Association between *ADIPOQ* rs2241766 polymorphism and risk of diabetic nephropathy

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ABSTRACT

Background: This meta-analysis was performed to derive a more comprehensive estimation over the role of the single nucleotide polymorphism (SNP) rs2241766 in *ADIPOQ* gene in the occurrence of DN.

Results: The overall ORs reflected a positive correlation between *ADIPOQ* rs2241766 polymorphism and susceptibility to DN under GG vs. TT and GG vs. TT + TG comparisons (OR = 1.51, 95% CI = 1.16–1.95; OR = 1.43, 95% CI = 1.11–1.85). After stratification analyses by ethnicity and disease type, a similar trend was also revealed in Caucasian and African subgroups as well as in type 2 diabetes mellitus (T2DM) subgroup.

Materials and Methods: Relevant studies were searched from digital databases such as Embase, PubMed, Wanfang, and Chinese National Knowledge Infrastructure (CNKI). Odds ratios (ORs) with their corresponding 95% confidence intervals (95% CIs) were pooled by means of fixed- or random-effects models. Inter-study heterogeneity was examined using *Q* test and I^2 statistic, and sensitivity analysis was implemented to test the statistical stability of overall estimates. Begg's funnel plot and Egger's test were applied to inspect potential publication bias among included studies.

Conclusions: *ADIPOQ* rs2241766 polymorphism may be associated with an increased risk of DN, especially in Caucasian and African populations as well as in T2DM patients.

INTRODUCTION

In diabetic patients, microvascular lesions and accelerated atherosclerosis tend to trigger complications leading to severe morbidity [1]. Diabetic nephropathy (DN) is a representative microvascular complication in type 1 and type 2 diabetes mellitus (T1DM and T2DM) which can cause end-stage renal disease (ESRD) [2–4]. Reports show that about one third of diabetic patients will finally develop DN, so it is of great significance to find risk factors for DN occurrence [5]. Patients suffering from DN may require hemodialysis or even kidney transplantation in the end, thus causing serious economic burden on health care budgets [6, 7]. DN is a multifactorial disease occurring as a result of both environmental and hereditary factors [8]. The ethnic disparity in DN development may be attributed to an important role of genetic factors; and gender has also been demonstrated to influence the predisposition of diabetic patients to developing kidney diseases, with males having a relatively higher incidence rate [8–11].

One of the candidate genes for DN is adiponectin (*ADIPOQ*), which has been indicated to be linked to the susceptibility to cardiovascular disease, metabolic syndrome, and T2DM [12]. The *ADIPOQ* gene mapped to chromosome 3q27 is consisted of three exons and two introns [13–15]. This adipokine can exert anti-inflammatory and anti-atherogenic effects and regulate glucose and lipid metabolism as well as insulin action [16, 17]. The chromosomal region containing the *ADIPOQ*

gene has been reported to be one of the cardiovascular risk factors as well [18, 19]. Additionally, abnormal levels of serum adiponectin have already been shown to be correlated with T2DM, insulin resistance, obesity, cardiovascular diseases and nephropathy [8, 16, 20–22]. Reportedly, the development of microalbuminuria in T1DM cases may be predicted by high adiponectin levels [23]. Several single nucleotide polymorphisms (SNPs) have been identified in the *ADIPOQ* gene and their associations with the risk of DN in T1DM and T2DM patients have been investigated in diverse populations in many case-control studies, but the results remain inconclusive.

In the present meta-analysis, we selected one commonly-studied SNP rs2241766 in exon 2 of *ADIPOQ* gene to clarify its effects on DN occurrence based on previously published case-control studies on this topic.

RESULTS

Characteristics of studies

The publication search is described in Figure 1. Initially, altogether 174 articles were identified from the database search. During the further reviewing, 163 articles were deleted for editorials (7), on rats (6), not about DN or merely about diabetes (63), obvious irrelevancy (71), concerning the prognosis of DN (8), meta-analysis (3), and with no detailed data about genotype and allele frequencies (5). At last, 14 case-control studies with 3343 cases and 7859 controls were incorporated into the present meta-analysis [1, 20, 24–32]. All of the controls in our meta-analysis were diabetic patients without nephropathy. Additionally, the most of included studies were high-quality (NOS score more than 6). Table 1 summarizes general characteristics of the incorporated studies.

