis [124]. In an animal study, ACE activity was higher in male mice than in female mice, and this gender difference disappeared after gonadectomy [125]. In previous reports, sensitivity to androgens was stated to be higher in Caucasians than in Asians [126]. Blood androgen levels in Caucasians and Asians showed no significant differences [127,128]. On the basis of previous studies, we hypothesized that the dissimilar gender-dependent effect of ACE I/D polymorphisms on CKD risk in Caucasians and Asians might be accounted for by dissimilar sensitivity to androgens. The gender difference of male sex hormone utilization was higher in Asians than in Caucasians. Therefore, the additive effect of the D allele and male gender was also higher in Asians than in Caucasians.

In subgroup analyses, the above additive effect was borderline significant in the diabetic nephropathy subgroup, but there was no evidence that diabetic mellitus might contribute to this additive effect. Although the additive effect also could explain why two populations with different ethnicities had different heterogeneity before adjustment for any moderators, the calculated risk ratio of ACE I/D polymorphisms on CKD risk may have been affected by the gender-dependent effect in Asians.

Our study had three limitations. First, we relied on tabular data rather than on individual patient data, possibly leading to an inflated standard error in pooled analyses. However, we still observed a significant gender-dependent effect difference in different ethnicities. Second, estimates of diabetes mellitus and hypertension prevalence did not factor in the effects of therapy for them. Some subjects having higher blood glucose and blood pressure may have taken drugs, leading to normal biochemical values in reports. Third, we may have missed unpublished data for the non-diabetic nephropathy subgroup. But the results of this subgroup were similar to the results of previous studies and we still observed a significant result excluding the greatest impact of symmetry study; therefore, there is no evidence to question their reliability.

In conclusion, CKD risk was higher with the D allele than with the I allele. Asian ethnicity and hypertension had positive moderate effects, and their effects were more likely to be higher in patients with non-diabetic nephropathy. A gender-dependent effect of ACE I/D polymorphisms on CKD risk was confirmed in Asians; the D allele showed 3.75-fold greater risk for CKD than the I allele in hypertensive Asian males. These results suggest that Asian males should be offered testing for defects in ACE I/D polymorphisms, especially if they are hypertensive. We suggest that physicians should provide specific protection to D-allele carriers, for example by administering ACE inhibitors to hypertensive patients.

**Supporting Information**

Table S1 PRISMA 2009 Checklist. (DOC)

Table S2 Search strategies. Web sites and uniform resource locator: MEDLINE: http://www.ncbi.nlm.nih.gov/pubmed Cochrane Library: http://www.thecochranelibrary.com Embase: https://www.embase.com (DOC)

Table S3 Quality assessment tool in this meta-analysis based on Wells et al. [23]. (DOC)

**Author Contributions**

Conceived and designed the experiments: CL HYY SLS. Performed the experiments: CL HYY SLS. Analyzed the data: CL Contributed reagents/materials/analysis tools: CL CMC. Wrote the paper: CL HYY SLS. Critical review and comments: CCW HSL YFL KCL FHL SYK. Modify manuscript: CL HYY CGW HSL KCL SLS.

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