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Retraction notice

Journal of the Renin-Angiotensin-Aldosterone System
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DOI: 10.1177/1470320314557849
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The following articles have been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System* (*JRAAS*) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

jraas

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(1) 165–171

DOI: 10.1177/1470320314557849
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RETRACTED: Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

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Abstract

Background and objective: The association of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism with type-2 diabetic nephropathy (T2DN) susceptibility and the risk of type-2 diabetes mellitus (T2DM) developing into T2DN in Caucasian populations is still controversial. A meta-analysis was performed to evaluate the association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in Caucasian populations.

Method: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: Sixteen articles were identified for the analysis of the association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in Caucasian populations. ACE I/D gene polymorphism was not associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. Sensitivity analysis according to sample size of case (<100 vs. ≥100) was also performed, and the results were similar to the non-sensitivity analysis.

Conclusions: ACE I/D gene polymorphism was not associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. However, more studies should be performed in the future.

Keywords

Type-2 diabetic nephropathy (T2DN), type-2 diabetes mellitus (T2DM), angiotensin-converting enzyme (ACE), insertion/deletion (I/D) gene polymorphism, meta-analysis

Date received: 14 September 2014; accepted: 28 September 2014

Introduction

Angiotensin-converting enzyme (ACE), converting angiotensin I into angiotensin II, inactivates bradykinin via the kallikrein–kininogen system, and angiotensin II is the main effector molecule of the renin–angiotensin system, is pleiotropic, and is a mediator of the development and progression of diseases.[1] The ACE insertion/deletion (I/D) gene polymorphism is a 287-bp sequence of DNA in intron 16 of the ACE gene.[2] The ACE gene consists of either an insertion (I) allele or a deletion (D) allele that form three possible genotypes: II, ID or DD.[3] In adults, plasma ACE does not change with age and is influenced by environmental or lifestyle factors only to a minor extent.[2] Compared with II homozygotes, circulating ACE levels in plasma were found to be nearly 30% and 60% higher in ID heterozygotes and DD homozygotes, respectively.[3] Moreover, DD homozygotes also have higher tissue levels of ACE. The ACE I/D gene polymorphism, correlating with circulating ACE concentration, may be implicated in

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the etiology of type-2 diabetic nephropathy (T2DN) and has been investigated in numerous epidemiologic studies to date.

Diabetes mellitus includes type-1 diabetes mellitus and type-2 diabetes mellitus (T2DM), and the incidence of diabetes mellitus has increased dramatically over the last several decades.[4] Diabetic nephropathy (DN), a serious complication of diabetes mellitus, includes type-1 diabetic nephropathy (T1DN) due to type-1 diabetes mellitus and T2DN due to T2DM.[4,5] Some 30–40% of diabetic patients develop DN, associated with a poor life expectancy and end-stage renal disease, causing serious socioeconomic problems.[6]

The present epidemiologic study aims to evaluate the association of the ACE I/D gene polymorphism in the etiology of T2DN and the risk of patients with T2DM developing T2DN. However, the available evidence reported to date is weak, due to sparseness of data or disagreements among studies. There is little meta-analysis exploring the association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. We performed this meta-analysis from all reports published in English to investigate the relationship between ACE I/D gene polymorphism and T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations, with the intention to provide a much more reliable finding on the significance of the association.

Materials and methods

Search strategy

Relevant studies were identified from the PubMed and Cochrane Library electronic databases on 1 March 2014. The term "(diabetic nephropathy) AND (angiotensin-converting enzyme) AND (polymorphism OR variant)" was entered into PubMed and the Cochrane Library. The search in PubMed was limited to humans and English language. We also extended the search spectrum to the "related articles" and the bibliographies of all recruited studies. If multiple publications from the same study group occurred, we only used the most complete paper for our analysis.

Inclusion and exclusion criteria

Inclusion criteria were: (1) a case–control study; (2) the outcome had to be T2DN; (3) there had to be at least two comparison groups (T2DN group vs. control group); and (4) the study should be conducted in a Caucasian population.

Exclusion criteria were: (1) review articles, editorials and case reports; (2) articles that did not provide detailed genotype data; (3) articles investigating the association of other genes with T2DN; (4) articles investigating the role of ACE in diseases; and (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by two investigators: first author's surname, year of publication, ethnicity of study population, and the number of cases and controls for ACE I/D genotype. Frequencies of the D allele were calculated for case group and control group, from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5, Oxford, UK) and analyzed. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the p-value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. A value of $p < 0.05$ was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies. Sensitivity analysis was performed according to sample size of case (<100 vs. ≥100). The Begg adjusted rank correlation test[18] and the Egger regression asymmetry test[19] were used for exploring publication bias ($p < 0.1$ was considered significant) when the sample number was more than 10.

Results

Study characteristics

The search yielded 261 references, 260 from PubMed and one from Cochrane Library. According to the inclusion and exclusion criteria, 16 articles[7-22] were identified for the analysis of ACE I/D gene polymorphism and T2DN susceptibility and the risk of T2DM developing into T2DN in Caucasian populations in our review. Five studies[7-11] were conducted on the relationship between ACE I/D gene polymorphism and T2DN susceptibility (Table 1), and 15 reports[7-10,12-22] were conducted on the relationship between ACE I/D gene polymorphism and the susceptibility of T2DM developing into T2DN (Table 2).

Association of the ACE I/D gene polymorphisms with T2DN risk

In this meta-analysis, ACE I/D gene polymorphisms was not associated with T2DN risk in Caucasian populations (D allele: OR = 1.10, 95% CI: 0.95–1.28, $p = 0.19$; DD genotype: OR = 1.11, 95% CI: 0.84–1.47, $p = 0.46$; II

Table 1. Characteristics of the studies evaluating the effects of ACE I/D gene polymorphism on T2DN risk.

First author, year	T2DN						Control					
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total(allele)
Gutiérrez, 1997	–	–	–	60	76	120	–	–	–	90	104	180
Schmidt, 1997	121	129	61	311	371	622	83	119	54	256	285	512
Araz, 2001	34	64	18	116	132	232	52	65	21	138	169	276
Arzu Ergen, 2004	9	11	5	25	29	50	10	22	5	37	42	74
Buraczynska, 2004	–	–	–	–	158	282	–	–	–	–	548	1040

Table 2. Characteristics of the studies evaluating the effects of ACE I/D gene polymorphism on T2DM developing into T2DN.

First author, year	T2DN						T2DM					
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)
Fujisawa, 1995	7	23	24	54	37	108	6	12	17	35	24	70
Dudley, 1995	47	85	31	163	179	326	70	148	49	267	288	534
Ringel, 1997	44	84	33	161	172	322	35	69	36	140	139	280
Schmidt, 1997	121	129	61	311	371	622	131	154	62	347	416	694
Gutiérrez, 1997	–	–	–	–	76	120	–	–	–	–	62	200
Jeffers, 1997	23	–	–	50	–	–	139	–	–	459	–	–
Grzeszczak, 1998	129	230	103	462	488	924	73	118	63	254	264	508
Huang, 1998	9	11	4	24	29	48	22	30	7	59	74	118
Araz, 2001	34	64	18	116	132	232	43	57	23	123	143	246
Fradin, 2002	38	61	18	117	137	234	44	54	20	118	142	236
Hadjadj, 2003	1119	1468	552	3139	3706	6278	208	282	115	605	698	1210
Arzu Ergen, 2004	9	11	5	25	29	50	24	21	5	50	69	100
Canani, 2005	126	181	66	373	433	746	181	308	120	609	670	1218
Eroglu 2008	16	17	13	46	49	92	19	24	13	56	62	112
Palomo–Piñón, 2009	43	105	87	235	191	470	24	91	85	200	139	400

genotype: OR = 0.97, 95% CI: 0.69–1.37, $p = 0.87$; Figure 1 and Table 3).

Sensitivity analysis for the relationship between ACE I/D gene polymorphism and T2DN risk in Caucasian populations was also performed according to sample size of case (<100 vs. ≥100). We found that the results were similar to the non-sensitivity analysis. ACE I/D gene polymorphisms were not associated with T2DN risk in Caucasian populations (Table 3).

Association of ACE I/D gene polymorphisms with the risk of T2DM patients developing into T2DN

In this meta-analysis, ACE I/D gene polymorphisms were also not associated with the risk of patients with T2DM developing T2DN in Caucasian populations (D allele: OR = 1.10, 95% CI: 0.97–1.26, $p = 0.15$; DD genotype: OR = 1.08, 95% CI: 0.97–1.20, $p = 0.16$; II genotype: OR = 0.92, 95% CI: 0.81–1.04, $p = 0.16$; Figure 2 for D allele, Figure 3 for DD genotype and Figure 4 for II genotype; Table 3).

Sensitivity analysis for the relationship between ACE I/D gene polymorphism and the risk of T2DM developing into T2DN in Caucasian populations was also performed according to sample size of case (<100 vs. ≥100). We found that the results were similar to the non-sensitivity analysis. ACE I/D gene polymorphisms were not associated with the risk of patients with T2DM developing T2DN in Caucasian populations (Table 3).

Evaluation of publication bias

No significant publication bias was found in the comparison of T2DN vs. T2DM (Begg $p = 1.000$, Egger $p = 0.895$; Figure 5 for Begg test).

Discussion

The dysfunction of ACE generation brought about by gene polymorphism is considered the major deterioration factor to associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. There are few data about genetic molecular markers

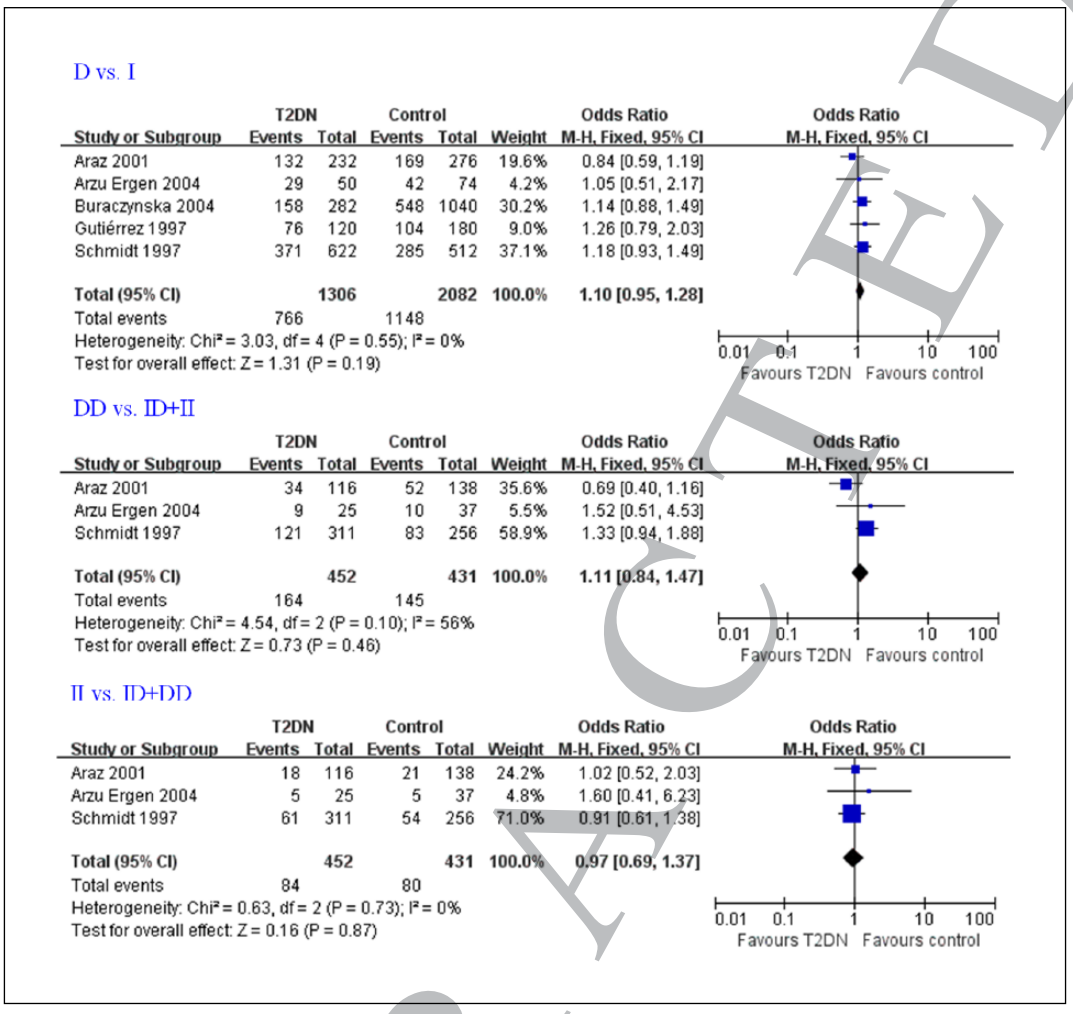

Figure 1. Association of ACE I/D gene polymorphism on T2DN susceptibility (T2DN vs. Control).

to predict the onset of T2DN and the risk of patients with T2DM developing into T2DN in Caucasian populations. This meta-analysis was performed to explore whether the ACE I/D gene polymorphism could predict the susceptibility of T2DN susceptibility and the risk of patients with T2DM developing into T2DN in Caucasian populations.