Meta-analysis results

The relationship between *ADIPOQ* rs2241766 polymorphism and DN susceptibility is illustrated in Table 2. The combined results demonstrated that *ADIPOQ* rs2241766 polymorphism increased the susceptibility to DN under two genetic comparisons of GG vs. TT (Figure 2) and GG vs. TT + TG (OR = 1.51, 95% CI = 1.16–1.95; OR = 1.43, 95% CI = 1.11–1.85). A risk-increasing effect of the polymorphism was also shown in Caucasian (GG + TG vs. TT: OR = 1.27, 95% CI = 1.01–1.60; allele G vs. allele T: OR = 1.12, 95% CI = 1.01–1.25), African (GG vs. TT: OR = 9.06, 95% CI = 3.00–27.34 (Figure 2); GG + TG vs. TT: OR = 4.80, 95% CI = 2.86–8.03; GG vs. TT + TG: OR = 4.34, 95% CI = 1.48–12.68; allele G vs. allele T: OR = 3.16, 95% CI = 2.12–4.71; TG vs. TT: OR = 4.26, 95% CI = 2.50–7.28), and T2DM (GG vs. TT+TG: OR = 1.68, 95% CI = 1.18–2.39) groups after subgroup analyses by ethnicity and disease type.

Heterogeneity test

The statistical *Q* test and I^2 statistic revealed significant heterogeneity under GG + TG vs. TT, G vs. T and TG vs. TT contrasts, so the random-effects model was chosen for calculating ORs in these cases, while the fixed-effects model was adopted under the other two genetic comparisons where heterogeneity was negligible.

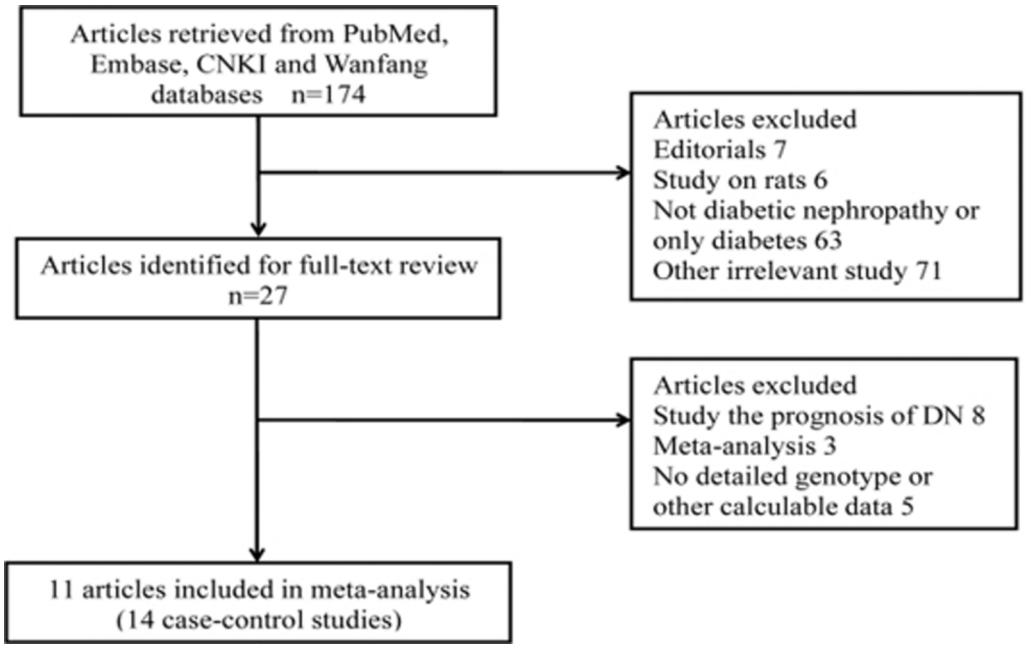

Figure 1: Flowchart illustrating the process of study identification, inclusion and exclusion.

