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Association between *AGTR1* A1166C polymorphism and the susceptibility to diabetic nephropathy

Evidence from a meta-analysis

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Abstract

Background: Diabetic nephropathy (DN) is a common complication in patients with diabetic mellitus (DM). Growing evidences have demonstrated that the polymorphisms of angiotensin II receptor type 1 (*AGTR1*) showed significant association with DN onset, but no consensus has been achieved yet. Therefore, we performed this meta-analysis to combine the findings of previous researches for a more comprehensive conclusion.

Methods: Eligible publications were identified through electronic databases. The intensity of the correlation between *AGTR1* A1166C polymorphism and DN susceptibility was evaluated through calculating pooled odds ratios (ORs) with their 95% confidence intervals (95% CIs). Heterogeneity among included studies was examined with *Q* test. When *P*-value less than .05, significant heterogeneity presented, random-effects model was used to calculate the pooled ORs, otherwise, the fixed-effects model was used. Stratification analyses were also performed based on ethnicity and the type of DM.

Results: Seventeen eligible articles were finally included in the present meta-analysis. The analysis results showed that *AGTR1* A1166C polymorphism was significantly related to increased risk of DN under CC versus AA (OR = 1.723, 95% CI = 1.123–2.644), CC + AC versus AA (OR = 1.179, 95% CI = 1.004–1.383), CC versus AA + AC (OR = 1.662, 95% CI = 1.112–2.486), and C versus A (OR = 1.208, 95% CI = 1.044–1.397) genetic models. Additionally, a similar result was also found in Asian and T2DM (type 2 diabetic mellitus) groups after subgroup analyses of ethnicity and DM type.

Conclusion: *AGTR1* A1166C polymorphism may increase the susceptibility to DN, especially in Asians and T2DM population.

Abbreviations: 95% CIs = 95% confidence intervals, ACE = angiotensin I-converting enzyme, AGT = angiotensinogen, AGTR1 = angiotensin II receptor type 1, CNKI = China National Knowledge Infrastructure, CVD = cardiovascular diseases, DM = diabetic mellitus, DN = diabetic nephropathy, HWE = Hardy–Weinberg equilibrium, NOS score = Newcastle-Ottawa quality assessment scale, ORs = odds ratios, RAS = renin-angiotensin system, T1DM = type 1 diabetic mellitus, T2DM = type 2 diabetic mellitus.

Keywords: AGTR1, diabetic nephropathy, polymorphism, renin-angiotensin system

1. Introduction

Diabetic nephropathy (DN) refers to diabetic glomerulosclerosis, representing one of the frequently observed diabetes mellitus (DM) systemic microvascular complications.[1,2] According to statistics, the incidence rate of DN shows an increasing tendency in the past few years.[3] It is predicted by WHO that DM will be prevalent in developing countries in the 21st century.[4] Once persistent proteinuria occurs, it will progressively develop to end-stage renal disease.[5] DN is one of the leading causes of disability and death in DM patients, being a critical topic in medical research.[6] Until now, the pathogenesis of DN could not be completely explained. Research data have shown that the occurrence of DN is related to multiple factors, such as changes in hemodynamics, metabolic disorders, and the involvement of growth factors and genetic elements.[7,8] While in recent modern medical studies, hereditary factors have been demonstrated to occupy an extremely vital position in the occurrence of DN.[9] For instance, a meta-analysis based on 1894 DN cases and 1746 controls demonstrated that *NADPH* oxidase p22phox C242T SNP showed obvious association with macroalbuminuria in patients with diabetes.[10] To investigate the genetic factors may provide a new insight into the pathogenesis of DN.

Renal hemodynamic abnormalities play an important role in the initiation and progression of DN. The abnormalities in renin-angiotensin system (RAS), especially the local RAS of kidney, are the major cause of renal hemodynamic abnormalities.[11] Given the function roles of RAS in onset of DN, the alterations in RAS system genes might be involved in development of DN.[12] RAS is consisted of renin, angiotensin I-converting enzyme (ACE),

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angiotensinogen (AGT) and angiotensin II receptor, type 1 (AGTR1).[13] AGTR1 is widely expressed in various tissues, such as vessel walls, lung and kidney, and after being activated. AGTR1 can not only lead to water–sodium retention and elevated blood pressure but also participate in the microvascular disorders in type 2 DM (T2DM).[14] Meanwhile, activation of AGTR1 may regulate renal function.[15,16] The expression pattern of AGTR1 shows significant association with nephropathy.[17] There are several polymorphisms in the *AGTR1* gene, including A1166C, T573C, A1062G, G1517T, and A1878G. Among them, the A1166C polymorphism is located at the 3′ untranslated region of the gene, which does not affect the encoding process of AGTR1 protein in theory. But it still has the potential to influence the stability of the mRNA expression of the gene.[18,19] Growing evidences have proved the significant association between *AGTR1* A1166C SNP and DN.[20–23] However, due to the differences in study ethnic population, type of DM, as well as the sample size, no conclusive result has been achieved yet.

