European Review for Medical and Pharmacological Sciences 2019; 23: 1652-1660

I/D polymorphism of ACE and risk of diabetes-related end-stage renal disease: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: We conducted a meta-analysis on exploring the correlation between I/D polymorphism of ACE and risk of diabetes mellitus-related end-stage renal disease.

MATERIALS AND METHODS: Researches on the correlation between I/D polymorphism of ACE and the risk of diabetes-related end-stage renal disease were searched in the three online databases (PubMed, Embase, and Cochrane Library). Citations of related researches were manually examined and enrolled. This study systematically searched relative literature for cohort studies or case-control studies published in the English language until December 1, 2018. Researches containing odds ratio (OR) and 95% confidence interval (CI) calculated based on the correlation between I/D polymorphism of ACE and the risk of diabetes-related end-stage renal disease were enrolled. The included data were weighted by an inverse variance and then analyzed by a fixed or random effects model. Researches met the inclusion criteria were extracted for relevant data and subjected to a heterogeneity test. The effect size was calculated by STATA 12.0 software for meta-analysis.

RESULTS: A total of 15 articles including 1199 cases of diabetes-related end-stage renal disease and 2939 cases of controls were enrolled. I/D polymorphism of ACE remarkably increased the risk of diabetes-related end-stage renal disease. In the subgroup analysis by ethnicity, a significant difference in risk of diabetes-related ESRD was only detected in the Asian population with I/D polymorphism of ACE. However, no significant difference in disease risk was found in the Caucasian population.

CONCLUSIONS: This meta-analysis suggested that I/D polymorphism of ACE can markedly increase the incidence of diabetes-related end-stage renal disease, especially in Asian populations.

Key Words:
I/D polymorphism of ACE, Risk, Diabetes-related end-stage renal disease, Meta-analysis.

Introduction

Diabetes mellitus and chronic kidney disease are prominent global health problems. Diabetes is the leading cause of chronic kidney disease[1,2]. Lifestyle changes, aging, and prevalence of consumptive diseases all lead to the increased incidence of diabetes. Moreover, the prevalence of chronic kidney disease continues to worsen in recent years[3,4]. Diabetic kidney disease (DKD) is a long-term, highly prevalent microvascular complication caused by diabetes, which is manifested as abnormalities in renal structure and function[5-7]. It is reported that DKD is the leading cause of end-stage renal disease (ESRD), and is closely related to cardiovascular diseases[7,8]. However, the pathogenesis of diabetes-related ESRD remains unclear. Currently, it is believed that interactions of genetic factors and high-glucose stimulation trigger a series of pathological cascades, ultimately impairing kidneys and other important organs[8,9]. Although great advances have been made in exploring the pathological mechanism of ESRD, effective drugs are still lacked for alleviating or curing diabetes-related ESRD[10,11]. Hence, early diagnosis, intervention, and treatment of diabetes-related ESRD are of great significance[11].

ACE (angiotensin converting enzyme) is located on 17q23 containing 26 exons and 25 introns, with the gene spans of 21 kb[12,13]. Currently, 6 polymorphism markers of ACE have been identified. Among them, Alu insertion (I) and/or deletion (D) fragment with 287 bp in the 16th intron are the most explored. Based on this polymorphic marker locus, ACE polymorphism could be divided into DD homozygote, ID heterozygote, and II homozygote[13,14]. DNA polymorphism is the difference in nucleotide arrangement among

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chromosome alleles. There are two or more forms of alleles or fragments in the DNA region, which can be divided into sequence polymorphism and sequence length polymorphism[14]. Sequence length polymorphisms occur in tandem or scattered on chromosomes by repetitive sequences with their respective core sequences, which are formed by insertion/deletion (e.g., Alu repetitive sequences)[15]. This polymorphism is currently the most valuable genetic marker, and as long as there is an allele in a population, there will be two or more genotypes and corresponding phenotypes1[5,16]. The identification of ACE gene polymorphism broadens genetic researches on cardiovascular diseases. A large number of studies supported the conclusion that ACE level and I/D polymorphism of ACE are closely related to diabetes-related ESRD[16]. D allele and DD genotype in I/D polymorphism of ACE s are considered as independent risk factors for coronary heart disease[17,18].