Table 1: Main characteristics of included studies of the present meta-analysis

First author (year)	Country	Ethnicity	Control source	Type	Sample size	Case genotype and allele					Control genotype and allele					Genotyping method	NOS score
					Case/ control	TT	TG	GG	T	G	TT	TG	GG	T	G		
Ma (2007)	Sweden	Caucasian	Diabetic	T1DM	196/236	180	15	1	375	17	213	22	1	448	24	PCR-DASH	7
Choe (2013)	Korea	Asian	Diabetic	T2DM	245/448	124	95	26	343	147	216	204	28	636	260	SNaPShot	7
Chung (2014)	China	Asian	Diabetic	T2DM	144/422	77	57	10	211	77	206	186	30	598	246	multiplex PCR	8
El-Shal (2014)	Egypt	African	Diabetic	T2DM	196/100	53	113	30	219	173	64	32	4	160	40	PCR-RFLP	7
Jaziri (2010)	France	Caucasian	Diabetic	T2DM	75/3011	46	25	4	117	33	2223	728	60	5174	848	PCR-MB	8
Peng (2012)	China	Asian	Diabetic	T2DM	42/40	25	14	3	64	20	19	18	3	56	24	DS	7
Ranjbar (2011)	Iran	Caucasian	Diabetic	T2DM	28/205	20	8	0	48	8	142	56	7	340	70	PCR-RFLP	7
Sikka (2014)	India	Asian	Diabetic	T2DM	145/152	124	20	1	268	22	128	22	2	278	26	PCR-RFLP	6
Vionnet (2006)	Denmark	Caucasian	Diabetic	T1DM	489/463	393	91	5	877	101	377	82	4	836	90	Ampli-Fluor	7
Vionnet (2006)	Finland	Caucasian	Diabetic	T1DM	387/469	349	37	1	735	39	416	51	2	883	55	Ampli-Fluor	7
Vionnet (2006)	France	Caucasian	Diabetic	T1DM	300/391	221	73	6	515	85	303	82	6	688	94	Ampli-Fluor	7
Blech (2011)	Israel	Caucasian	Diabetic	T2DM or T1DM	852/1473	532	283	37	1347	357	966	454	53	2386	560	Not available	7
Rudofsky (2004)	Germany	Caucasian	Diabetic	T1DM	73/166	47	26		/	/	147	19		/	/	PCR-RFLP	8
Rudofsky (2004)	Germany	Caucasian	Diabetic	T2DM	174/283	137	37		/	/	239	44		/	/	PCR-RFLP	8

PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; PCR-MB: PCR-molecular beacon; PCR-DASH: PCR-dynamic allele specific hybridization; DS: Direct sequencing.

Under the three contrasts where significant heterogeneity was revealed, meta regression analysis was conducted, and the results demonstrated that differences in ethnic origin could explain the vast majority or even total of the sources of the significant heterogeneity.

Sensitivity analysis

In sensitivity analysis, recalculated ORs after removing any one single eligible study showed no qualitative difference from original ones (Figure 3, with a lower CI of 1.01 and an upper CI of 2.29), implying that our results were reliable and robust.

Publication bias

Potential publication bias among the included studies was assessed through the visual inspection of Begg's funnel plots accompanied by statistical result from Egger's test. The symmetrical shape of the funnel plots (Figure 4) and *P* value of Egger's linear regression test ($P = 0.520$) indicated the absence of significant publication bias.

DISCUSSION

According to existing evidences, chronic kidney failure, renal failure, and high adiponectin levels in T1DM and T2DM patients may be all related to nephropathy pathogenesis [23, 33–37]. The adiponectin protein encoded by the *ADIPOQ* gene can prevent vascular remodeling by inhibiting the proliferation and migration of smooth muscle cells and reduce TNF-α production to modulate the inflammatory response of endothelial cells [38, 39]. In addition, adiponectin can protect vasculature through its pleiotropic actions on endothelial progenitor cells, endothelial cells, macrophages, and smooth muscle cells [40]. What's more, it may also prevent the injury and dysfunction of endothelial cells due to its protective effects [40]. Genetic polymorphisms in the *ADIPOQ* gene can affect the adiponectin levels, and their contribution to occurrence of DN, a common micorvascular complication, has been frequently discussed, but conflicting results are yielded.