In this study, we aimed to obtain a reliable result about the genetic association of *AGTR1* A1166C polymorphism and DN susceptibility through a meta-analysis.

2. Materials and methods

2.1. Study design

The present meta-analysis was performed based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The PRISMA checklist presented in the form of "Supplement information."

2.2. Literature searching

A systemic search was performed in the databases of PubMed, EMBASE, Google Scholar Web, China National Knowledge Infrastructure (CNKI), and Wanfang for eligible articles published in English or Chinese language, using the combination of the following key terms: "angiotensin II receptor, type 1" or "AT_1 receptor" or "AGTR1" or "AT1," "polymorphism" or "mutation" or "variant," and "diabetic nephropathy" or "DN" or "nephropathy." Besides, the reference lists of relevant articles were also manually checked for additional publications.

2.3. Selection criteria

All eligible articles had to satisfy the following criteria: with a case–control design; the individuals in control group were DM without DN patients, while the individuals in case group were DN cases; DM diagnosis and classification were according to World Health Organization (WHO) criteria, and DN was confirmed by the duration of DM, and the presence of urine albuminuria; evaluating the association between *AGTR1* gene A1166C polymorphism and DN susceptibility; offering sufficient data on genotype distribution both in case and control groups; with reasonable grouping method, the case and control groups came from the same ethnical population, and were matched in gender and age; and focusing on human beings. Those publications were excluded from our study if they conformed to any one of the following conditions: case-only studies; with duplicated data; based on families or siblings; and letters, editorials, case reports, review articles, and conference abstracts.

2.4. Data extraction

Principal information of each eligible article was extracted independently by 2 reviewers, and contained first author's name, publication year, original country, ethnicity, genotyping method, numbers of cases and controls, genotype frequencies in case and control groups as well as *P*-value for Hardy–Weinberg equilibrium (HWE) in control group. If more than 1 study/cohort were incorporated into 1 article, their data were extracted as separated ones. As for the disagreements on abstracted data, they were settled through discussion between the 2 reviewers; if no consensus was reached via discussion, a third reviewer would be consulted.

2.5. Quality assessment for eligible studies

Newcastle-Ottawa quality assessment scale (NOS score) was used to estimate the quality of the eligible studies. Eligible studies were classified into low, moderate, and high quality based on the NOS score 0 to 3, 4 to 6, and 7 to 9 scores.

2.6. Statistical analysis

All statistical analyses were completed with STATA 12.0 software (Stata Corporation, College Station, TX). The strength of the association between *AGTR1* gene A1166C polymorphism and DN susceptibility was assessed by pooled odds ratios (ORs) with their corresponding 95% confidence intervals (95% CIs). Between-study heterogeneity was inspected with Chi-square-based Q test and I^2 test. When $P < .05$ and $I^2 > 50\%$, significant heterogeneity presented, and random-effects model was used to calculate the pooled OR, otherwise, the fixed-effects model was used. Subgroup analysis based on ethnicity and DM type was performed to find the source of heterogeneity. Sensitivity analysis was conducted through sequential omitting each included study to test the stability of the final results. Begg funnel plot and Egger regression test were adopted to investigate the publication bias among the included studies visually and statistically, respectively.

3. Results

3.1. Characteristics of included studies

As shown in Fig. 1, a total of 265 potentially relevant publications were initially retrieved through database searching, and 45 of them were excluded for duplicates. Two hundred twenty potential articles were assessed through title and abstract, and 197 articles were removed, including unrelated articles (81), reviews (4), not about the selected genetic polymorphism (47), irrelevant to DN risk (65). The remaining 23 articles needed to be estimated through full text, and 6 studies were without data. Consequently, 17 eligible articles (including 19 independent studies) were ultimately incorporated into the present meta-analysis.[12,20–35]Table 1 describes the primary information of all included studies. Nine studies focused on Caucasian population and type 1 DM (T1DM), while, 10 studies focused on Asian population and T2DM.