Al-Rubeaan et al.[23] conducted a meta-analysis to explore the relationship between ACE I/D gene polymorphism and the risk of T2DM, and reported that the ACE I/D polymorphism was found to be significantly associated with T2DM risk among the Arab population, whereas among Caucasians, this association was not found. However, was there an association between ACE I/D gene polymorphism and T2DN susceptibility or the risk of patients with T2DM developing into T2DN in Caucasian population? The meta-analysis was performed to assess this relationship.

In our meta-analysis, the relationship between ACE I/D gene polymorphism and the susceptibility of T2DN in Caucasian populations was assessed. We found that ACE I/D gene polymorphism was not associated with T2DN susceptibility in Caucasian populations. Furthermore, the results from the sensitivity analysis were similar to those from the non-sensitivity analysis. However, the number of included studies was small (only five studies included for meta-analysis), and the evidence was less robust. More studies should be performed in the future.

In this meta-analysis, the relationship between ACE I/D gene polymorphism and the risk of patients with T2DM developing T2DN in Caucasian populations was also assessed. We found that ACE I/D gene polymorphism was not associated with T2DN susceptibility. Furthermore, the results from the sensitivity analysis were similar to those from the non-sensitivity analysis, and there was no significant publication bias. The number of included studies was large, and the evidence may be robust to some extent.

In our investigation, we found that ACE I/D gene polymorphism was not associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN. However, these findings should be regarded with caution because many other factors, such as heterogeneity of

Table 3. Meta-analysis of the association of ACE I/D gene polymorphism with risk of T2DN and the T2DM developing into T2DN.

Genetic contrasts	Number of studies	*Q* test *p*-value	Model selected	OR (95%CI)	*p*
T2DN vs. Control					
D vs. I	5	0.55	Fixed	1.10(0.95, 1.28)	0.19
DD vs. (ID+II)	3	0.10	Fixed	1.11(0.84, 1.47)	0.46
II vs. (ID+DD)	3	0.73	Fixed	0.97(0.69, 1.37)	0.87
T2DN vs. Control (Sensitivity analysis: ≥100)					
D vs. I	3	0.26	Fixed	1.09(0.93, 1.28)	0.29
DD vs. (ID+II)	2	0.04	Random	0.98(0.52, 1.87)	0.96
II vs. (ID+DD)	2	0.78	Fixed	0.94(0.66,1.34)	0.73
T2DN vs. Control (Sensitivity analysis: <100)					
D vs. I	2	0.68	Fixed	1.20(0.80, 1.78)	0.38
DD vs. (ID+II)	1	–	Fixed	1.52(0.51, 4.53)	0.45
II vs. (ID+DD)	1	–	Fixed	1.60(0.41, 6.23)	0.50
T2DN vs. T2DM					
D vs. I	14	0.001	Random	1.10(0.97, 1.26)	0.15
DD vs. (ID+II)	14	0.54	Fixed	1.08(0.97, 1.20)	0.16
II vs. (ID+DD)	13	0.94	Fixed	0.92(0.81, 1.04)	0.16
T2DN vs. T2DM (Sensitivity analysis: ≥ 100)					
D vs. I	9	0.87	Fixed	1.07(0.99, 1.15)	0.08
DD vs. (ID+II)	9	0.63	Fixed	1.07(0.96, 1.20)	0.23
II vs. (ID+DD)	9	0.96	Fixed	0.90(0.79, 1.02)	0.10
T2DN vs. T2DM (Sensitivity analysis: < 100)					
D vs. I	5	<0.0001	Random	1.17(0.58, 2.36)	0.66
DD vs. (ID+II)	5	0.25	Fixed	1.18(0.81, 1.71)	0.39
II vs. (ID+DD)	4	0.66	Fixed	1.22(0.73, 2.05)	0.45

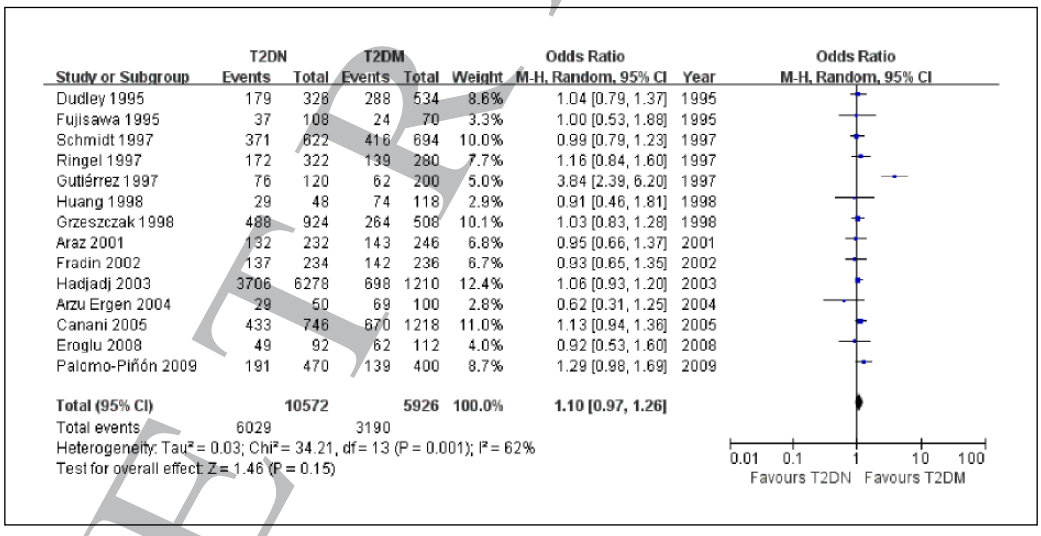

Figure 2. Association of ACE D allele on the risk of T2DM developing into T2DN (T2DN vs. T2DM).

enrolled cases, limited statistical power, variable study designs and different interventions, could affect the results. Undoubtedly, the limitations mentioned above might affect our final conclusions.

In conclusion, the results in our study support that ACE I/D gene polymorphism was not associated with T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations. However, more association investigations on larger, stratified populations are required to further clarify the role of ACE I/D gene polymorphism in T2DN susceptibility and the risk of patients with T2DM developing T2DN in Caucasian populations.

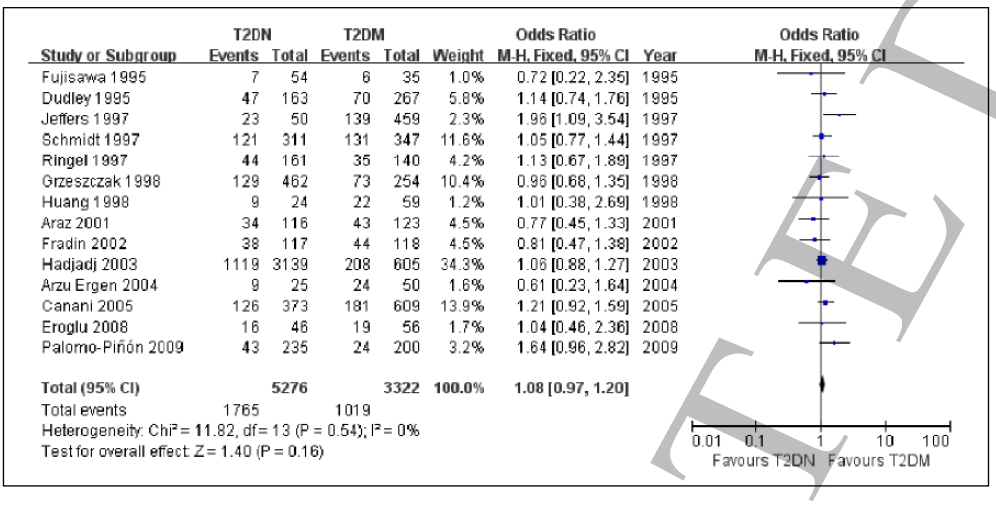

Figure 3. Association of ACE DD genotype on the risk of T2DM developing into T2DN (T2DN vs. T2DM).

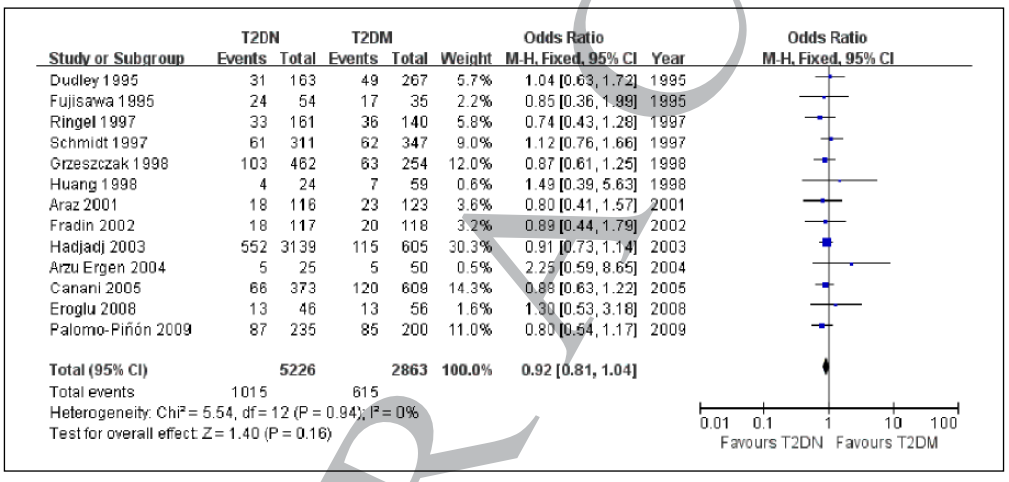

Figure 4. Association of ACE II genotype on the risk of T2DM developing into T2DN (T2DN vs. T2DM).

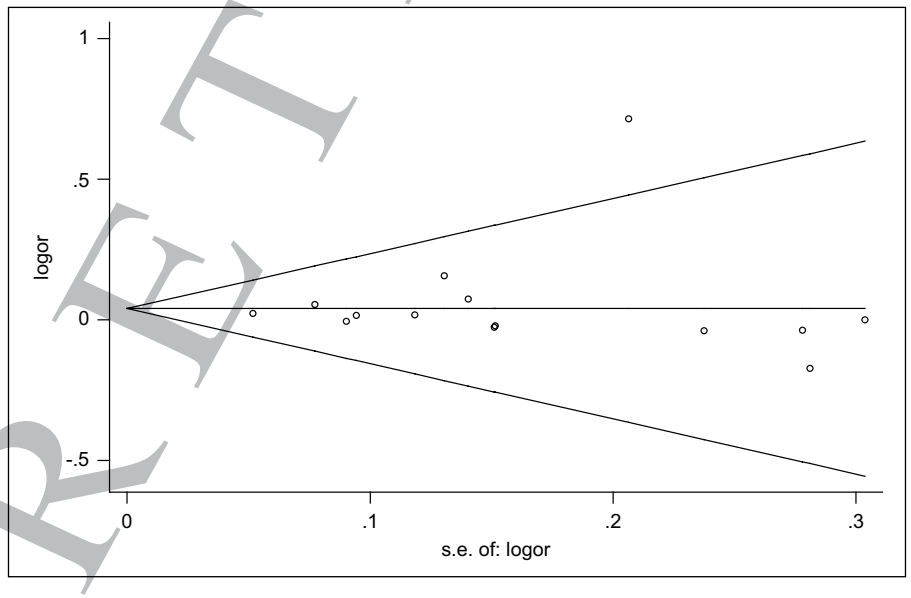

Figure 5. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of ACE I/D gene polymorphism with the risk of T2DM developing into T2DN.