We therefore performed the present meta-analysis including 3343 cases and 7859 controls aiming to obtain a better insight into the linkage between *ADIPOQ* rs2241766 polymorphism and DN risk. After data syntheses, we

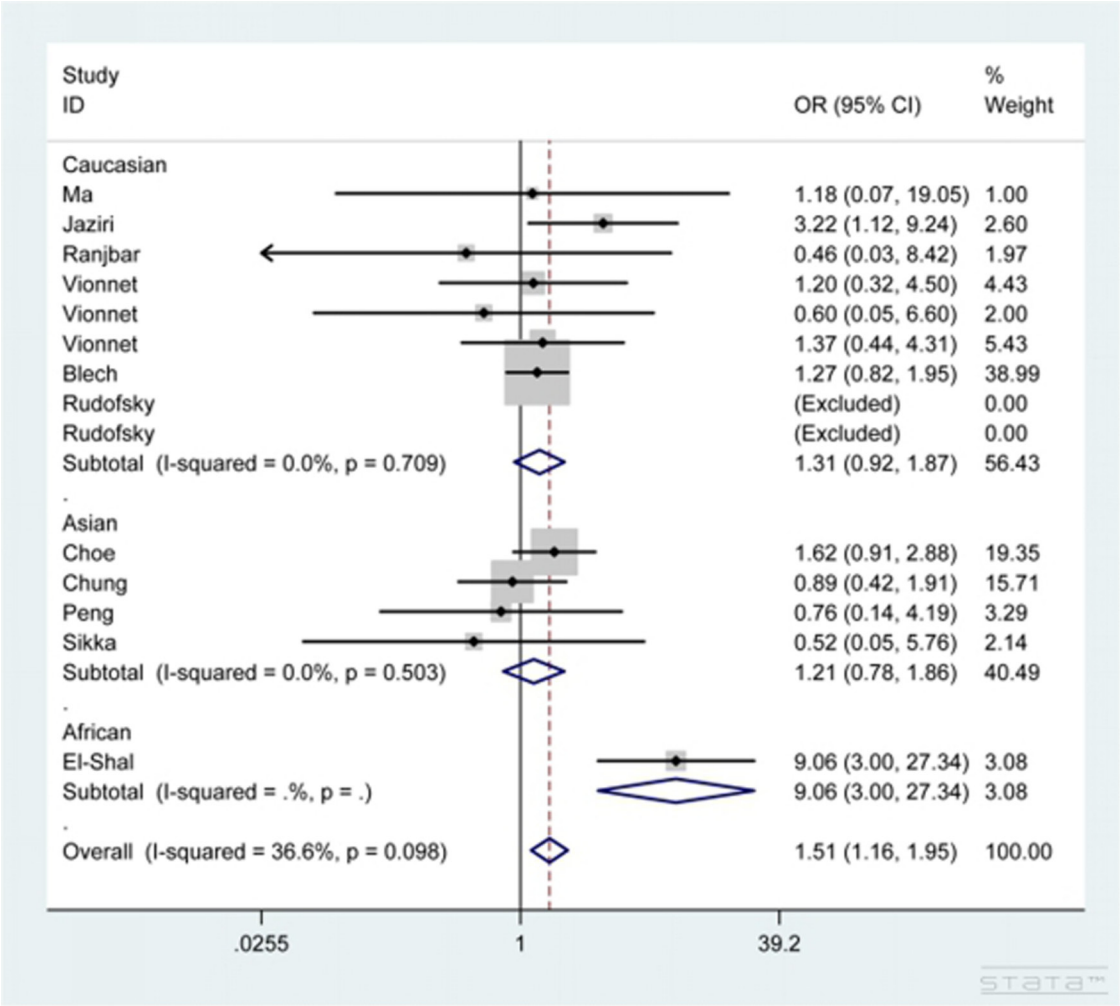

Figure 2: Forest plot for the association between *ADIPOQ* rs2241766 polymorphism and DN risk under GG vs. TT contrast. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