3.2. Quality assessment of the included studies

According to the inclusion and exclusion criteria, 17 eligible researches including 19 independent studies were included in this study. NOS score was used to evaluate the quality of the studies. Among the 19 independent studies, 8 with high quality and 11

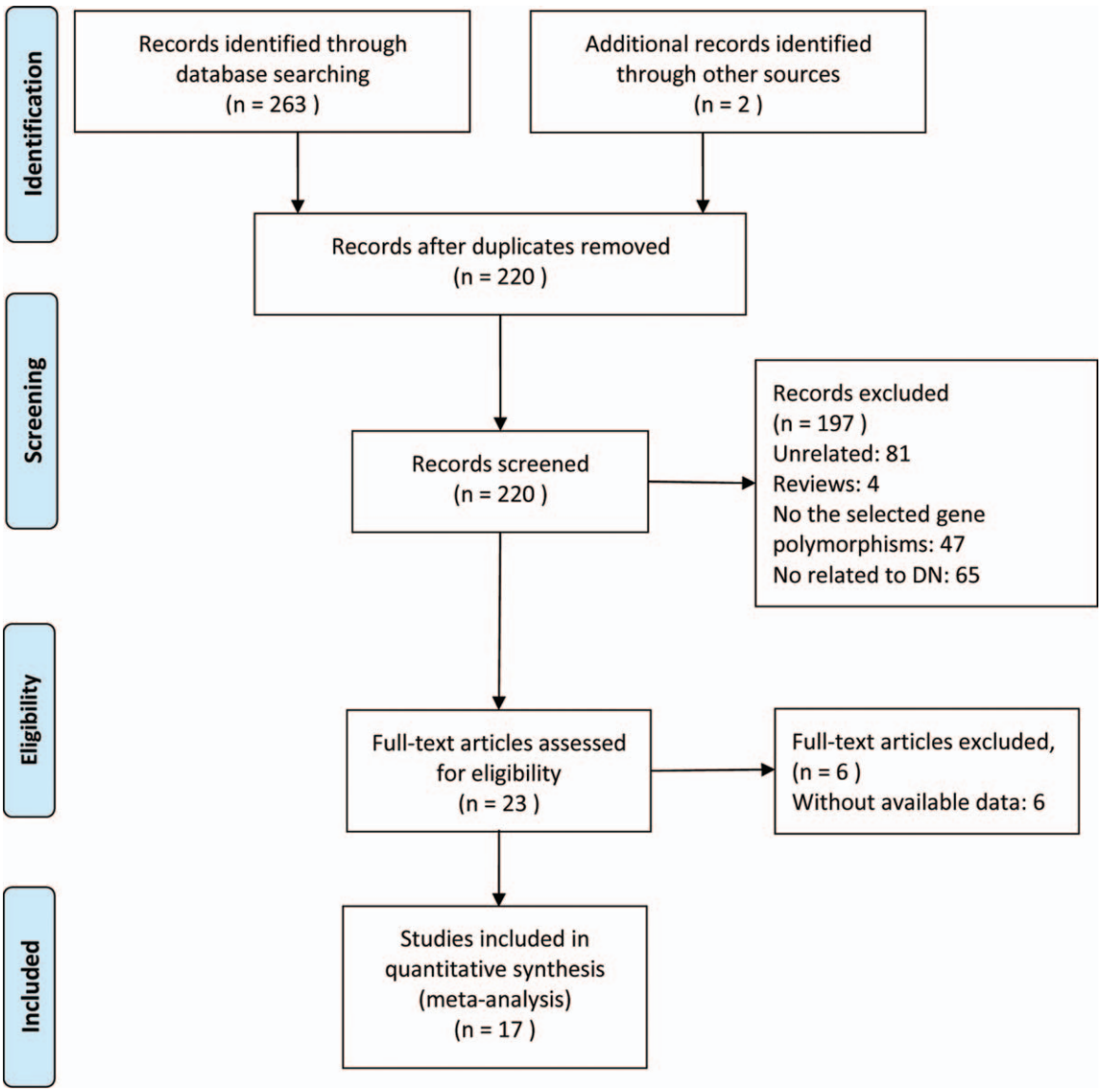

Figure 1. Flow diagram for the process of study selecting with detailed reasons for exclusion.

Table 1

Primary information of included studies in the meta-analysis.