Previous researches have pointed out that I/D polymorphism of ACE increases the risk of diabetes-related ESRD. In this study, we collected literature on the risk of I/D polymorphism of ACE in the diagnosis of diabetes-related ESRD. We further evaluated the potential influence of I/D polymorphism of ACE on diabetes-related ESRD.

Materials and Methods

Literature Search

This study systematically searched articles on the correlation between I/D polymorphism of ACE and the risk of diabetes-related ESRD from Embase, PubMed, and Cochrane Library published until December 2018. Case-control studies and cohort studies were enrolled. "Diabetes mellitus", "diabetes", "chronic renal disease", "chronic renal failure", "chronic kidney failure", "end-stage renal disease" and "risk", "susceptibility" and "ACE I/D gene polymorphism" were used as key words. Citations of enrolled literature were manually examined. There were no limitations on the year and region of publication. Two researchers independently screened the literature through the retrieved literature titles and abstracts, and further determined the inclusion. To avoid under-enumeration, online search and manual search were combined to double-check all enrolled literature. Any disagreements were solved by consensus. Repeated data or overlapped data were solved by including literature with larger sample size or latest published.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Cohort study or case-control study; (2) Studies on the correlation between diabetes-related ESRD and I/D polymorphism of ACE; (3) OR and 95%CI of diabetes-related ESRD, or relative data that could be used to calculate OR and 95%CI were provided in the literature.

Exclusion criteria: (1) Cross-sectional study, case report study, review or abstract; (2) Studies on diabetes-related ESRD alone; (3) OR and 95%CI of diabetes-related ESRD, or relative data that could be used to calculate OR and 95%CI were unavailable; (4) Repeated reporting, poor-quality documents.

Data Extraction

Baseline data extraction included: first author, study type (cohort study or case-control study, prospective or retrospective study), sample size, study region, study period, confounding factors, OR and 95%CI of I/D polymorphism of ACE. Data acquisition was independently carried out by two reviewers using an accurate data acquisition table. Disagreements from the two reviewers were re-evaluated by a third reviewer. Study with a rigorous design and detailed report was selected if the same or repeated samples were in multiple articles.

Statistical Analysis

Statistical heterogeneity was firstly evaluated, followed by pooled analysis. Stata software (version 12.0, Stata Corporation, College Station, TX, USA) was used for statistical analysis. $p<0.05$ was considered to be statistically significant.

Heterogeneity Analysis

Heterogeneity analysis was performed using the chi-square test. The I2-test was conducted for analyzing statistical heterogeneity in enrolled studies. $\alpha = 0.10$. A random-effects model was used for meta-analysis with $I2>50\%$ or $p<0.10$. Otherwise, a fixed effect model was used. The sources of heterogeneity were explored by subgroup stratification and meta-regression analysis.

Meta-Analysis

Test level of the meta-analysis was set to $\alpha=0.05$. Hardy Weinberg genetic balance test was performed on the genotypes of the included studies. Meta-analysis was performed using STATA 12.0 software to calculate OR and 95% CI. Categorical data were expressed as composition ratio