Conflict of interest

None declared.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP51

DOI: 10.1177/1470320314568521
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This article has been included in a multiple retraction:

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

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After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System* (*JRAAS*) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

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Original Article

jraas

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP52–NP56

DOI: 10.1177/1470320314568521
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RETRACTED: Association of the *ACE* I/D gene polymorphism with sepsis susceptibility and sepsis progression

Chun-Hua Yang[1] and Tian-Biao Zhou[2]

Abstract

Aim: Association of the angiotensin-converting enzyme (*ACE*) insertion/deletion (I/D) gene polymorphism with sepsis susceptibility and sepsis progression is still controversial. This study was performed to evaluate the association of the *ACE* I/D gene polymorphism with sepsis susceptibility and sepsis progression using a meta-analysis method.

Methods: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: The *ACE* DD genotype was associated with sepsis susceptibility (DD genotype: OR = 0.69, 95% CI: 0.51–0.92, p = 0.01). However, the *ACE* D allele and II genotype were not associated with sepsis susceptibility. Furthermore, the *ACE* I/D gene polymorphism was not associated with sepsis progression.

Conclusions: The *ACE* DD genotype was associated with sepsis susceptibility. However, more studies should be performed in the future.

Keywords

Sepsis susceptibility, sepsis progression, angiotensin-converting enzyme (*ACE*), insertion/deletion (I/D) gene polymorphism, meta-analysis

Date received: 08 December 2014; accepted: 16 December 2014

Introduction

Sepsis is a systemic inflammatory response that follows bacterial infection, and sepsis and sepsis-associated multi-organ failure represent the major cause of mortality in intensive care units worldwide.[1,2] Sepsis progression (mortality) is most often attributed to the development of multiple organ failure. In sepsis, inflammation-mediated endothelial activation, defined as a proinflammatory and procoagulant state of the endothelial cells, has been associated with severity of disease.[3]

The angiotensin-converting enzyme (*ACE*) insertion/deletion (I/D) gene polymorphism is a 287-bp sequence of DNA in the intron 16 of the *ACE* gene, and the *ACE* gene includes either an insertion (I) allele or a deletion (D) allele that form three possible genotypes: II, ID or DD.[4,5] *ACE*, directly involved in the process of cell proliferation, differentiation, apoptosis and angiogenesis,[6] can convert angiotensin I into angiotensin II, and angiotensin II is the main effector molecule of the renin-angiotensin system, is pleiotropic, and is a mediator of the development and progression of diseases.[7] The *ACE* I/D gene polymorphism, correlating with circulating ACE concentration, might be implicated in the etiology of sepsis and has been investigated in some epidemiologic studies.

Present epidemiologic studies show that the *ACE* I/D gene polymorphism has been implicated in the etiology of sepsis and sepsis progression. However, the available evidence reported to date is weak owing to the sparseness of the data or disagreements among studies. We performed this meta-analysis to investigate the relation between the *ACE* I/D gene polymorphism and sepsis susceptibility and sepsis progression.

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Table 1. Characteristics of the studies evaluating the effects of *ACE* I/D gene polymorphism on sepsis susceptibility and sepsis progression.

First author, year	Case						Control					
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)
Sepsis susceptibility												
Villar, 2008[8]	77	94	41	212	248	424	152	155	57	364	459	728
Cogulu, 2008[9]	21	52	25	98	94	196	102	129	56	287	333	574
Bunker-Wiersma, 2008[10]	16	26	11	53	58	106	38	64	33	135	140	270
Davis, 2010[11]	5	15	8	28	25	56	12	22	19	53	46	106
Spiegler, 2010[12]	60	142	44	246	262	492	281	482	200	963	1044	1926
Sepsis progression												
Villar, 2008[8]	32	46	17	95	110	190	45	48	24	117	138	234
Cogulu, 2008[9]	4	6	4	14	14	28	17	46	21	84	80	168
Tsantes, 2012[13]	66	90	31	187	222	374	60	90	31	181	210	362

ACE: angiotensin-converting enzyme; I/D: insertion/deletion.

Materials and methods

Search strategy

The relevant studies were searched from the electronic databases of PubMed and Cochrane Library on October 1, 2014. The terms "Sepsis AND (angiotensin converting enzyme OR ACE)" were entered into PubMed and Cochrane Library for the search. We also extended the search spectrum to "related articles" and the bibliographies of all recruited studies.

Inclusion and exclusion criteria

Inclusion criteria. Inclusion criteria included: (1) a case-control study or a prospective study; (2) the outcome had to be sepsis; (3) there had to be at least two comparison groups (sepsis group vs control group or sepsis group vs sepsis progression group).

Exclusion criteria. Exclusion criteria included: (1) review articles, editorials and case reports; (2) articles that did not provide the detailed genotype data; (3) investigating the association of other genes with sepsis; (4) investigating the role of *ACE* in diseases; (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by two investigators: first author's surname, year of publication, and the number of cases and controls for the *ACE* I/D genotype. Frequencies of the D allele were calculated for the case group and control group from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5, Oxford, UK) and analyzed. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the p value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. $P < 0.05$ was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies.

Results

Study characteristics

The search yielded 144 references, 141 from PubMed, and three from Cochrane Library. According to the inclusion and exclusion criteria, six articles[8–13] were identified for the analysis between the *ACE* I/D gene polymorphism and sepsis susceptibility and sepsis progression in our meta-analysis. Five studies[8–12] were conducted on the relationship between the *ACE* I/D gene polymorphism and sepsis susceptibility (Table 1), and three reports[8,9,13] were conducted on the relationship between the *ACE* I/D gene polymorphism and sepsis progression (Table 1).

Association of the ACE I/D gene polymorphism with sepsis risk

In this meta-analysis, the *ACE* DD genotype was associated with sepsis risk, but the D allele and II genotype were not (DD genotype: OR = 0.75, 95% CI: 0.62–0.92, p = 0.006; D allele: OR = 0.81, 95% CI: 0.61–1.08, p = 0.15; II genotype: OR = 1.01, 95% CI: 0.81–1.27, p = 0.91; Figure 1 and Table 2).

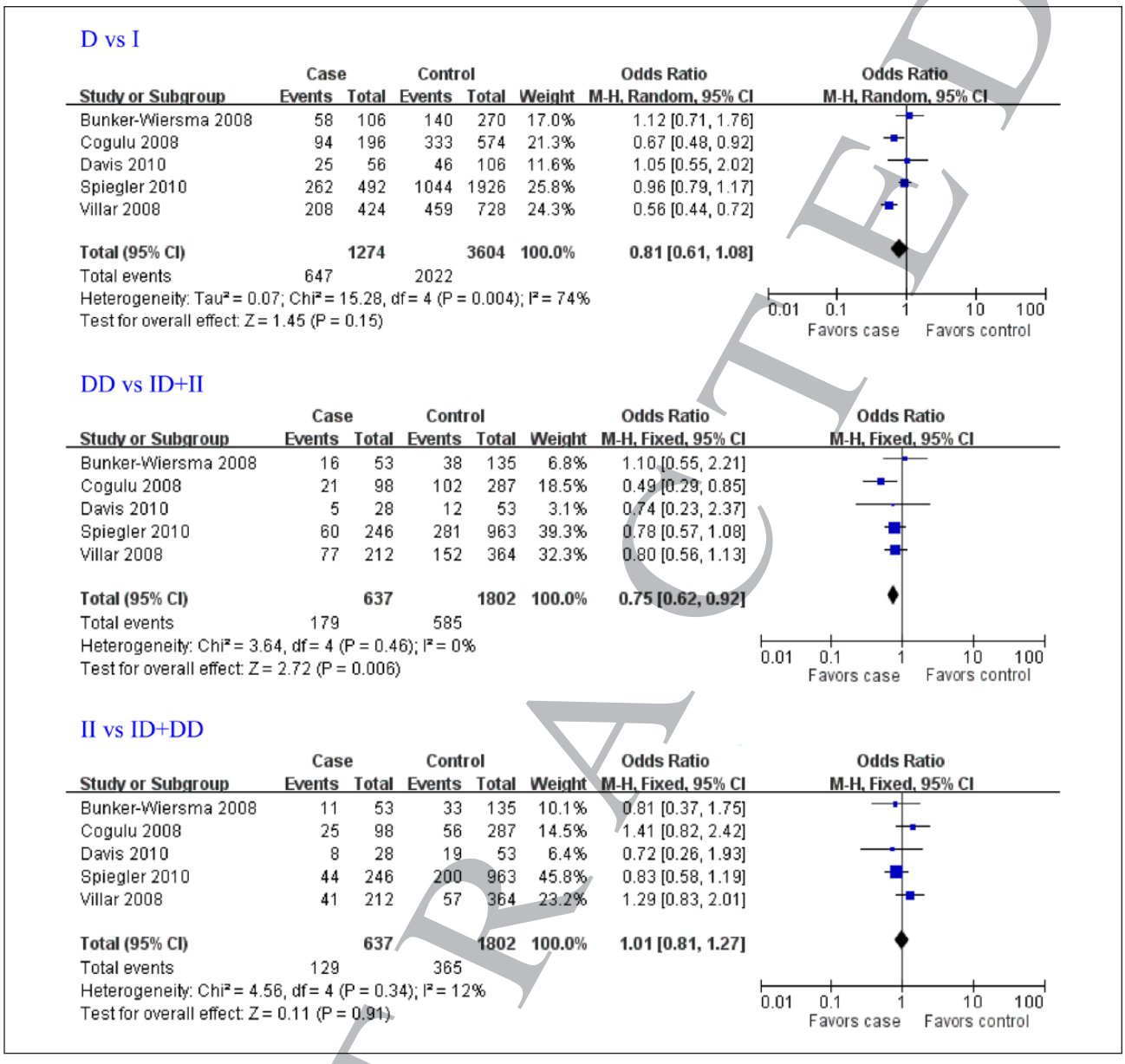

Figure 1. Association of *ACE* I/D gene polymorphism with sepsis susceptibility.
ACE: angiotensin-converting enzyme; I/D: insertion/deletion; M-H: Mantel-Haenszel; CI: confidence interval.

Association of ACE *I/D gene polymorphism with sepsis progression*

In this meta-analysis, the *ACE* I/D gene polymorphism was not associated with sepsis progression (D allele: OR = 1.03, 95% CI: 0.82–1.28, $p = 0.83$; DD genotype: OR = 1.01, 95% CI: 0.73–1.41, $p = 0.94$; II genotype: OR = 0.94, 95% CI: 0.63–1.41, $p = 0.76$; Figure 2 and Table 2).

Discussion

In our previous meta-analyses, we reported that the *ACE* I/D gene polymorphism was associated with the risk of some diseases.[4,14–16] Dysfunction of *ACE* generation brought by the *ACE* I/D gene polymorphism might be considered as an important deterioration factor to be associated with sepsis susceptibility and sepsis progression. There was a rare genetic molecular marker to predict the onset of sepsis and sepsis progression. This study using a meta-analysis method was performed to explore whether the *ACE* I/D gene polymorphism could predict the susceptibility of sepsis and sepsis progression.

In this meta-analysis, the association between the *ACE* I/D gene polymorphism and sepsis susceptibility/sepsis progression was assessed using a meta-analysis method. We found that the *ACE* DD genotype was associated with sepsis

Table 2. Meta-analysis of the association of *ACE* I/D gene polymorphism on sepsis susceptibility and sepsis progression.