First author	Year	Country	Ethnicity	DM type	Genotyping method	Case						Control						NOS score
						Sample size	AA	AC	CC	A	C	Sample size	AA	AC	CC	A	C	
Tarnow	1996	France	Caucasian	T1DM	AS-PCR	198	103	81	14	287	109	190	97	80	13	274	106	7
Chowdhury	1997	UK	Caucasian	T1DM	PCR-RFLP	264	116	137	11	369	159	136	69	59	8	197	75	6
Doria	1997	USA	Caucasian	T1DM	PCR-RFLP	73	35	29	9	99	47	79	47	25	7	119	39	6
van Ittersum	2000	Netherlands	Caucasian	T1DM	PCR-RFLP	200	91	88	21	270	130	100	37	53	10	127	73	6
Wu	2000	China	Asian	T2DM	PCR-RFLP	71	56	15	0	127	15	61	56	5	0	117	5	4
Xue	2001	China	Asian	T2DM	PCR-RFLP	153	139	14	0	292	14	86	84	2	0	170	2	5
Prasad	2006	India	Asian	T2DM	PCR-RFLP	196	169	25	2	363	29	225	194	29	2	417	33	5
Gallego	2008	Australia	Caucasian	T1DM	PCR	41	15	21	5	51	31	411	196	183	32	575	247	6
Möllsten	2008	Swedish	Caucasian	T1DM	ABI PRISM 7000	120	76	36	8	188	52	197	104	82	11	290	104	7
Ahluwalia	2009	India	Asian	T2DM	PCR-RFLP	240	104	112	24	320	160	255	131	119	5	381	129	7
Sun	2009	China	Asian	T2DM	PCR-RFLP	73	62	11	0	73	135	72	69	3	0	141	3	5
Currie	2010	British Isles	Caucasian	T1DM	TaqMan	707	370	289	48	1029	385	735	376	300	59	1052	418	6
Möllsten	2011	Mixed	Caucasian	T1DM	ABI PRISM 7000	2174	1262	785	127	3309	1039	1243	700	451	92	1851	635	7
Shah	2013	India	Asian	T2DM	PCR-RFLP	240	104	112	24	320	160	255	131	119	5	381	129	7
Shah	2013	India	Asian	T2DM	PCR-RFLP	260	112	122	26	346	174	215	109	101	4	319	109	7
Shah	2013	India	Asian	T2DM	PCR-RFLP	96	39	45	12	123	69	92	50	40	2	140	44	7
Yin	2013	China	Asian	T2DM	PCR-RFLP	152	131	20	1	282	22	141	133	8	0	274	8	7
Ilić	2014	Serbia	Caucasian	T1DM	PCR-RFLP	46	22	17	7	61	31	33	16	15	2	47	19	6
Moradi	2015	Iran	Asian	T2DM	PCR-RFLP	94	71	21	2	163	25	41	28	13	0	69	13	5

AS-PCR = allele-specific-PCR, DM = diabetic mellitus, GE = gel electrophoresis, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle-Ottawa quality assessment scale, PCR = polymerase chain reaction, PCR-RFLP = PCR-restriction fragment length polymorphism, T1DM = type 1 diabetic mellitus, T2DM = type 2 diabetic mellitus, TaqMan = TaqManSNP.

Table 2

***AGTR1* A1166C polymorphism and diabetic nephropathy susceptibility.**

Group		No. of studies	Odds ratio (95% confidence interval)/*P-value* for heterogeneity									
			CC vs AA		CC+AC vs AA		CC vs AA+AC		C vs A		AC vs AA	
Ethnicity	Caucasian	9	0.873 (0.717-1.064)	.586	0.971 (0.841–1.122)	.188	0.886 (0.731–1.074)	.630	0.965 (0.877–1.063)	.315	0.975 (0.835–1.139)	.166
	Asian	10	5.325 (3.174–8.934)	.773	1.479 (1.174–1.863)	.141	4.924 (2.957–8.199)	.833	1.562 (1.266–1.826)	.186	1.333 (1.041–1.706)	.105
DM type	T1DM	9	0.865 (0.705–1.060)	.586	0.971 (0.841–1.122)	.188	0.886 (0.731–1.074)	.630	0.965 (0.877–1.063)	.315	0.975 (0.835–1.139)	.166
	T2DM	10	5.325 (3.174–8.934)	.773	1.479 (1.174–1.863)	.141	4.924 (2.957–8.199)	.833	1.562 (1.266–1.826)	.186	1.333 (1.041–1.706)	.105
Total		19	1.723 (1.123–2.644)	.000	1.179 (1.004–1.383)	.002	1.662 (1.112–2.486)	.000	1.208 (1.044–1.397)	.000	1.106 (0.954–1.282)	.019
Model for analysis			Random		Random		Random		Random		Random	

DM = diabetic mellitus, T1DM = type 1 diabetic mellitus, T2DM = type 2 diabetic mellitus.

with moderate quality, no low quality study was included in this meta-analysis (Table 1).