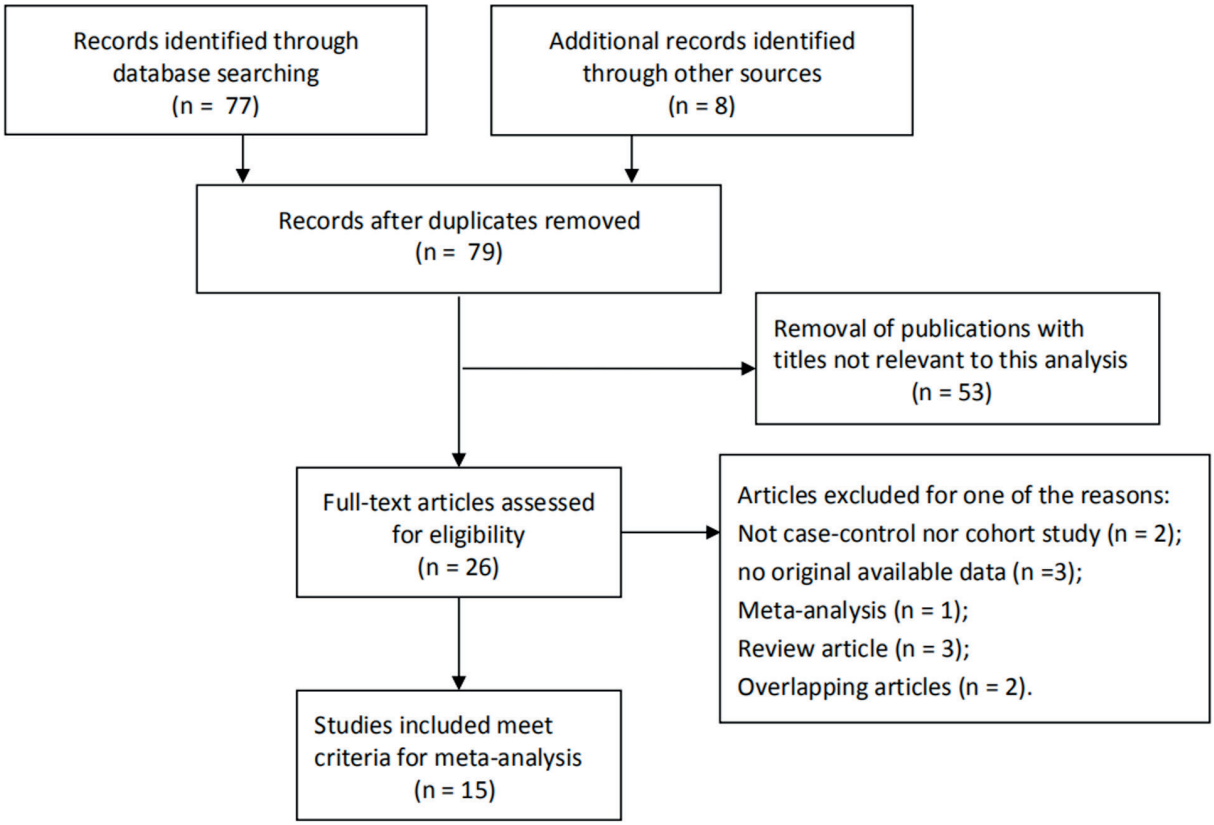

Figure 1. Flow diagram of literature search and selection process.

and measurement data were expressed as $\bar{x}\pm s$. Measurement data of skewed distribution were expressed in M (Q1, Q3).

Sensitivity and Publication Bias Analysis

Publication bias was evaluated by Begg's funnel plot. Sensitivity analysis was conducted to examine the result's stability. Test level was set to $\alpha = 0.10$.

Results

Characteristics of the Studies

In this meta-analysis, 15 independent randomized case-control studies were enrolled, including 1199 patients with diabetes-related ESRD and 2939 cases in control group17-31. Table I depicted study characteristics of I/D polymorphism of ACE and diabetes-related ESRD. Flow diagram of literature search and selection process was detailed in Figure 1. Genotype distribution of HWE (Hardy Weinberg equilibrium) in the control group was consistent.

Quantitative Synthesis Results

Generally speaking, this paper suggested that I/D polymorphism of ACE increased the risk of diabetes-related ESRD (dominant model: OR=1.28, 95% CI: 1.09-1.51; recessive model: OR=1.14, 95% CI: 0.96-1.35; homozygote model: OR=1.73, 95% CI: 1.23-2.43; heterozygote model: OR=1.13, 95% CI: 0.95-1.35; allele model: OR=1.34, 95% CI: 1.15-1.58) (Figure 2).

In the subgroup analysis by ethnicity, significant difference in the risk of diabetes-related ESRD was only observed in Asian populations (dominant model: OR=1.32, 95% CI: 1.07-1.62; recessive model: OR=1.63, 95% CI: 1.25- 2.13; homozygote model: OR=1.89, 95% CI: 1.18-3.03; heterozygote model: OR=1.18, 95% CI: 0.94-1.47; allele model: OR=1.36, 95% CI: 1.12-1.65). We did not observe such difference in the Caucasian population (dominant model: OR=1.23, 95% CI: 0.94-1.60; recessive model: OR=0.90, 95% CI: 0.72-1.12; homozygote model: OR=1.58, 95% CI: 0.95-2.64; heterozygote model: OR=1.19, 95% CI: 0.79-1.40; allele model: OR=1.34, 95% CI: 1.02-1.77) (Table II, Figure 2).