Genetic contrasts	Number of studies	*Q* test *p* value	Model selected	OR (95% CI)	*p*
Sepsis susceptibility					
D vs I	5	0.004	Fixed	0.81 (0.61, 1.08)	0.15
DD vs (ID+II)	5	0.46	Fixed	0.75 (0.62, 0.92)	0.006
II vs (ID+DD)	5	0.34	Fixed	1.01 (0.81, 1.27)	0.91
Sepsis progression					
D vs I	3	0.91	Fixed	1.03 (0.82, 1.28)	0.83
DD vs (ID+II)	3	0.55	Fixed	1.01 (0.73, 1.41)	0.94
II vs (ID+DD)	3	0.89	Fixed	0.94 (0.63, 1.41)	0.76

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; OR: odds ratio; CI: confidence interval.

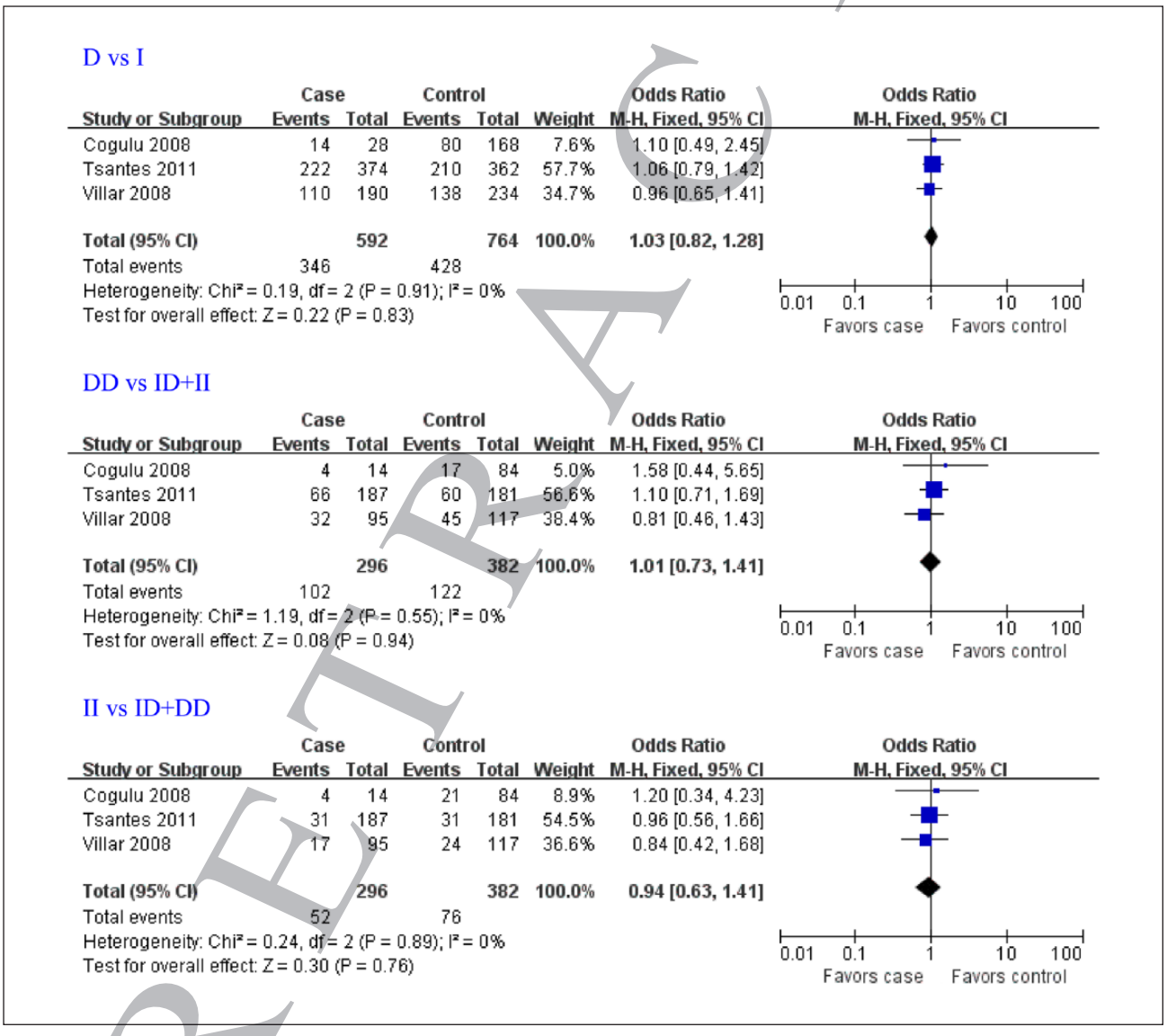

Figure 2. Association of *ACE* I/D gene polymorphism with sepsis progression.
ACE: angiotensin-converting enzyme; I/D: insertion/deletion; M-H: Mantel-Haenszel; CI: confidence interval.

susceptibility (DD genotype: OR = 0.69, 95% CI: 0.51–0.92, $p = 0.01$). However, the *ACE* D allele and II genotype were not associated with sepsis susceptibility. Interestingly, when the fixed model was chosen to calculate for the relationship between the D allele and sepsis risk, we found that the D allele was associated with sepsis risk, but the p value of heterogeneity test was 0.004. The number of included studies was small, and the results should be confirmed in the future. More studies should be performed in the future.

Furthermore, the *ACE* I/D gene polymorphism was not associated with sepsis progression. There were only three included studies recruited into this meta-analysis, and the results should be confirmed in the future. More studies should be performed in the future too.

In this meta-analysis, we found that the *ACE* DD genotype was associated with sepsis susceptibility. However, these findings should be regarded cautiously because many other factors, such as heterogeneity of enrolled cases, limited statistical power, variable study designs and different interventions, were closely related to affect the results. Undoubtedly, the limitations mentioned above might affect our final conclusion.

In conclusion, the results of our study support that the *ACE* DD genotype was associated with sepsis susceptibility. However, the *ACE* D allele and II genotype were not associated with sepsis susceptibility. Furthermore, the *ACE* I/D gene polymorphism was not associated with sepsis progression. However, more association investigations on larger, stratified populations are required to further clarify the role of the *ACE* I/D gene polymorphism in the susceptibility of sepsis and sepsis progression.

Conflict of interest

None declared.

Funding

This work was supported by sub-item 985 of the Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation, no. 88000-3311300).

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Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP35

DOI: 10.1177/1470320314566019
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Retraction notice

This article has been included in a multiple retraction:

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Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP36–NP44

DOI: 10.1177/1470320314566019
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RETRACTED: Association between the *ACE* I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Weiqiang Zhong[1], Zongpei Jiang[2] and Tian-Biao Zhou[2]

Abstract

Background and objective: The association between the angiotensin-converting enzyme (*ACE*) insertion/deletion (I/D) gene polymorphism and type-2 diabetic nephropathy (T2DN) susceptibility and the risk of type-2 diabetes mellitus (T2DM) developing into T2DN in the Asian population is still controversial. This study was performed to evaluate the association of the *ACE* I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in the Asian population using a meta-analysis method.

Methods: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: Twenty-nine articles were identified for an analysis of an association of the *ACE* I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in the Asian population. The *ACE* I/D gene polymorphism was associated with T2DN susceptibility. Furthermore, the *ACE* D allele and II genotype were associated with the risk of patients with T2DM developing T2DN in the Asian population.

Conclusions: The *ACE* I/D gene polymorphism was associated with T2DN susceptibility, and the *ACE* D allele and II genotype were associated with the risk of patients with T2DM developing T2DN in the Asian population. However, more studies should be performed in the future.

Keywords

Type-2 diabetic nephropathy (T2DN), type-2 diabetes mellitus (T2DM), angiotensin-converting enzyme (ACE), insertion/deletion (I/D) gene polymorphism, meta-analysis

Date received: 27 October 2014; accepted: 29 November 2014

Introduction

Diabetes mellitus (DM), a multifactorial metabolic disease characterized by post-prandial hyperglycemia, is the most common cause of chronic kidney disease and end-stage renal disease (ESRD).[1] DM includes type-1 diabetes mellitus (T1DM) and type-2 diabetes mellitus (T2DM), and the incidence of DM has increased dramatically over the last several decades.[2] Diabetic nephropathy (DN), a serious complication of DM, includes type-1 diabetic nephropathy (T1DN) due to type-1 DM and type-2 diabetic nephropathy (T2DN) due to type-2 DM.[2,3] DN as a cause of ESRD is associated with a poor life expectancy, causing serious socioeconomic problems.[4]

The angiotensin-converting enzyme gene (*ACE*) insertion/deletion (I/D) gene polymorphism is a 287-bp sequence of DNA in the intron 16 of the *ACE* gene.[5] The *ACE* gene consists of either an insertion (I) allele or a deletion (D) allele that forms three possible genotypes: II, ID or DD.[6] *ACE*, directly involved in the process of cell proliferation, differentiation, apoptosis and angiogenesis,[7] can convert angiotensin I into angiotensin II, and angiotensin II is the main effector molecule of the renin-angiotensin system, is pleiotropic, and is a mediator of the

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WZ and ZJ contributed equally to this work.

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development and progression of diseases.[8] When compared with II homozygotes, circulating *ACE* levels in plasma were nearly 30% and 60% higher in ID heterozygotes and DD homozygotes, respectively.[6] Moreover, DD homozygotes also have been associated with higher tissue levels of *ACE*. The *ACE* I/D gene polymorphism, correlating with circulating *ACE* concentration, might be implicated in the etiology of T2DN and has been investigated in numerous epidemiologic studies.

Present epidemiologic studies show that the *ACE* I/D gene polymorphism has been implicated in the etiology of T2DN and the risk of patients with T2DM developing T2DN. However, the available evidence reported to date is weak, owing to sparseness of data or disagreements among studies. We performed this meta-analysis to investigate the relation between the *ACE* I/D gene polymorphism and T2DN susceptibility and the risk of patients with T2DM developing T2DN in the Asian population.

Materials and methods

Search strategy

The relevant studies were searched from the electronic databases of PubMed and Cochrane Library on March 1, 2014. The terms "(diabetic nephropathy) AND (angiotensin-converting enzyme) AND (polymorphism OR variant)" were entered into PubMed and Cochrane Library for search. The search in PubMed was limited to humans and the English language. We also extended the search spectrum to the "related articles" and the bibliographies of all recruited studies.

Inclusion and exclusion criteria

Inclusion criteria. The inclusion criteria were: (1) a case-control study or a prospective study; (2) the outcome had to be T2DN; (3) there had to be at least two comparison groups (T2DN group vs control group); and (4) the study should be conducted in the Asian population.

Exclusion criteria. The exclusion criteria were: (1) review articles, editorials and case reports; (2) articles did not provide detailed genotype data; (3) investigating the association of other genes with T2DN; (4) investigating the role of *ACE* in diseases; and (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by two investigators: first author's surname, year of publication, ethnicity of study population, and the number of cases and controls for the *ACE* I/D genotype. Frequencies of the D allele were calculated for the case group and control group, from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5, Oxford, UK) and analyzed. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the p value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. $P < 0.05$ was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies. Sensitivity analysis was performed according to sample size of each case (< 100 vs ≥ 100). The Begg adjusted rank correlation test[9] and the Egger regression asymmetry test[10] were used for exploring publication bias ($p < 0.1$ was considered significant).

Results

Study characteristics

The search yielded 261 references, 260 from PubMed, and one from Cochrane Library. According to the inclusion and exclusion criteria, 29 articles[11–39] were identified for the analysis of the association between the *ACE* I/D gene polymorphism and T2DN susceptibility and the risk of T2DM developing into T2DN in the Asian population in our review. Fourteen studies[11–24] were conducted on the relationship between the *ACE* I/D gene polymorphism and T2DN susceptibility (Table 1), and 27 reports[11–17,20–39] were conducted on the relationship between the *ACE* I/D gene polymorphism and the susceptibility of T2DM developing into T2DN (Table 2).