3.3. Quantitative data synthesis

The main results of the meta-analysis are displayed in Table 2. In total analysis, *AGTR1* gene A1166C polymorphism expressed a significantly increasing effect on DN susceptibility under CC versus AA (OR = 1.723, 95% CI = 1.123–2.644), CC + AC versus AA (OR = 1.179, 95% CI = 1.004–1.383), CC versus AA + AC (OR = 1.662, 95% CI = 1.112–2.486) (Fig. 2), and C versus A (OR = 1.208, 95% CI = 1.044–1.397) (Fig. 3) genetic models. Additionally, a similar influence of the polymorphism was also shown in Asian [under CC vs AA, CC + AC vs AA (Fig. 2), CC vs AA + AC, C vs A and AC vs AA contrasts] and T2DM [under CC vs AA, CC + AC vs AA, CC vs AA + AC, C vs A (Fig. 3) and AC vs

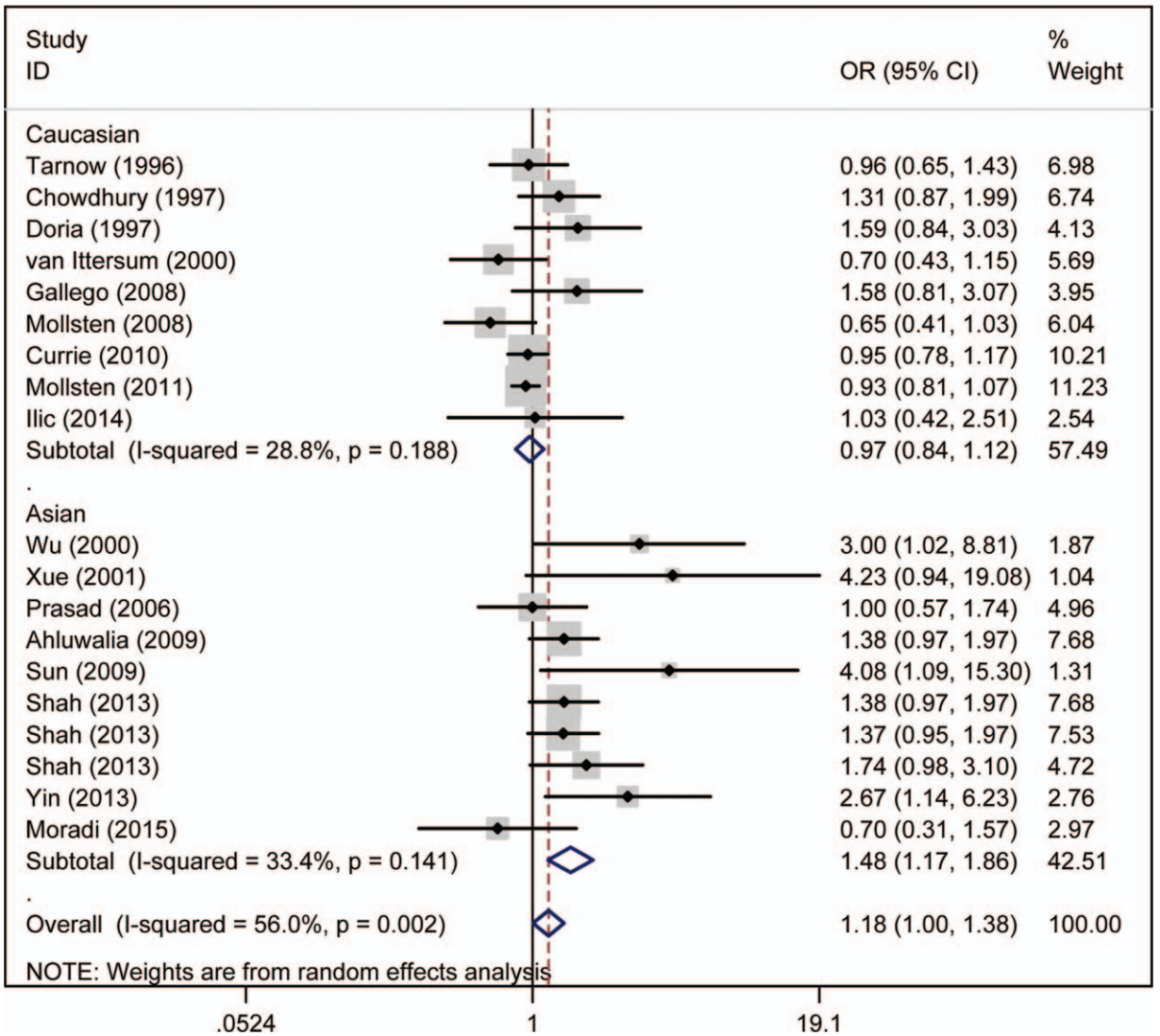

Figure 2. Forest plot for the association between *AGTR1* A1166C polymorphism and the susceptibility to diabetic nephropathy under CC + AC vs AA contrast after stratified by ethnicity.