Table I. Characteristics of studies on correlation between ACE I/D polymorphisms and risk of diabetes-related end-stage renal disease.

Author	Year	Country	Ethnicity	No. of case	No. of control	Case (No.)			Control (No.)			HWE
						DD	ID	II	DD	ID	II	
Fawwaz	2017	Lebanon	Caucasian	33	64	20	10	3	21	29	14	Y
Mansouri	2017	Morocco	Caucasian	130	85	76	42	12	47	32	6	Y
Wang	2016	China	Asian	54	74	20	26	8	15	33	26	Y
Shaikh	2014	Pakistan	Caucasian	110	115	38	45	27	41	41	33	N
Zsom	2011	Hungary	Caucasian	66	200	23	33	10	46	110	44	Y
Jayapalan	2010	Malaysia	Asian	60	137	8	25	27	20	56	61	Y
Buraczynska	2006	Poland	Caucasian	141	520	48	61	32	140	268	112	Y
Park	2005	Korea	Asian	103	88	27	49	27	7	51	30	N
Chang	2003	China	Asian	129	116	13	60	56	14	42	60	Y
Ha	2003	Korea	Asian	39	200	14	14	11	38	105	57	Y
Gohda	2001	Japan	Asian	127	621	25	55	47	91	259	271	N
Wong	1999	China	Asian	41	108	4	17	20	13	46	49	Y
Ringel	1997	Germany	Caucasian	42	259	11	19	12	68	134	57	Y
Schmidt	1997	Germany	Caucasian	61	256	35	23	3	83	119	54	Y
Yoshida	1996	Japan	Asian	63	96	17	24	22	7	46	43	Y

HWE: Hardy-Weinberg equilibrium.