Association of the ACE I/D gene polymorphism with T2DN risk

In this meta-analysis, the *ACE* I/D gene polymorphism was associated with T2DN risk in the Asian population (D allele: OR = 1.32, 95% CI: 1.13–1.54, $p = 0.0006$; DD genotype: OR = 1.44, 95% CI: 1.04–1.98, $p = 0.03$; II genotype: OR = 0.74, 95% CI: 0.65–0.85, $p < 0.0001$; Figure 1 and Table 3).

Sensitivity analysis for the relationship between the *ACE* I/D gene polymorphism and T2DN risk in the Asian population was also performed according to case sample size (< 100 vs ≥ 100). In the sensitivity analysis according to case sample size ≥100, we found that the results were also similar with the non-sensitivity analysis, except for DD genotype. Furthermore, the *ACE* I/D gene polymorphism was associated with T2DN risk in the Asian

Table 1. Characteristics of the studies evaluating the effects of the *ACE* I/D gene polymorphism on T2DN risk.

First author, year	T2DN						Control					
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)
Mizuiri 1995[11]	19	50	11	80	88	160	14	37	25	76	65	152
Doi 1996[12]	14	30	20	64	58	128	15	42	48	105	72	210
Ohno 1996[13]	15	38	26	79	68	158	8	34	32	74	50	148
Hanyu 1998[14]	4	13	7	24	21	48	13	27	17	57	53	114
Wu 1998[15]	12	18	21	51	42	102	23	44	43	110	90	220
Hsieh 2000[16]	40	59	80	179	139	358	24	106	133	263	154	526
Lee 2002[17]	40	137	117	294	217	588	66	277	330	673	409	1346
Chang 2003[18]	13	60	56	129	86	258	14	42	60	116	70	232
Park 2005[19]	27	49	27	103	103	206	7	51	30	88	65	176
Movva 2007[20]	39	88	47	174	166	348	24	52	35	111	100	222
Naresh 2009[21]	15	11	4	30	41	60	1	17	12	30	19	60
Jayapalan 2010[22]	21	77	77	175	119	350	20	56	61	137	96	274
Al-Harbi 2011[23]	59	39	12	110	157	220	142	160	58	360	444	720
Kumar 2013[24]	98	170	139	407	366	814	72	77	83	232	221	464

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T2DN: type-2 diabetic nephropathy.

Table 2. Characteristics of the studies evaluating the effects of the *ACE* I/D gene polymorphism on T2DM developing into T2DN.

First author, year	T2DN						T2DM					
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)
Mizuiri 1995[11]	19	50	11	80	88	160	9	11	11	31	29	62
Panagiotopoulos 1995[25]	30	50	20	100	110	200	37	38	25	100	112	200
Doi 1996[12]	14	30	20	64	58	128	12	56	56	124	80	248
Ohno 1996[13]	15	38	26	79	68	158	5	15	33	53	25	106
Nakajima 1996[26]	6	25	16	47	37	94	4	19	18	41	27	82
Yoshida 1996[27]	1	–	–	36	–	–	6	–	–	60	–	–
Hanyu 1998[14]	4	13	7	24	21	48	2	5	7	14	9	28
Wu 1998[15]	12	18	21	51	42	102	1	11	6	18	13	36
Kuramoto 1999[28]	3	13	13	29	19	58	9	16	8	33	34	66
Tomino 1999[29]	93	337	311	741	523	1482	54	190	163	407	298	814
Wong 1999[30]	8	38	54	100	54	200	14	45	41	100	73	200
Hsieh 2000[16]	40	59	80	179	139	358	21	50	86	157	92	314
Gohda 2001[31]	85	222	229	536	392	1072	31	92	89	212	154	424
Viswanathan 2001[32]	24	45	17	86	93	172	5	8	10	23	18	46
Lee 2002[17]	40	137	117	294	217	588	39	170	208	417	248	834
Okuno 2003[33]	5	12	21	38	22	76	3	8	1	12	14	24
Prasad 2006[34]	55	75	66	196	185	392	52	97	76	225	201	450
So 2006[35]	93	364	407	864	550	1728	150	526	549	1225	826	2450
Movva 2007[20]	39	88	47	174	166	348	27	74	74	175	128	350
Naresh 2009[21]	15	11	4	30	41	60	7	11	12	30	25	60
Tien 2009[36]	132	64	44	240	328	480	89	117	49	255	295	510
Jayapalan 2010[22]	21	77	77	175	119	350	19	31	31	81	69	162
Al-Harbi 2011[23]	59	39	12	110	157	220	96	75	25	196	267	392
Felehgari 2011[37]	32	30	6	68	94	136	26	32	14	72	84	144
Rahimi 2011[38]	23	36	13	72	82	144	26	32	14	72	84	144
Rahimi 2012[39]	55	66	19	140	176	280	26	32	14	72	84	144
Kumar 2013[24]	98	170	139	407	366	814	56	68	61	185	180	370

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T2DM: type-2 diabetes mellitus; T2DN: type-2 diabetic nephropathy.

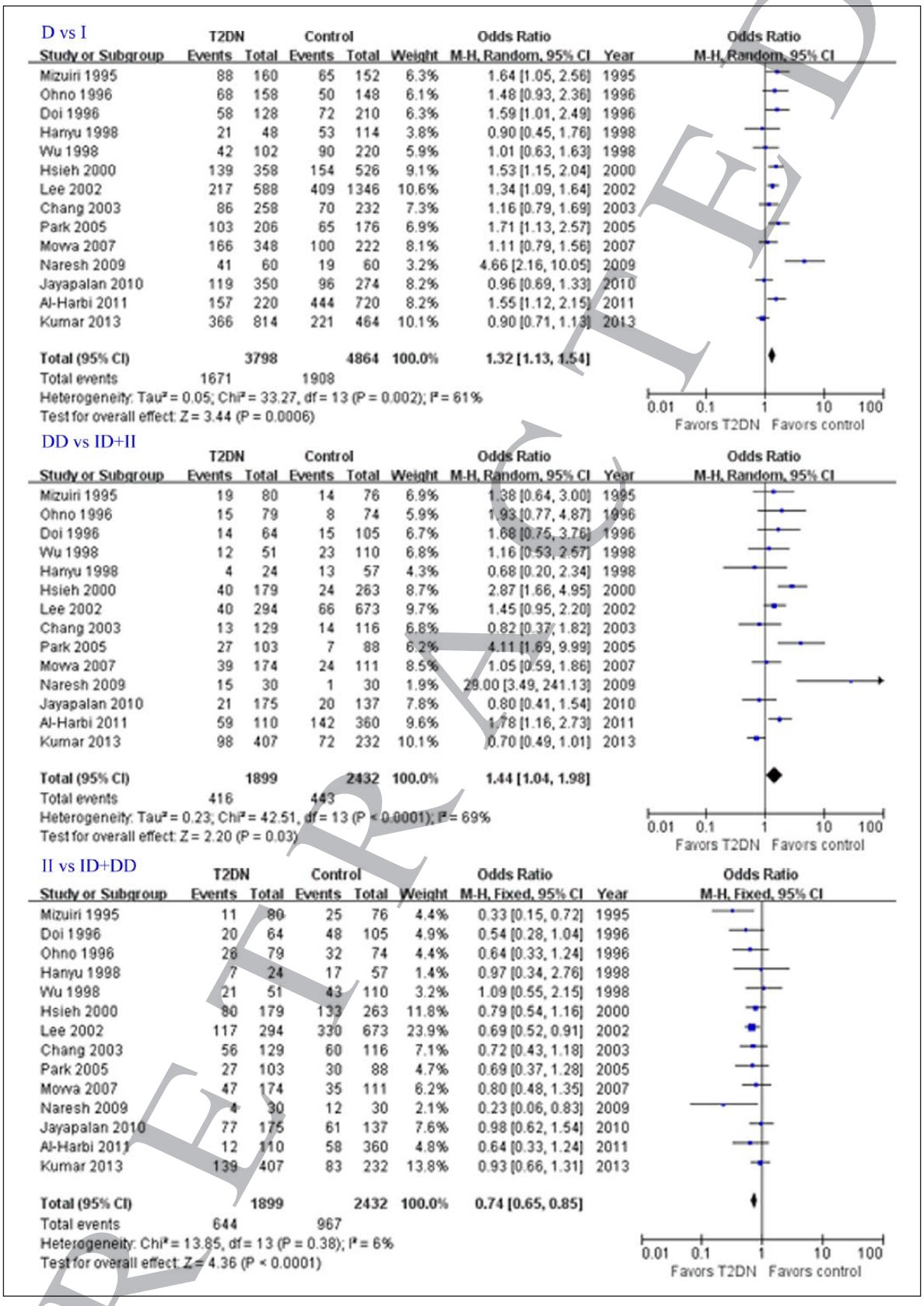

Figure 1. Association of the *ACE* I/D gene polymorphism on T2DN susceptibility (T2DN vs control).
ACE: angiotensin-converting enzyme; I: insertion; D: deletion; T2DN: type-2 diabetic nephropathy; CI: confidence interval; M-H: Mantel-Haenszel test.

Table 3. Meta-analysis of the association of the *ACE* I/D gene polymorphism with risk of T2DN and the T2DM developing into T2DN.

Genetic contrasts	Number of studies	Q test *p* value	Model selected	OR (95% CI)	*p*
T2DN vs control					
D vs I	14	0.002	Random	1.32 (1.13, 1.54)	0.0006
DD vs (ID+II)	14	<0.0001	Random	1.44 (1.04, 1.98)	0.03
II vs (ID+DD)	14	0.38	Fixed	0.74 (0.65, 0.85)	<0.0001
T2DN vs control (sensitivity analysis: ≥ 100)					
D vs I	7	0.02	Random	1.20 (1.01, 1.42)	0.04
DD vs (ID+II)	7	0.0004	Random	1.22 (0.82, 1.80)	0.32
II vs (ID+DD)	7	0.77	Fixed	0.79 (0.68, 0.92)	0.002
T2DN vs control (sensitivity analysis: < 100)					
D vs I	7	0.03	Random	1.55 (1.16, 2.07)	0.003
DD vs (ID+II)	7	0.03	Random	1.89 (1.08, 3.33)	0.03
II vs (ID+DD)	7	0.21	Fixed	0.62 (0.47, 0.82)	0.0007
T2DN vs T2DM					
D vs I	26	<0.00001	Random	1.61 (1.02, 1.32)	0.03
DD vs (ID+II)	27	<0.0001	Random	1.14 (0.94, 1.38)	0.18
II vs (ID+DD)	26	<0.00001	Random	0.81 (0.68, 0.96)	0.02
T2DN vs T2DM (sensitivity analysis: ≥ 100)					
D vs I	12	<0.0001	Random	1.11 (0.96, 1.27)	0.16
DD vs (ID+II)	12	0.0002	Random	1.15 (0.91, 1.45)	0.23
II vs (ID+DD)	12	0.01	Random	0.92 (0.78, 1.07)	0.28
T2DN vs T2DM (sensitivity analysis: < 100)					
D vs I	14	<0.0001	Random	1.24 (0.94, 1.64)	<0.0001
DD vs (ID+II)	15	0.02	Random	1.13 (0.78, 1.63)	0.53
II vs (ID+DD)	14	0.0007	Random	0.66 (0.44, 0.99)	0.04

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T2DM: type-2 diabetes mellitus; T2DN: type-2 diabetic nephropathy; OR: odds ratio; CI: confidence interval.

population in the sensitivity analysis according to case sample size < 100 (Table 3), and the results were similar to those in the nonsensitivity analysis.

Association of the ACE *I/D gene polymorphism with the risk of T2DM patients developing T2DN*

In this meta-analysis, the *ACE* D allele and II genotype were associated with the risk of T2DM patients developing T2DN in the Asian population (D allele: OR = 1.61, 95% CI: 1.02–1.32, $p = 0.03$; II genotype: OR = 0.81, 95% CI: 0.68–0.96, $p = 0.02$; Figure 2 for the D allele, and Figure 3 for the II genotype; Table 3), but this association was not found for the DD genotype (OR = 1.06, 95% CI: 0.90–1.24, $p = 0.52$; Figure 4 for the DD genotype).