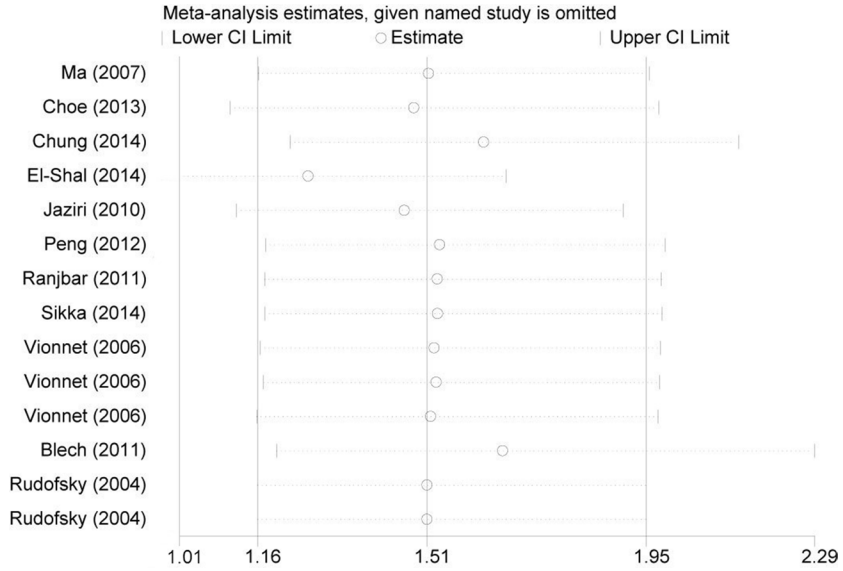

Figure 3: Sensitivity analysis for test the stability of overall estimate under GG vs. TT contrast.

Table 2: Meta-analysis of the association between *ADIPOQ* rs2241766 polymorphism and DN risk

Model		Ethnicity			Type			Total
		Caucasian	Asian	African	T1DM	T2DM	T2DM or T1DM	
GG vs. TT	OR (95%CI)	1.31 (0.92, 1.87)	1.21 (0.78, 1.86)	9.06 (3.00, 27.34)	1.18 (0.54, 2.56)	1.72 (0.84, 3.51)	1.27 (0.82, 1.95)	1.51 (1.16, 1.95)
	Ph	0.709	0.503	/	0.945	0.016	/	0.098
	I^2 test	0.0%	0.0%	/	0.0%	61.6%	/	36.6%
GG + TG vs. TT	OR (95%CI)	1.27 (1.01, 1.60)	0.86 (0.69, 1.07)	4.80 (2.86, 8.03)	1.26 (0.82, 1.93)	1.25 (0.81, 1.93)	1.15 (0.96, 1.37)	1.25 (0.98, 1.59)
	Ph	0.006	0.864	/	0.002	0.000	/	0.000
	I^2 test	62.9%	0.0%	/	77.1%	83.0%	/	77.9%
GG vs. TT + TG	OR (95%CI)	1.26 (0.88, 1.79)	1.34 (0.88, 2.03)	4.34 (1.48, 12.68)	1.15 (0.53, 2.50)	1.68 (1.18, 2.39)	1.22 (0.79, 1.87)	1.43 (1.11, 1.85)
	Ph	0.800	0.483	/	0.955	0.229	/	0.537
	I^2 test	0.0%	0.0%	/	0.0%	26.1%	/	0.0%
G vs. T	OR (95%CI)	1.12 (1.01, 1.25)	0.95 (0.80, 1.13)	3.16 (2.12, 4.71)	1.05 (0.87, 1.26)	1.19 (0.81, 1.75)	1.13 (0.97, 1.31)	1.13 (0.93, 1.38)
	Ph	0.245	0.690	/	0.540	0.000	/	0.000
	I^2 test	24.1%	0.0%	/	0.0%	82.8%	/	71.4%
TG vs. TT	OR (95%CI)	1.12 (0.98, 1.27)	0.81 (0.65, 1.02)	4.26 (2.50, 7.28)	1.04 (0.85, 1.27)	1.18 (0.72, 1.91)	1.13 (0.94, 1.36)	1.11 (0.88, 1.40)
	Ph	0.547	0.885	/	0.580	0.000	/	0.000
	I^2 test	0.0%	0.0%	/	0.0%	82.7%	/	70.3%

Note: *Ph*: *P* value of heterogeneity; If *Ph* > 0.05, a fixed-effect model was used to calculate OR and 95% CI, or else, the random-effect model was conducted.

observed a risk-increasing effect of *ADIPOQ* rs2241766 polymorphism on DN susceptibility under GG vs. TT, and GG vs. TT+TG models. The subgroup analyses based on ethnicity and disease type also revealed such a positive correlation between the SNP and the disease risk in Caucasian, African and T2DM groups.