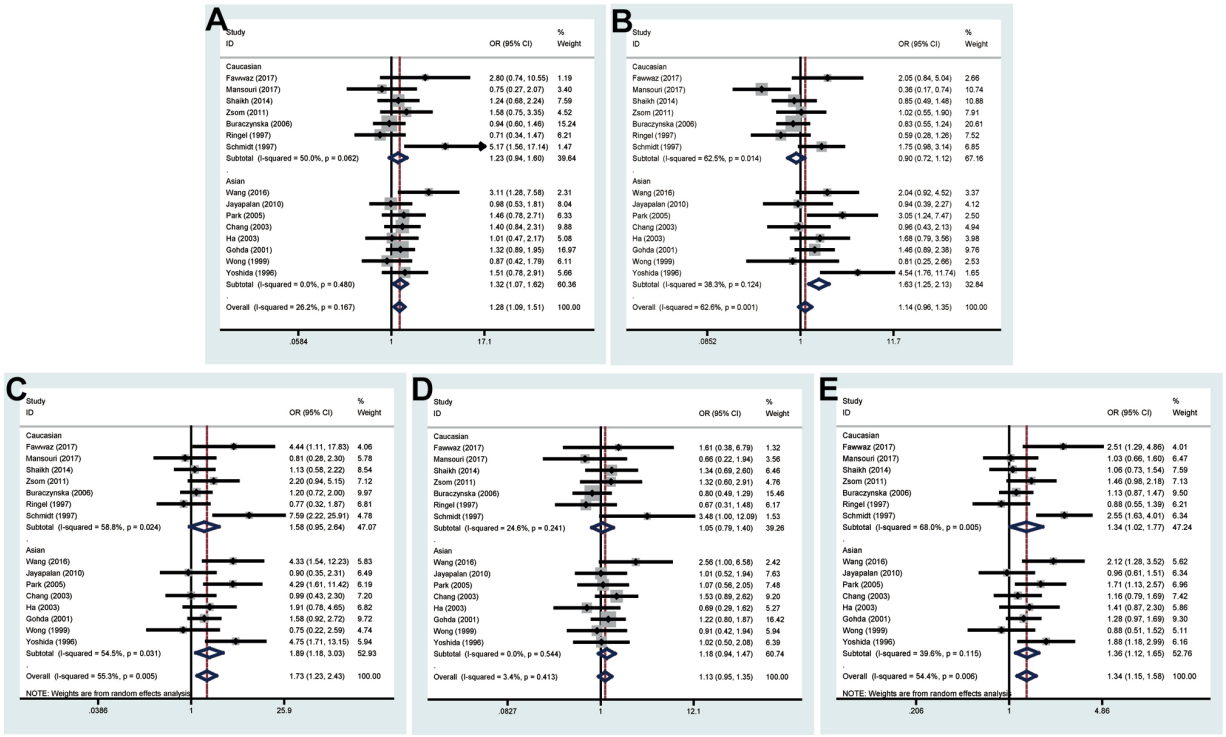

Figure 2. Forest plots of the association between ACE I/D polymorphism and susceptibility of diabetes-related end-stage renal disease. ***A,*** Dominant model; ***B,*** Recessive model; ***C,*** Homozygote model; ***D,*** Heterozygote model; ***E,*** Allele model.

Test of Heterogeneity

Heterogeneity was observed in the five models. Interestingly, subgroup analysis can reduce heterogeneity. Galbraith plot of the association between I/D polymorphism of ACE and diabetes-related ESRD susceptibility was depicted in Figure 3, showing no significant heterogeneity in the studies.

Sensitivity Analysis

Sensitivity analysis was performed by reviewing each study. OR was re-calculated throu-

Table II. Meta-analysis results of association between ACE I/D polymorphism and the risk of diabetes related end-stage renal disease.

			Dominant model		Recessive model		Homozygote model		Heterozygote model		Allele model	
	N[a]	Sample Size	OR (95%CI)	p^b	OR (95%CI)*	p^b	OR (95%CI)	p^b	OR (95%CI)	p^b	OR (95%CI)	p^b
Total	15	4138	1.28 (1.09-1.51)	0.167	1.14 (0.96-1.35)	0.031	1.73 (1.23-2.43)	0.005	1.13 (0.95-1.35)	0.413	1.34 (1.15-1.58)	0.006
Ethnicity												
Caucasian	7	2082	1.23 (0.94-1.60)	0.062	0.90 (0.72-1.12)	0.014	1.58 (0.95-2.64)	0.024	1.19 (0.79-1.40)	0.241	1.34 (1.02-1.77)	0.005
Asian	8	2056	1.32 (1.07-1.62)	0.480	1.63 (1.25-2.13)	0.124	1.89 (1.18-3.03)	0.031	1.18 (0.94-1.47)	0.544	1.36 (1.12-1.65)	0.115

[a] umber of studies; [b]*p*-value of Q test for heterogeneity; *Random-effects model was used when *p*-value for heterogeneity test <0.05; otherwise, fixed-effects model was used.