Sensitivity analysis for the relationship between the *ACE* I/D gene polymorphism and the risk of T2DM patients developing into T2DN in the Asian population was also performed according to case sample size (< 100 vs ≥ 100). In the sensitivity analysis according to case sample size ≥100, we found that *ACE* I/D gene polymorphism were not associated with the risk of T2DM patients developing into T2DN in Asian population (Table 3). However, in the sensitivity analysis according to case sample size <100, the results were similar to those in the nonsensitivity analysis (Table 3).

Evaluation of publication bias

No significant publication bias was shown in the comparison of T2DN vs T2DM (Begg $p = 0.967$, Egger $p = 0.600$; Figure 5 for Begg test).

Discussion

Some meta-analyses reported that the *ACE* I/D gene polymorphism was associated with the risk of some renal diseases.[5,40–42] Dysfunction of *ACE* generation brought by the *ACE* I/D gene polymorphism is considered to be the important deterioration factor associated with the T2DN susceptibility and the risk of patients with T2DM developing T2DN in the Asian population. There was a rare genetic molecular marker to predict the onset of T2DN and the risk of patients with T2DM developing T2DN in Asian population. This study using a meta-analysis

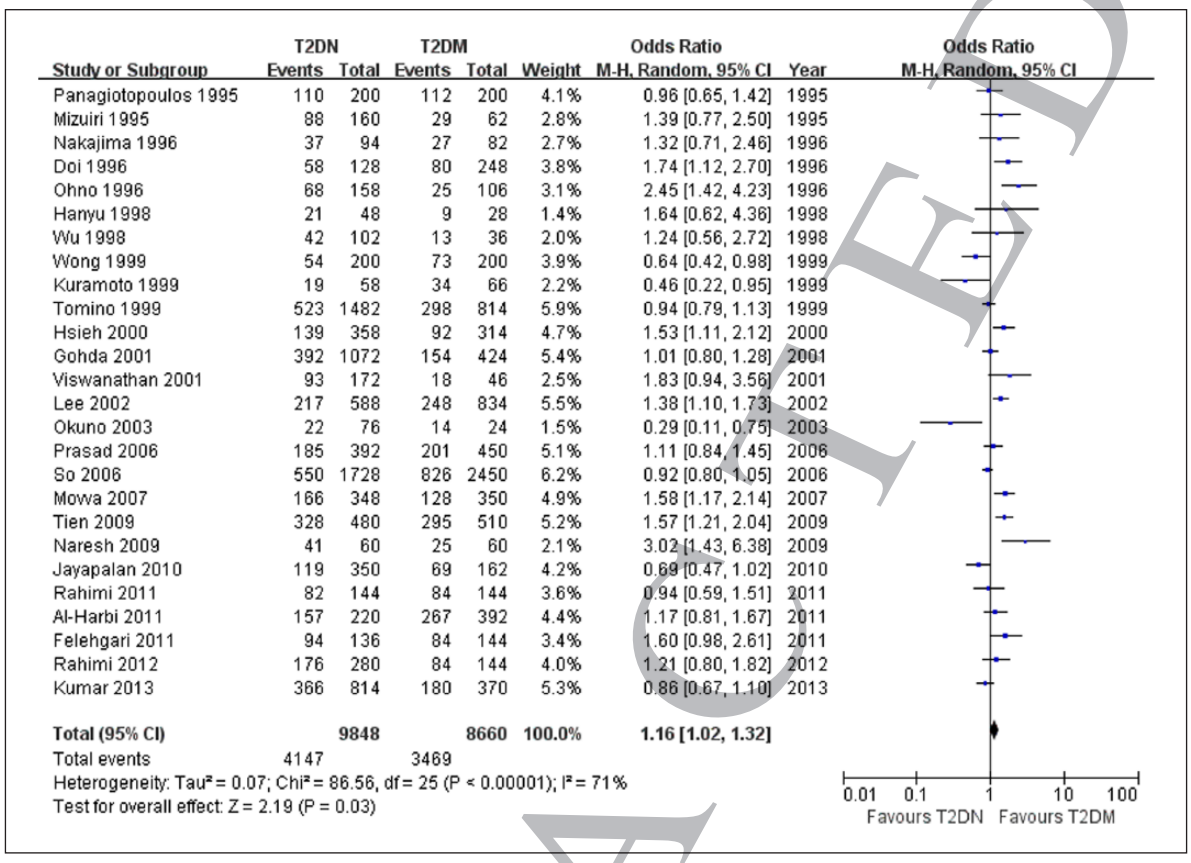

Figure 2. Association of the *ACE* D allele on the risk of T2DM developing into T2DN (T2DN vs T2DM).
ACE: angiotensin-converting enzyme; type-2 diabetes mellitus; I: insertion; D: deletion; T2DN: type-2 diabetic nephropathy; CI: confidence interval; M-H: Mantel-Haenszel test.

method was performed to explore whether the *ACE* I/D gene polymorphism could predict the susceptibility of T2DN susceptibility and the risk of patients with T2DM developing T2DN in the Asian population.

In this meta-analysis, the association between the *ACE* I/D gene polymorphism and T2DN susceptibility in the Asian population was assessed using a meta-analysis method. We found that the *ACE* I/D gene polymorphism was associated with T2DN susceptibility in the Asian population. Furthermore, sensitivity analysis was performed according to sample size of case (< 100 vs ≥ 100), and the results from the sensitive analysis according to case sample size < 100 were similar to those from the nonsensitive analysis. In the sensitivity analysis according to case sample size ≥100, we found that the results were also similar to the nonsensitivity analysis, except for the DD genotype. The small sample size in some included studies might draw a more positive result. More studies should be performed in the future.

The relationship between the *ACE* I/D gene polymorphism and the risk of patients with T2DM developing T2DN in the Asian population was also assessed in this meta-analysis. The results indicated that the *ACE* D allele and II genotype were associated with the risk of T2DM patients developing T2DN in the Asian population, but this association was not found for the DD genotype. Furthermore, sensitivity analysis was performed according to case sample size (< 100 vs ≥ 100), and the results from the sensitive analysis according to case sample size < 100 were similar to those from the non-sensitive analysis. However, in the sensitivity analysis according to case sample size ≥100, we found that the *ACE* I/D gene polymorphism was not associated with the risk of patients with T2DM developing T2DN in the Asian population, and the result for the D allele and II genotype were not similar to those in the nonsensitive analysis. There was no significant publication bias among the studies on the relationship between the *ACE* I/D gene polymorphism and the risk of patients with T2DM developing T2DN in the Asian population, and the results might be more robust. However, the small sample size in some included studies might draw a more positive result, and more studies should be performed in the future.

In this meta-analysis, we found that the *ACE* D allele, DD genotype and II genotype were associated with T2DN susceptibility and the *ACE* D allele and II genotype were associated with the risk of patients with T2DM developing T2DN in the Asian population. However, these findings should be regarded cautiously because many other factors, such as heterogeneity of enrolled cases, limited statistical

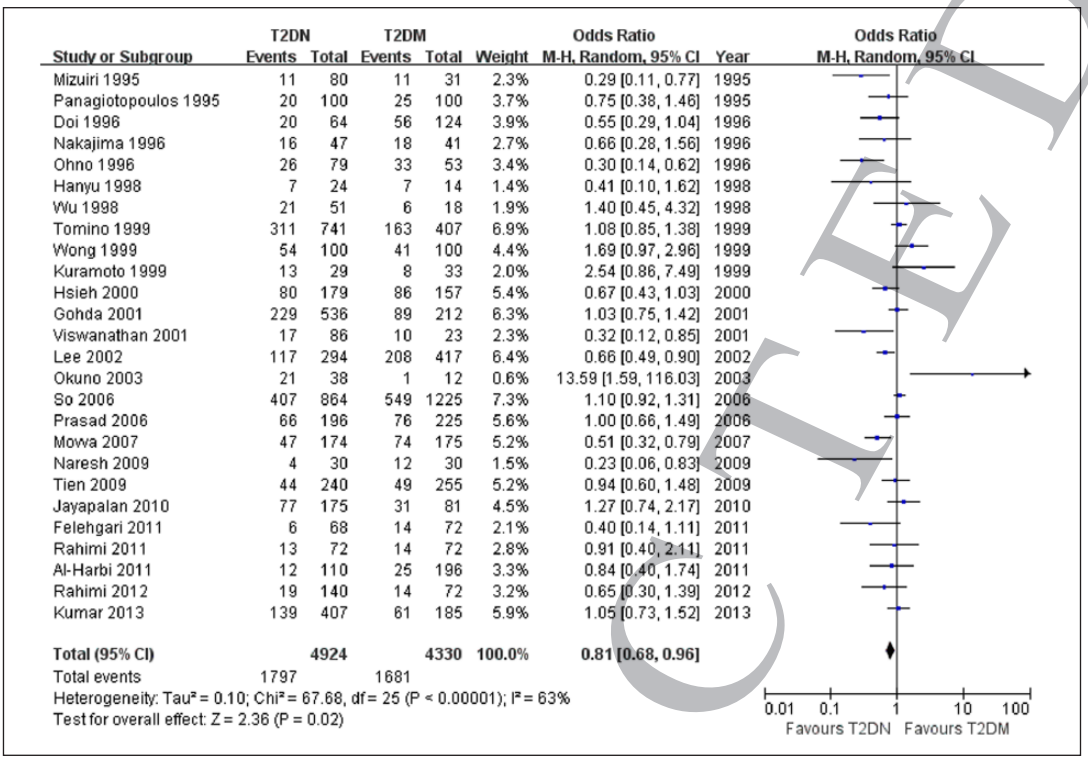

Figure 3. Association of the *ACE* II genotype on the risk of T2DM developing into T2DN (T2DN vs T2DM).
ACE: angiotensin-converting enzyme; type-2 diabetes mellitus; I: insertion; D: deletion; T2DN: type-2 diabetic nephropathy; CI: confidence interval; M-H: Mantel-Haenszel test.

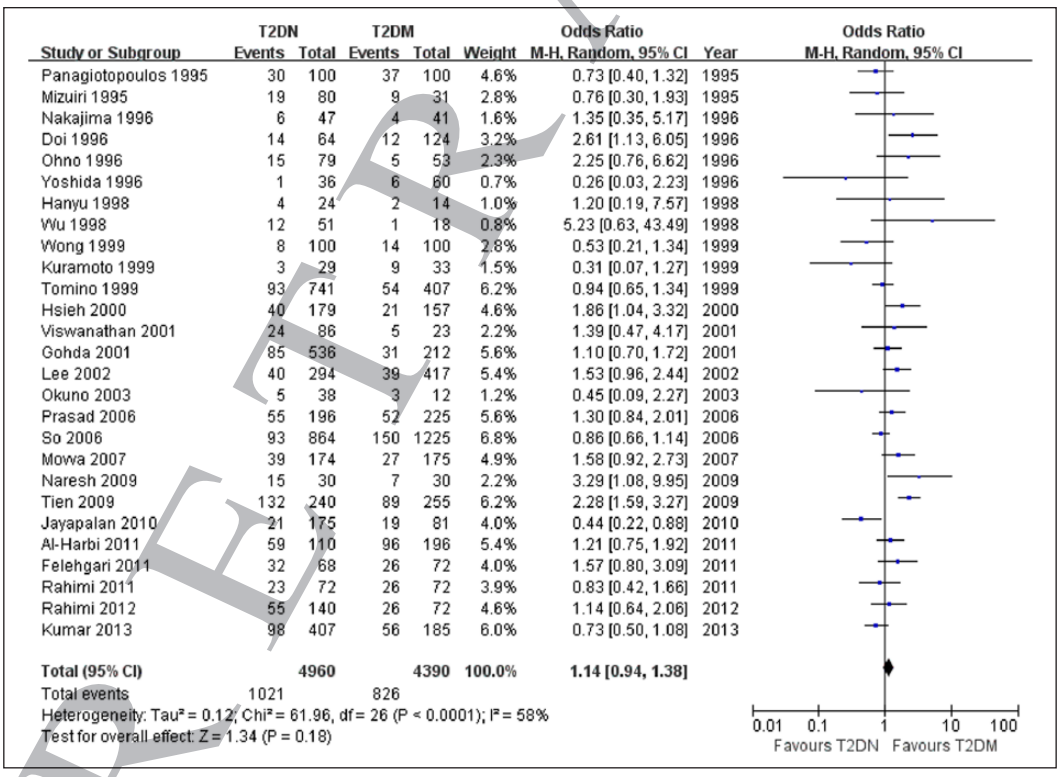

Figure 4. Association of the *ACE* DD genotype on the risk of T2DM developing into T2DN (T2DN vs T2DM).
ACE: angiotensin-converting enzyme; type-2 diabetes mellitus; I: insertion; D: deletion; T2DN: type-2 diabetic nephropathy; CI: confidence interval; M-H: Mantel-Haenszel test.