Results of previous studies regarding the effects of *ADIPOQ* rs2241766 polymorphism on susceptibility to DN remains confusing. In a study among patients with T2DM, the GG genotype of the polymorphism rs2241766 was found to be significantly associated with the risk of DN after adjusting interfering factors [24]. In a study

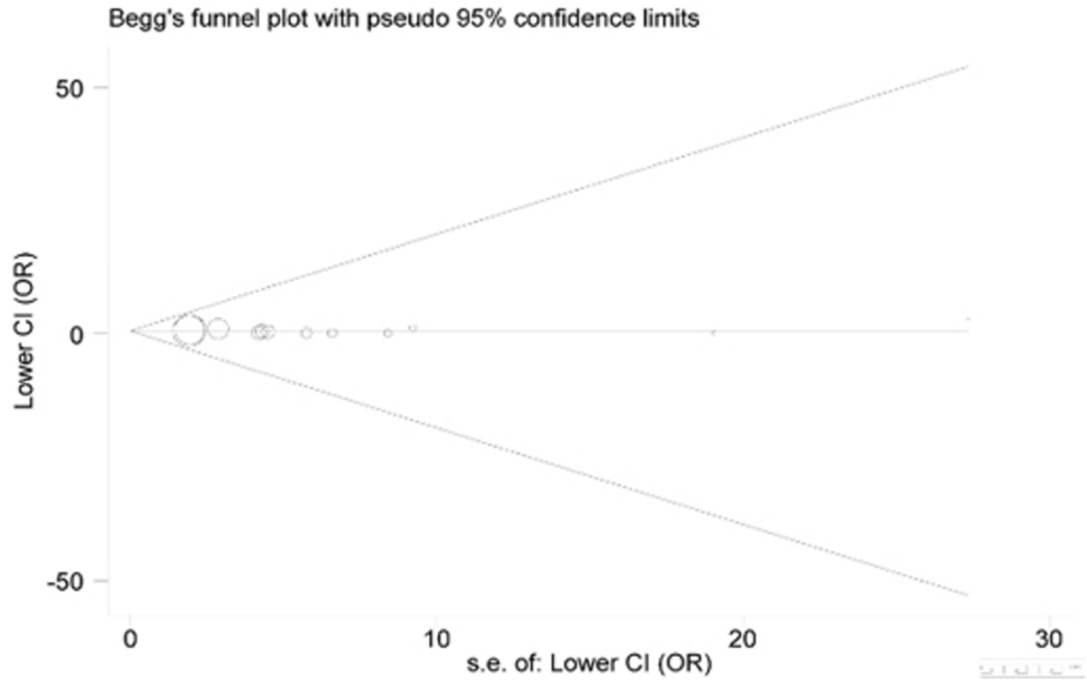

Figure 4: Begg's funnel plot for publication bias under GG vs. TT contrast. Each point represents a separate study for the indicated association. Log(OR), natural logarithm of OR. Horizontal line, mean effect size.

among Taiwanese by Chung et al., the SNP was also observed to participate the progression of DN under TT vs. GT+GG, GG/GT/TT, and allele T vs. allele G models among male subjects [28]. Another study among an Egyptian population also suggested a similar correlation of the SNP with DN susceptibility [29]. In contrast, Ma et al. found no independent role of rs2241766 in nephropathy development among Swedish Caucasians [25]. Neither did in three other studies by Sikka et al., Peng et al., and Rudofsky et al., respectively [27, 30, 31].