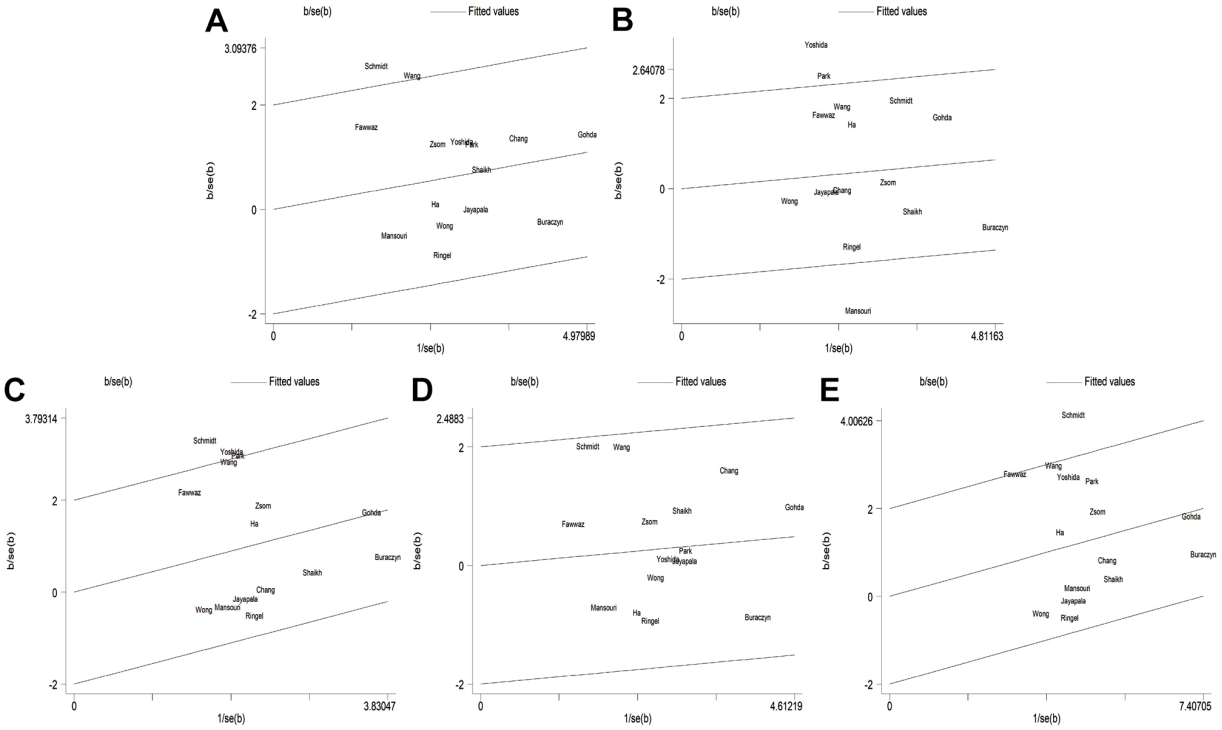

Figure 3. Galbraith plot of the association between ACE I/D polymorphism and diabetes-related end-stage renal disease susceptibility. ***A,*** Dominant model; ***B,*** Recessive model; ***C,*** Homozygote model; ***D,*** Heterozygote model; ***E,*** Allele model.