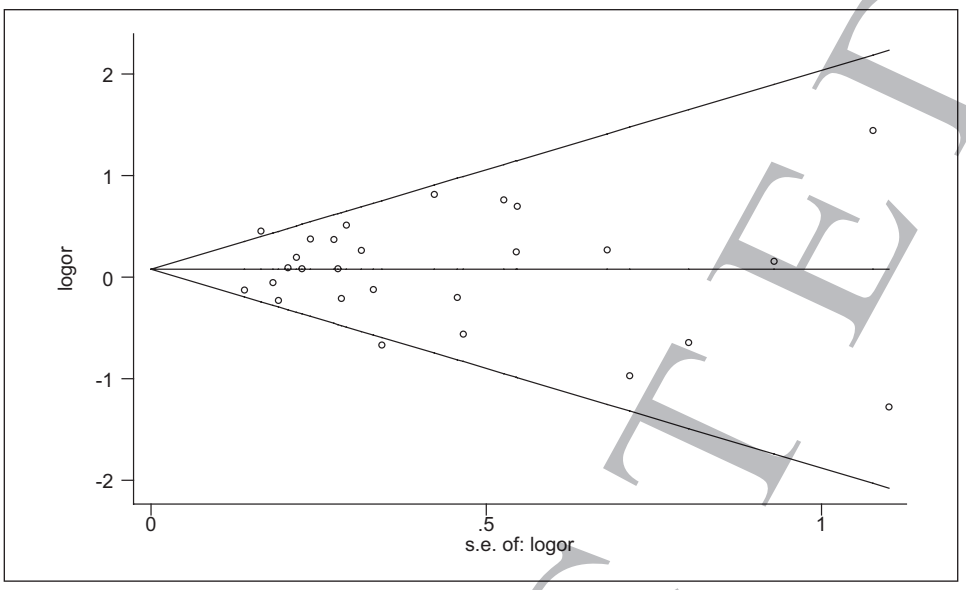

Figure 5. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of the *ACE* I/D gene polymorphism with the risk of T2DM developing into T2DN.
ACE: angiotensin-converting enzyme; type-2 diabetes mellitus; I: insertion; D: deletion; T2DN: type-2 diabetic nephropathy.

power, variable study designs and different interventions, were closely related to affect the results. Undoubtedly, the limitations mentioned above might affect our final conclusions.

In conclusion, the results in our study support that the *ACE* I/D gene polymorphism was associated with T2DN susceptibility and the *ACE* D allele and II genotype were associated with the risk of patients with T2DM developing T2DN in the Asian population. However, more association investigations on larger, stratified populations are required to further clarify the role of the *ACE* I/D gene polymorphism in T2DN susceptibility and the risk of patients with T2DM developing T2DN in the Asian population.

Conflict of interest

None declared.

Funding

This work was supported by the sub-item of 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation; No. 88000-3311300).

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Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP45

DOI: 10.1177/1470320314566221
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Retraction notice

This article has been included in a multiple retraction:

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System* (*JRAAS*) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

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Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System Septembr 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

jraas

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP46–NP50

DOI: 10.1177/1470320314566221
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RETRACTED: Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Chun-Hua Yang[1] and Tian-Biao Zhou[2]

Abstract

Aim: The relationship between the angiotensinogen (AGT) A1166C gene polymorphism and the risk of diabetes mellitus (DM) developing into diabetic nephropathy (DN) is still controversial. This study was performed to evaluate the association of the AGT A1166C gene polymorphism with susceptibility of the subject's DM developing into DN, using a meta-analysis method.

Methods: We performed a predefined literature search and selection of eligible relevant studies, to collect data from electronic databases.

Results: Nine articles were identified for the analysis of the association of the AGT A1166C gene polymorphism with the subject's susceptibility of DM to develop into DN. The AGT CC genotype was associated with the susceptibility of DM to develop into DN in the overall population, but the C allele and AA genotype were not. Furthermore, the AGT C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population, but the AA genotype was not; however, the AGT A1166C gene polymorphisms were not associated with susceptibility of DM developing into DN, in the Caucasian population.

Conclusions: The AGT CC genotype was associated with the susceptibility of DM developing into DN in the overall population and in the Asian population, and the C allele was associated with the susceptibility of DM to develop into DN, in Asians; however, more studies should be performed.

Keywords

Angiotensinogen, diabetes mellitus, diabetic nephropathy, gene polymorphisms, meta-analysis, racial differences

Introduction

Diabetes mellitus (DM), an important public health problem, is a chronic disease with high morbidity and mortality among patients, which impair their health and quality of life.[1] Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes; and it can lead to end-stage renal disease.[2] DN includes Type-1 diabetic nephropathy (T1DN), due to Type-1 diabetes mellitus, and Type-2 diabetic nephropathy (T2DN) due to Type-2 diabetes mellitus.[3,4] Some investigations suggest that genetic factors might act with a key role in the susceptibility of DM developing into DN.

The renin-angiotensin system is a major determinant of blood pressure regulation and it is associated with the risk of renal diseases.[5] The angiotensinogen (AGT) gene, located on chromosome 1q41-qter, regulates the expression of angiotensinogen; its cleavage by renin liberates angiotensin I, which is converted into angiotensin II by the angiotensin-converting enzyme. The AGT A1166C gene polymorphism, correlated with circulating and cellular AGT concentration, has been implicated in the etiology of DM developing into DN and has been investigated in numerous epidemiologic

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studies at present; however, the available evidence reported to date is weak, due to a sparseness of data or disagreements among studies. We performed this meta-analysis to investigate the relationship between the AGT A1166C gene polymorphism and the susceptibility for DM developing into DN.

Materials and methods

Search strategy

Relevant studies were screened from the search engines of PubMed and Cochrane Library on 1 August 2014. We used '(angiotensinogen OR AGT) AND (diabetic nephropathy)' in PubMed and the Cochrane Library to complete the search. We also extended the search spectrum to 'related articles' and the bibliographies of all retrieved studies. If multiple publications of the same data from the same study group occurred, we only recruited the later paper for analysis.

Inclusion criteria

- A case–control study;
- The outcome had to be DN; and
- There had to be at least two comparison groups (DN group versus DM group).

Exclusion criteria

- Review articles, editorials and case reports;
- Articles that did not provide the detailed genotype data of A1166C;
- Investigations of the association of other genes with DN;
- Investigations of the role of drugs to diseases; and
- Multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study, independently, by two investigators: First author's surname, year of publication, ethnicity of study population, the number of cases and controls for the A1166C genotype. Frequencies of the C allele were calculated for the case group and control group, from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data was entered into the Cochrane Review Manager (RevMan, version 5) and analyzed. The pooled statistic was counted using the fixed effects model, but a random effects model was conducted when the p value of the heterogeneity test was < 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% CI were also calculated; $p < 0.05$ was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies. We classified the investigations into studies for Asians and for Caucasians, because genotype frequencies and prevalence of DN were different among ethnic groups. We used the Begg adjusted rank correlation test[6] and the Egger regression asymmetry test[7] to explore publication bias ($p < 0.1$ was considered significant), when the sample number was more than five.

Results

Study characteristics

The search yielded 162 references: 162 from PubMed and 0 from the Cochrane Library. According to the inclusion and exclusion criteria, nine articles[8–16] were identified for the analysis of the between AGT A1166C gene polymorphism and the susceptibility of DM developing into DN, in our review (Table 1).

Association of the AGT A1166C gene polymorphism with the risk of DM patients developing into DN

In this meta-analysis, the AGT CC genotype was associated with the susceptibility of DM developing into DN in the overall population, but the C allele and AA genotype were not (CC genotype: OR = 1.42; 95% CI 0.97–2.08; $p = 0.07$ and C allele: OR = 1.26; 95% CI 0.96–1.65; $p = 0.10$; and AA genotype: OR = 0.81; 95% CI 0.56–1.18, $p = 0.28$; with Figure 1 for the C allele, Figure 2 for the CC genotype and Figure 3 for the AA genotype; and Table 2).

In the meta-analysis according to ethnicity, we found that the AGT C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population, but the AA genotype was not (Table 2); however, the AGT A1166C gene polymorphisms were not associated with the susceptibility of DM developing into DN in the Caucasian population (Table 2).

A sensitivity analysis for the relationship between the AGT A1166C gene polymorphism and the susceptibility of DM developing into DN was also performed according to the types of DM. In the sensitivity analysis, the AGT A1166C gene polymorphisms were not associated with the susceptibility of T1DM developing into T1DN in the overall population (Table 2); however, the AGT CC genotype was associated with the susceptibility of T2DM developing into T2DN in the overall population, while the C allele and AA genotype were not (Table 2).

Evaluation of publication bias

No significant publication bias was shown in this meta-analysis (Begg $p = 1.000$, Egger $p = 0.826$; Figure 4 has the Begg test results).

Table 1. Characteristics of the studies evaluating the effects of AGT A1166C gene polymorphism on DM developing into DN.

First author, year	Ethnicity	Type of DM	DN						DM					
			CC	AC	AA	Total	C allele	Total (allele)	CC	AC	AA	Total	C allele	Total (allele)
Doria, 1997	Caucas	T1DM	9	29	35	73	47	146	7	25	47	79	39	158
Tomino, 1999	Asian	T2DM	–	–	128	745	–	–	–	–	61	407	–	–
Van Ittersum, 2000	Caucas	T1DM	21	88	91	200	130	400	10	53	37	100	73	200
Fradin, 2002	Caucas	T2DM	12	31	74	117	55	234	5	52	61	118	62	236
Prasad, 2006	Asian	T2DM	5	22	169	196	32	392	2	29	194	225	33	450
Möllsten, 2008	Caucas	T1DM	1	20	52	73	22	146	5	56	136	197	66	394
Gallego, 2008	Caucas	T1DM	5	21	15	41	31	82	32	183	196	411	247	822
Ahluwalia, 2009	Asian	T2DM	24	112	104	240	160	480	5	119	131	255	129	510
Yin, 2013	Asian	T2DM	1	20	131	152	22	304	0	8	133	141	8	282

AGT: angiotensinogen; Caucas : caucasian; DM: diabetes mellitus; DN: diabetic nephropathy

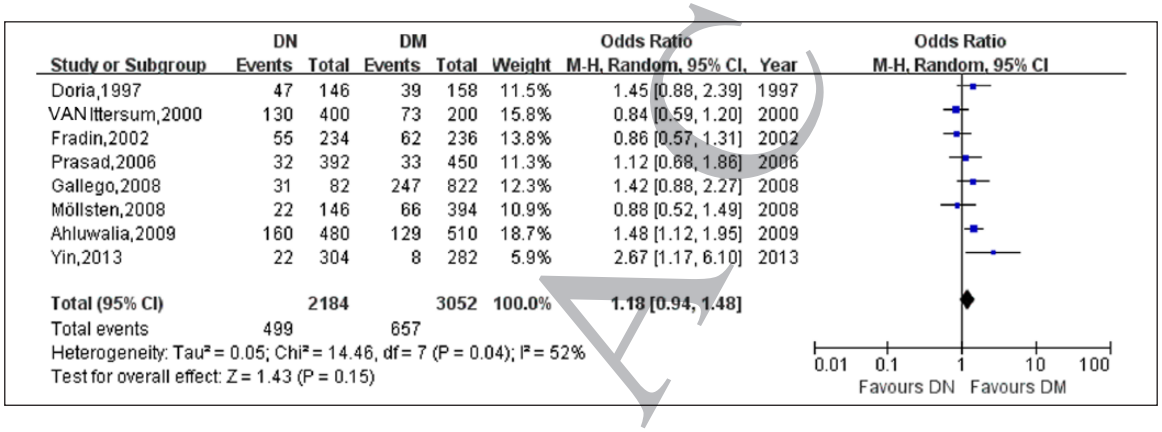

Figure 1. Association of the AGT C allele regarding the risk of DM developing into DN.
AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy

Discussion

We included nine studies into this meta-analysis and we found that the AGT CC genotype was associated with the susceptibility of DM developing into DN in the overall population, but the C allele and AA genotype were not. Furthermore, the AGT C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population, but the AA genotype was not; however, the AGT A1166C gene polymorphisms were not associated with the susceptibility of DM developing into DN in the Caucasian population. There was no publication bias in this meta-analysis and the results for overall populations might be robust to some extent; however, the number of included studies for the Asian and Caucasian populations were small, so more studies in these populations should be performed in the future.