There are several possible reasons leading to the above controversy. First of all, subjects recruited by the above studies belonged to different ethnic lines. Secondly, confounding exogenous factors such as age, gender, and lifestyles were not adjusted in all studies. Thirdly, the limited number of study participants might reduce authoritativeness of some study results. Of course, some meta-analyses related to our studied topic have already been performed, such as the one by Lin et al. [41] and one by Cai et al. [42]. However, the meta-analysis by Lin and colleagues only enrolled 7 articles with 9 independent studies on our studied polymorphism while we selected 14 eligible studies from 11 papers. As for the meta-analysis by Cai and colleagues, it only concerned on DN in type 2 diabetes.

Our meta-analysis has many advantages compared to the above studies, such as a relatively larger sample size. However, some limitations of the present study should also be mentioned. To begin with, unpublished studies with null results were not enrolled in this meta-analysis, thus possibly introducing certain publication, though not significant. Next, the number of studies for stratification analyses was relatively small, thus affecting the comprehensiveness of conclusions. Finally, possible interplays of our studied SNP with other relevant factors were not analyzed owing to limited information.

All in all, the present meta-analysis indicated that *ADIPOQ* rs2241766 polymorphism might be related to increased risk of DN occurrence, which was more evident in Caucasian and Asian people, as well as among T2DM patients. In view of the above-mentioned limitations, these results need to be further verified in future by studies with larger scales.

MATERIALS AND METHODS

Search strategy

A comprehensive literature search was conducted in electronic databases including Embase, PubMed, Medline, Cochrane Library, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) using different combinations of the following keywords: "diabetic nephropathy" or "diabetic kidney disease" or "DN", "adiponectin" or "*ADIPOQ*", and "polymorphism" or "variant" or "mutant" or "single nucleotide polymorphism" or "SNP". Further relevant articles were obtained by reviewing the reference lists of articles included.

Selection criteria

The following inclusion criteria were set for the present meta-analysis: (1) with both case and control subjects; (2) evaluating the correlation between *ADIPOQ* rs2241766 polymorphism and susceptibility to DN; (3) providing sufficient information such as genotype frequency for evaluation of odds ratios (ORs) and 95% confidence intervals (95% CIs); and (4) full-text articles with human subjects. Studies meeting any one of the following criteria were considered ineligible for the present meta-analysis: (1) conference abstracts, comments, reviews, case reports, or editorials; (2) with insufficient data for OR calculation; (3) with no control group; and (4) animal studies.

Quality assessment

We evaluated the quality of all included studies using the Newcastle-Ottawa Scale (NOS). The NOS is composed of 3 aspects: selection, comparability and exposure, with a total score of 9. According to the final score, the studies could be categorized into high-quality (score more than 6), medium-quality (score between 4 and 6) and low-quality (score less than 4).

Data extraction

The data extraction was conducted by two reviewers independently. Conflicting opinions were resolved through discussion to reach a final consensus. The items extracted from each eligible study included: first author's name, publication year, region, ethnicity, disease type, total cases and controls, genotype and/or allele frequencies in case and control groups, genotyping method, and evidence for Hardy-Weinberg Equilibrium (HWE) in controls.

Statistical analysis

STATA software (version 12.0) was used to conduct all data syntheses in this meta-analysis. The strength of relationship between *ADIPOQ* rs2241766 polymorphism and DN susceptibility was determined by calculating pooled ORs and 95% CIs. The inter-study heterogeneity assumption was examined by means of χ^2-based Q-statistic and I^2 test. If heterogeneity was significant ($P < 0.05$ of the Q test or $I^2 > 50\%$), the summarized OR estimates were calculated utilizing the random-effects model (DerSimonian and Laird method); otherwise, the fixed-effects model (Mantel-Haenszel method) was applied. Additionally, when between-heterogeneity was significant, we would assume meta regression analysis to identify potential sources of such heterogeneity. Begg's funnel plots and Egger's

linear regression test were used to evaluate possible publication bias among included studies. The stability of combined results was examined by performing the sensitivity analysis, in which each of included studies was sequentially deleted and then summary ORs were recalculated so as to observe alteration between original and re-obtained ones. The statistical significance of all tests was denoted at $P < 0.05$.

CONFLICTS OF INTEREST

None.

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