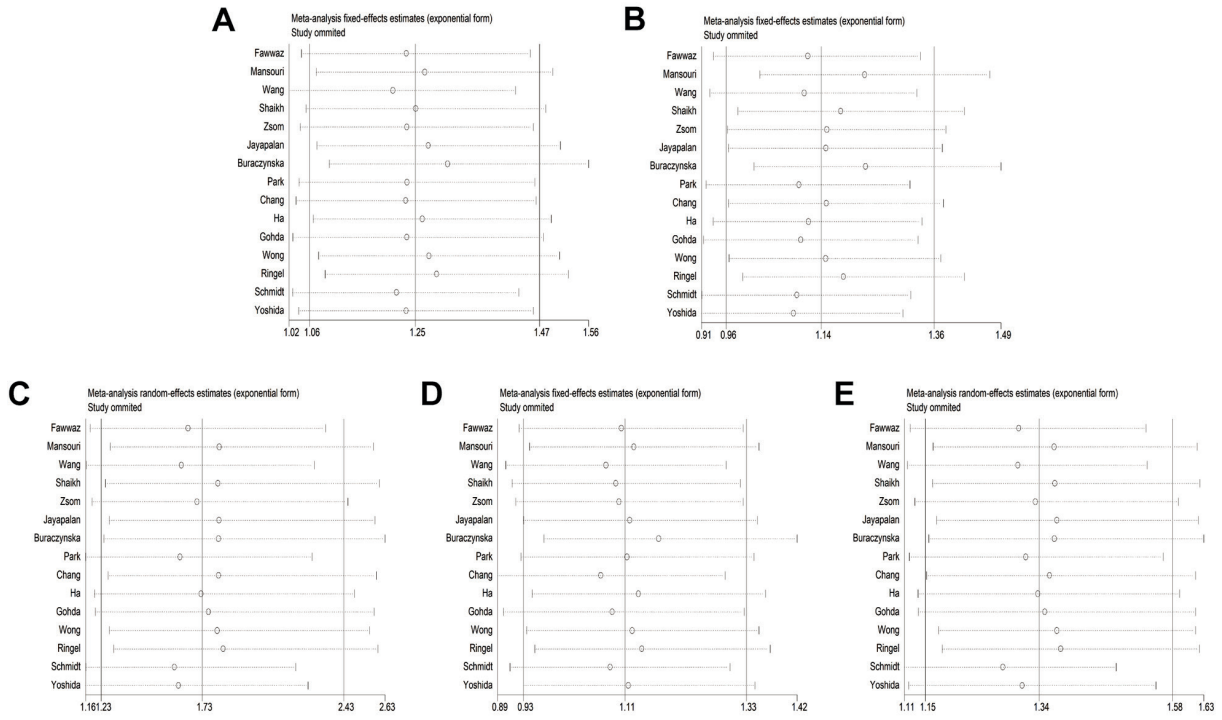

Figure 4. Sensitivity analysis of the association between ACE I/D polymorphism and the risk of diabetes-related end-stage renal disease. ***A,*** Dominant model; ***B,*** Recessive model; ***C,*** Homozygote model; ***D,*** Heterozygote model; ***E,*** Allele model.

gh regression analysis. Figure 4 illustrated the sensitivity analysis of the association between I/D polymorphism of ACE and diabetes-related ESRD, indicating that combined OR had no significant effect on study conclusions. Therefore, our meta-analysis results were believed to be robust and stable.

Publication Bias

Begg's funnel plot and Egger test were used to examine the publication bias of all data. A funnel plot was symmetrically distributed, indicating no remarkable publication bias in this study. Egger test further confirmed our conclusion (Figure 5).

Discussion

The incidence of diabetes-related ESRD increases with aging and has become one of the major diseases that threatens human health[3-5]. In many developed and developing countries, DKD has been the primary disease of ESRD[6,7]. ESRD is a refractory disease that poses a huge economic burden to patients and society. The complex pathogenesis of ESRD involves both genetic and environmental factors[8,9]. Genetic testing has been widely applied in clinical examinations. Detection of I/D polymorphism of ACE provides a novel approach for disease explorations[17,18]. Therefore, I/D polymorphism of ACE has been well concerned in early diagnosis and treatment of diabetes-related ESRD.

ACE (angiotensin-converting enzyme) is a key enzyme of the RAS (renin-angiotensin system), showing a vital role in the cardiovascular system through the renin-angiotensin system and kallikrein-kinin system[32]. ACE is located on 17q23 containing 26 exons and 25 introns, with the gene spans of 21 kb12,13. Multiple polymorphic markers in ACE have been identified, including T594lC, A240T, T93C, T1237C, I/D and 4656 (CT) 2/3, etc. Among them, I/D polymorphism of ACE is the mostly explored14. Three genotypes of ACE, namely DD homozygote, ID heterozygote, and II homozygote, are distinguished according to the insertion (I) or deletion (D) of 287 bp fragment in intron 1615. A great number of researches[17,18] have been carried out on the correlation between I/D polymorphism of ACE and diabetes-related ESRD. However, the conclusions were controversial. Some articles[17-21] pointed out the influence of I/D polymorphism of ACEs on the risk of diabetes-related ESRD.