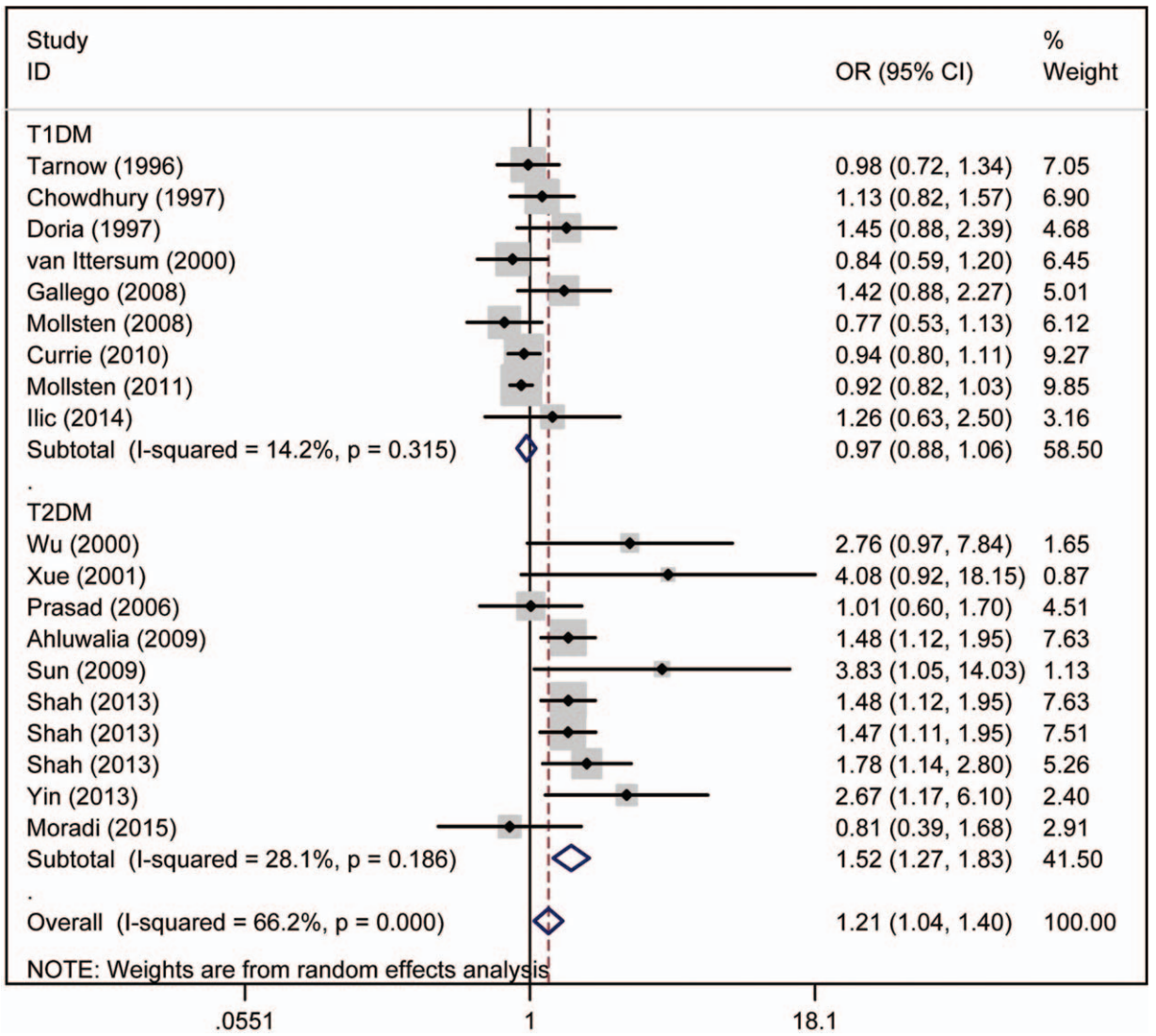

Figure 3. Forest plot for the association between *AGTR1* A1166C polymorphism and the susceptibility to diabetic nephropathy under C vs A contrast after stratified analysis by DM type.

AA contrasts] subgroups after stratification analysis by ethnicity and DM type. All these results illustrated that *AGTR1* A1166C polymorphism was closely related to increased risk of DN in T2DM patients, especially in Asians.