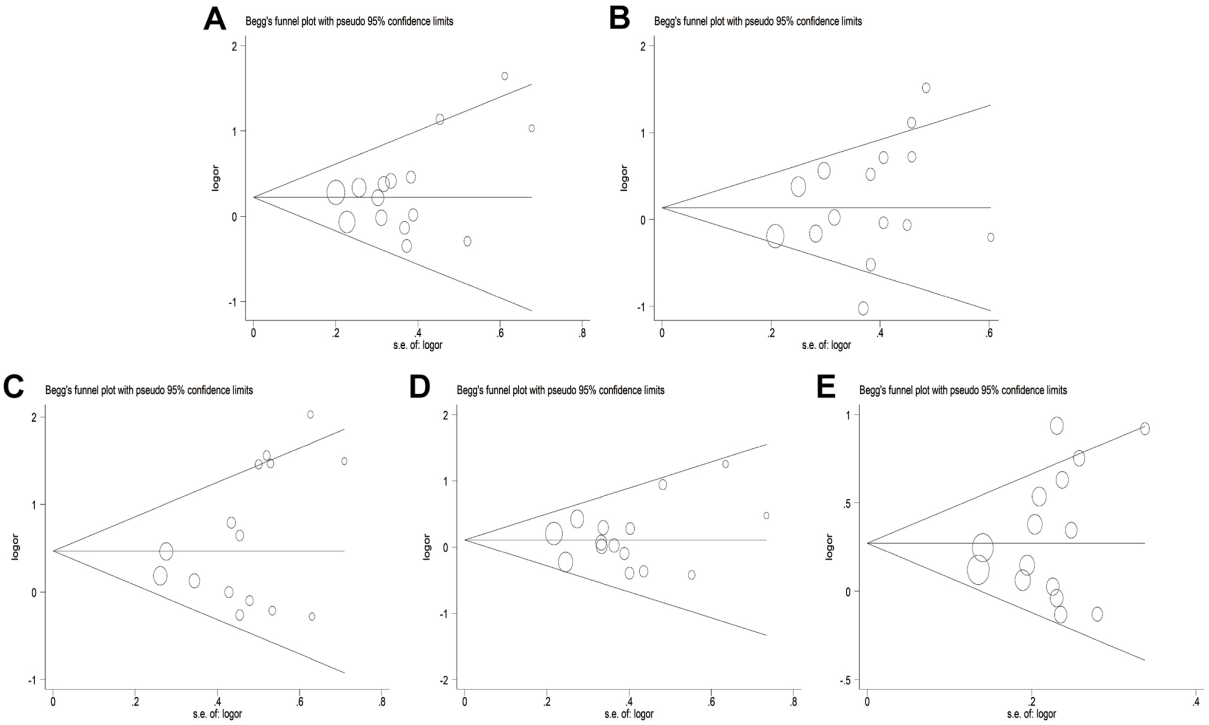

Figure 5. Begg's funnel plot of publication bias test. ***A,*** Dominant model; ***B,*** Recessive model; ***C,*** Homozygote model; ***D,*** Heterozygote model; ***E,*** Allele model.

Pathogenesis of diabetes-related ESRD still remains unclear[17-20]. This study enrolled articles on exploring the correlation between I/D polymorphism of ACE and risk of diabetes-related ESRD. A total of 15 articles containing 4138 subjects were included, and results confirmed that I/D polymorphism of ACE markedly increased the risk of diabetes-related ESRD. In the subgroup analysis by ethnicity, a significant difference in risk of diabetes-related ESRD was only detected in the Asian population with I/D polymorphism of ACE. However, no significant difference was found in the Caucasian population.

The inclusion criteria for this work were relatively strict and unlikely to be affected by bias and confounding variables, allowing our findings to be clear and reliable. Also, most of the studies included were cohort studies, showing stronger evidence of causality than other observational studies. However, there are still some limitations needed to be considered in this report: (1) We did not include mortality as a risk factor. The correlation between diabetes, CKD and ESRD may be different due to differences in the high mortality of diabetic patients. (2) There was heterogeneity in included studies. However, subgroup analysis and regression analysis indicated stable results, compensating for this deficiency to some extent. (3) The definition of diabetes-related ESRD and outcome indicators differed in these studies. Therefore, many alternative outcomes were used to re-calculate OR values, but were analyzed in a similar way. We believed the calculated OR value was still valid. (4) This result was obtained based on unadjusted estimates, which may be affected by multiple confounding factors, including age, lifestyle, environmental factors, etc. Besides, most of the studies in the mixed population were investigated, and it is recommended that the analysis results should be interpreted cautiously. Since the meta-analysis was limited by the sample size and objective conditions, it is impossible to cover all relative literature and may influence our argument strength. Large sample size and high-quality researches in a multi-center hospital are still needed to further confirm the reliability of the results. Gene-environment interactions should also be considered in the future explorations.

Conclusions

This meta-analysis suggested that I/D polymorphism of ACE can markedly increase the incidence of diabetes-related end-stage renal disease, especially in Asian populations. Therefore, large sample size and high-quality researches in a multi-center hospital are still needed to further confirm the reliability of the results.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Acknowledgements

This work was supported by grants from the Natural Science Foundation of Zhejiang Province (Grant Number: LY19H050002), and the Project of Scientific Research Foundation of Chinese Medicine (Grant Number: 2016ZQ007), the General Project of the Medical and Health of Zhejiang Province (Grant Number: 2014KYA018, 2015KYB035).

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