3.4. Heterogeneity test

Q test revealed significant heterogeneity ($P < .05$) under all the 5 genetic comparisons, so the random-effects model was selected for calculating ORs. Then subgroup analysis based on ethnicity and DM type was performed to find the source of heterogeneity. There was no significant heterogeneity in the subgroups, indicating that the ethnicity and DM type might be the potential source of heterogeneity.

3.5. Sensitivity analysis

Sensitivity analysis was completed via deleting each selected study in turn to observe alteration in pooled ORs. During the whole process, no qualitative change occurred in the final results (data not shown), revealing the statistical robustness of our findings.

3.6. Publication bias examination

The shape of the funnel plots seemed symmetrical (CC vs AA + AC, Fig. 4), implying publication bias was negligible. Furthermore, these results were all confirmed by statistical data from Egger test (CC vs AA + AC, $P = .142$).

4. Discussion

DN is a common chronic complication, posting a great threat to healthy among DM cases. In recent years, the incidence rate of DN exhibits an upward trend in developed countries. In order to improve the management of DN, more and more researches are devoted to explore the pathogenesis of DN. Relevant data have confirmed that RAS possesses an important effect on the initiation and progression of DN via diverse mechanisms.

Widely distributed among diverse tissues, AGTR1 mediates numerous vital biological effects, such as contracting vascular smooth muscle, stimulating the proliferation and thickening of vascular smooth muscle, and accelerating the release of aldosterone which are all related to blood pressure maintenance

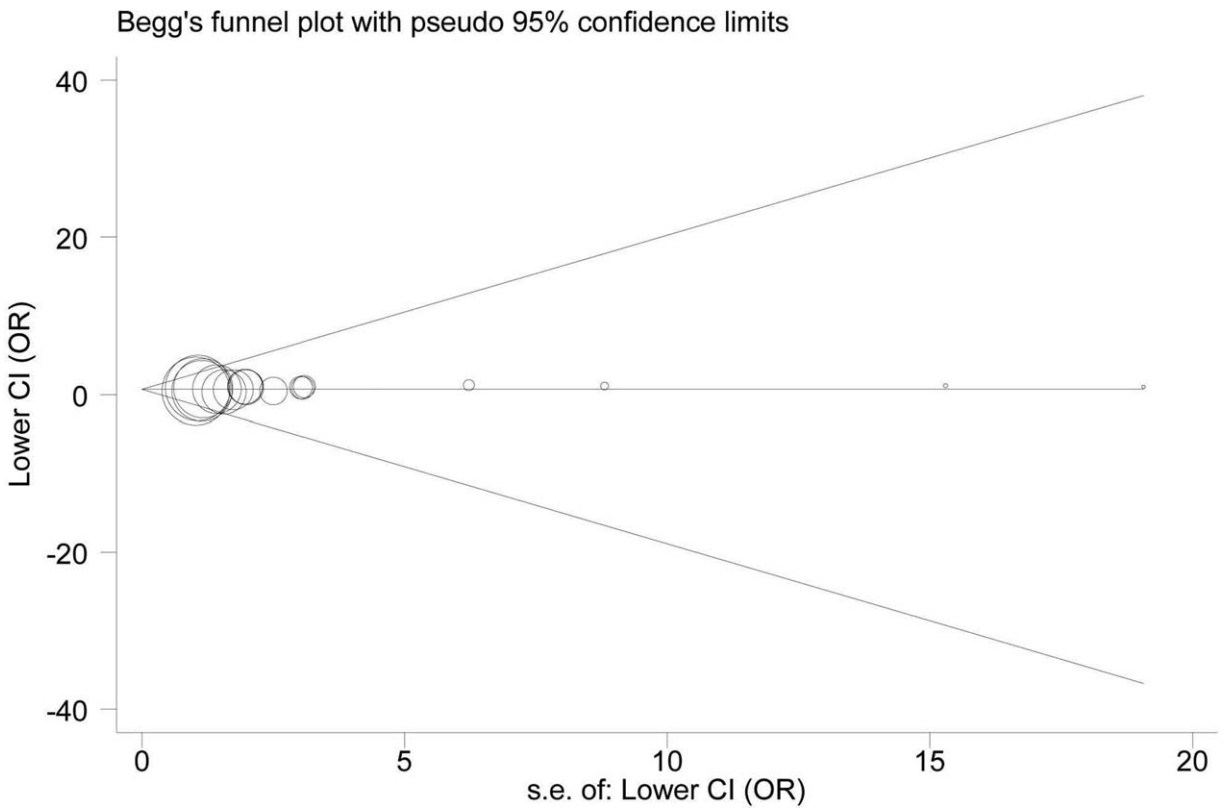

Figure 4. Begg funnel plot for publication bias under CC vs AA+AC genetic model.

and target organ damages. As a G protein coupled receptor, AGTR1 has 7 highly conservative transmembrane functional domains. After binding with angiotensin, AGTR1 can activate G protein and 2 intracellular signal transduction pathways through inositol triphosphate and acetoglyceride. In one pathway, calcium releases activates protein kinases to promote the synthesis of proteins; while in the other pathway, cascade amplification of protein kinases activates MAPK which can prompt the expression of many protooncogenes after entering nucleus and thus further accelerating the division and proliferation of cells. In *AGTR1* gene, there are 5 polymorphisms identified, namely A1166C, T573C, A1062G, G1517T, and A1878G, of which the former three are more common. The polymorphism A1166C is located at the 3′ untranslated region of the gene, which has no effect on open reading frame and the encoding process of AGTR1 protein theoretically, but if it has linkage disequilibrium with adjacent chromosome positions with functional abnormalities, a series of impacts may occur in the stability of mRNA expression of the *AGTR1* gene, AGTR1 number and distribution density as well as the affinity of AGTR1 to angiotensin II, thus strengthening the reactivity of angiotensin II and inducing the occurrence and development of DN.[18,19]

Accumulating studies have discussed the relationship of the polymorphism A1166C with the susceptibility to DN, but no consistent opinion has been reached yet. For example, Doria et al[21] and Gallego et al[22] insisted there was no significant association between *AGTR1* A1166C polymorphism and DN risk in Caucasian populations. However, the study by Shah et al[29] revealed a significantly much higher frequency of the C allele of the *AGTR1* A1166C polymorphism in Indian DN patients, demonstrating the close relationship between the polymorphism and the disease in their studied population. In addition, Yin et al[20] in their research on Chinese also found that the C allele of the polymorphism is significantly more frequent in DN group than healthy control group and than DM without nephropathy group. All the discrepancies between the above findings might be partially attributed to different genetic backgrounds of participants in those studies, diverse selection criteria for study samples and uneven sample sizes. A system analysis was in urgent need to address the issues.

In order to obtain a reliable result about the genetic association of *AGTR1* A1166C polymorphism with DN risk, the present meta-analysis was performed according to the guidance of PRISMA. After statistical analysis, the outcomes showed that *AGTR1* A1166C polymorphism had significantly increasing-effect on DN susceptibility in total analysis, and a similar tendency was also revealed in Asian and T2DM groups after subgroup analyses of ethnicity and DM type. However, the significant association was not observed in Caucasian population and T1DM group. The results were partly consistent with the results of a similar meta-analysis carried out by Ding et al.[36] Their pooled analysis results demonstrated that *AGTR1* A1166C polymorphism was obviously associated with DN in T2DM patients. Moreover, the significant association was not changed after stratification analysis by ethnicity. There were several reasons resulting in the divergences. Firstly, our meta-analysis included 17 eligible studies including 19 independent studies, while there were 10 studies included in the analysis of Ding et al. There were multiple recently published articles included in our analysis. Secondly, in our meta-analysis, patients in control group were all DM cases, however, 2 of the included studies in the pooled analysis of Ding et al set the healthy individuals as control.[37,38] The purpose of the pooled analysis was to investigate the genetic association of *AGTR1* A1166C polymorphism with DN risk. The healthy

individuals as control might cause bias to the final results. Thus, our meta-analysis included more high-quality articles that might provide more reliable and representative conclusions on these issues.

In the present study, we investigated the effects of *AGTR1* A1166C polymorphism on susceptibility of DN. The results obtained in our study might be helpful in identifying the population with high risk of DN among DM patients, especially among Asian and T2DM populations. However, these findings still need to be applied prudently due to several inevitable limitations in our study. The number of included studies was relatively small, which might result from source and language limitations in literature searching strategy. The relative small sample size might reduce the comprehensiveness of the final results. Moreover, possible combination and interaction of our studied polymorphism with other relevant factors were not embraced into the present study. Additionally, the complete medical records for the case and control populations were not available in all the included studies. The potential differences in clinical parameters might also cause bias to the final results. In view of the above mentioned restrictions in the present meta-analysis, these results need to be further verified in studies with larger sample sizes and more consideration of potentially collective effects.

In summary, our study displayed a risk-increasing influence of *AGTR1* A1166C polymorphism on DN, especially among Asian and T2DM populations.

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