In the sensitivity analysis, the relationship between the AGT A1166C gene polymorphism and the susceptibility of DM developing into DN was also performed according to the types of DM. We found that the AGT A1166C gene polymorphism was not associated with the susceptibility of T1DM developing into T1DN, in the overall population; however, the AGT CC genotype was associated with the susceptibility of T2DM developing into T2DN in the overall population, but the C allele and AA genotype were not.

In our investigation, we found that the AGT CC genotype was associated with the susceptibility of DM to develop into DN in the overall population, and the AGT C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population. Furthermore, the AGT CC genotype was associated with the susceptibility of T2DM developing into T2DN in overall population; however, these findings should be regarded cautiously, because many other ingredients, such as the heterogeneity of the enrolled cases, limited statistical power, variable study designs and different interventions, were closely related to affecting the results. Furthermore, whether the AGT A1166C polymorphism is just linked with other discrete loci involved in the susceptibility of DM developing into DN is not clear at the moment.

Conclusions

In conclusion, the results in our study support that the AGT CC genotype was associated with the susceptibility of DM developing into DN in the overall population, and the AGT

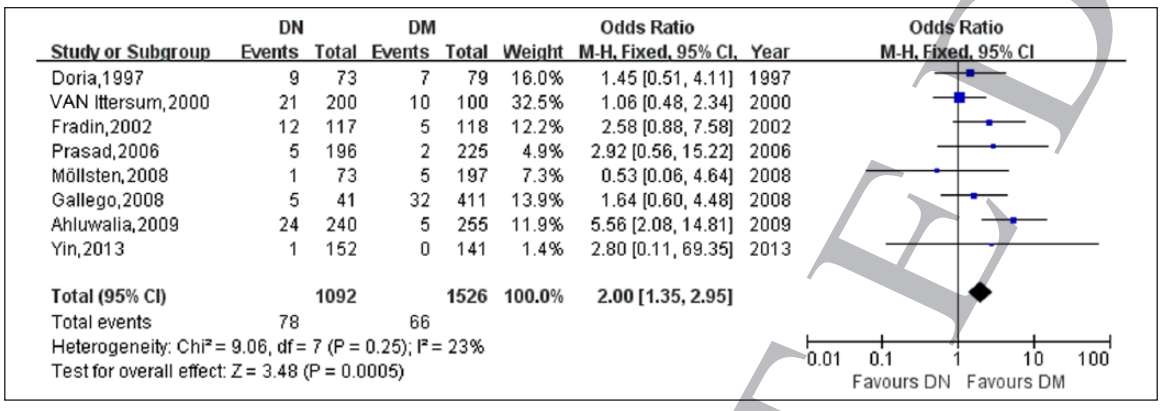

Figure 2. Association of the AGT CC genotype regarding the risk of DM developing into DN.
AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy

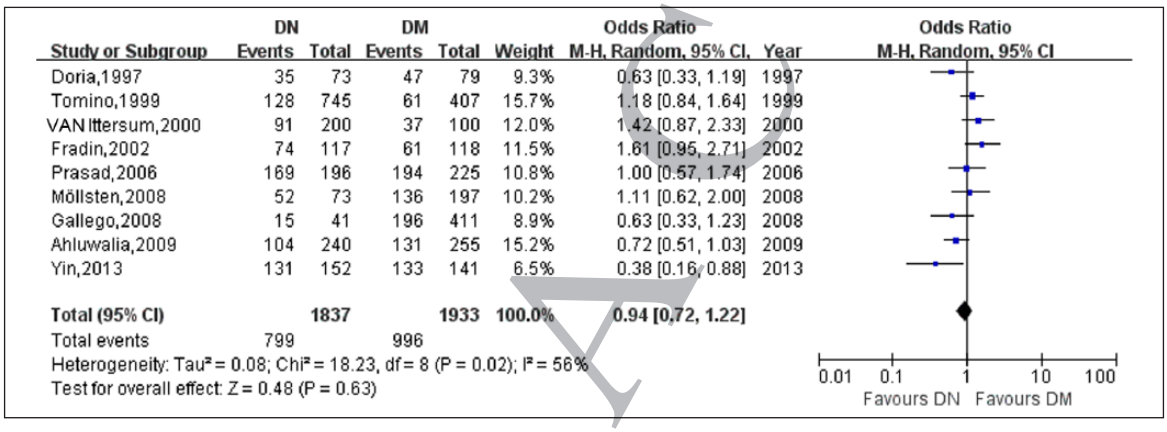

Figure 3. Association of the AGT AA genotype on the risk of DM developing into DN.
AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy

Table 2. Meta-analysis of the association of AGT A1166C gene polymorphism with risk of DM developing into DN.

Genetic contrasts	Group and subgroups	studies	Q test (*P* value)	Model selected	OR (95%CI)	*P*
C vs A	Overall	8	0.04	Random	1.18 (0.94, 1.48)	0.15
	Asian	3	0.21	Fixed	1.47 (1.17, 1.85)	0.001
	Caucas	5	0.21	Fixed	1.01 (0.83, 1.23)	0.91
CC vs (AC + AA)	Overall	8	0.25	Fixed	2.00 (1.35, 2.95)	0.0005
	Asian	3	0.77	Fixed	4.63 (2.06, 10.41)	0.0002
	Caucas	5	0.63	Fixed	1.41 (0.89, 2.25)	0.14
AA vs (AC + CC)	Overall	9	0.02	Random	0.94 (0.72, 1.22)	0.63
	Asian	4	0.04	Random	0.83 (0.56, 1.23)	0.35
	Caucas	5	0.07	Random	1.04 (0.71, 1.52)	0.83
T1DN						
C vs A	Overall	4	0.17	Fixed	1.06 (0.85, 1.32)	0.62
CC vs (AC + AA)	Overall	4	0.77	Fixed	1.21 (0.72, 2.04)	0.48
AA vs (AC + CC)	Overall	4	0.12	Fixed	0.96 (0.72, 1.29)	0.80
T2DN						
C vs A	Overall	4	0.05	Random	1.29 (0.89, 1.87)	0.17
CC vs (AC + AA)	Overall	4	0.75	Fixed	3.81 (2.00, 7.25)	<0.0001
AA vs (AC + CC)	Overall	5	0.01	Random	0.94 (0.64, 1.37)	0.74

AGT: angiotensinogen; Caucas : caucasian; DM: diabetes mellitus; DN: diabetic nephropathy ; vs: versus

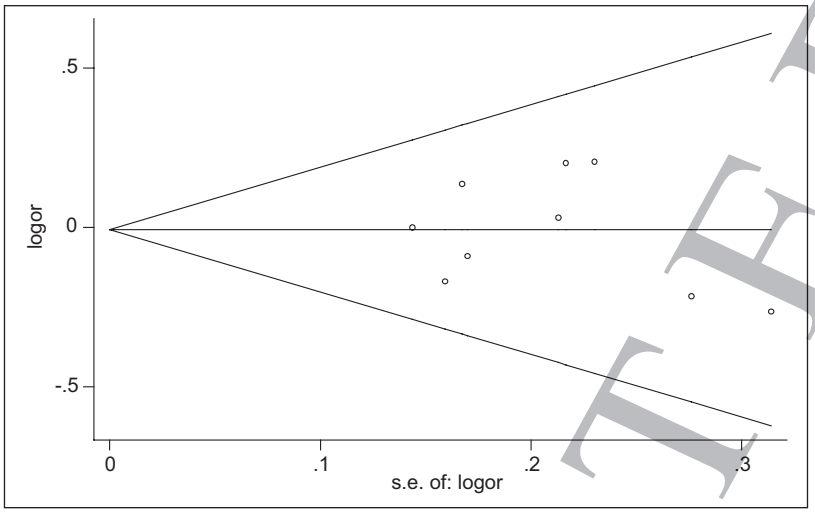

Figure 4. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of AGT A1166C gene polymorphism with the risk of DM developing into DN.
AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy; logor : loglinear-odds ratio; s.e.: standard error.

C allele and CC genotype were associated with the risk of DM developing into DN in the Asian population. Furthermore, the AGT CC genotype was associated with the susceptibility of T2DM to develop into T2DN in the overall population; however, more case-control association investigations on larger, stratified populations are required to further clarify the role of this AGT A1166C gene polymorphism in the susceptibility of DM developing into DN.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This work was supported by a sub-item of the 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation, grant number 88000-3311300).

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Retraction notice

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP11

DOI: 10.1177/1470320314563424
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The following article has been included in a multiple retraction:

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System (*JRAAS*) 1470320314563424, first published 18 December 2014. DOI: 10.1177/1470320314563424.

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *JRAAS* (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer-review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online-first articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou and Zongpei Jiang

Association of the angiotensinogen *M235T* gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

JRAAS 1470320314563426, first published 18 December 2014. DOI: 10.1177/1470320314563426.

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

JRAAS 1470320314563424, first published 18 December 2014. DOI:10.1177/1470320314563424.

Weiqiang Zhong, Zongpei Jiang and Tian-Biao Zhou

Association between the *ACE* I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

*JRAAS*1470320314566019, first published 26 January 2015. DOI: 10.1177/1470320314566019.

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang and Hong-Yan Li

Relationship between the *ACE* I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

JRAAS 1470320314563425, first published 1 February 2015. DOI:10.1177/1470320314563425.

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen *A1166C* gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

JRAAS 1470320314566221, first published 1 February 2015. DOI: 10.1177/1470320314566221.

Chun-Hua Yang and Tian-Biao Zhou

Association of the *ACE* I/D gene polymorphism with sepsis susceptibility and sepsis progression

JRAAS 1470320314568521, first published 3 February 2015. DOI: 10.1177/1470320314568521.

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang and Dongwen Zheng

Association of *ACE* I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

JRAAS March 2015; 16: 165–171, first published 14 November 2014. DOI: 10.1177/1470320314557849.

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang and Tian-Biao Zhou

Association of aldosterone synthase (*CYP11B2*) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

JRAAS September 2015; 16: 660–665, first published 20 August 2014. DOI: 10.1177/1470320314524011.

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Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP12–NP17

DOI: 10.1177/1470320314563424
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RETRACTED: Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Tian-Biao Zhou[1], Hong-Yan Li[2], Zong-Pei Jiang[1], Jia-Fan Zhou[1], Miao-Fang Huang[1] and Zhi-Yang Zhou[3]

Abstract

Background and objective: The purpose of this study is to explore the effects of renin-angiotensin-aldosterone system (RAAS) inhibitors in radiation nephropathy (RD) diseases.

Method: Studies including randomized studies comparing treatment with RAAS inhibitors versus without RAAS inhibitors in patients/animals with RD disease were identified using a predefined search strategy. Data of blood urea nitrogen (BUN), serum creatinine (Scr), blood pressure (BP), ratio of urine protein to urine creatinine (UP/UC), and time to develop renal failure (TDRF) were extracted and compared by RevMan 5.1 (The Cochrane Collaboration, Oxford, UK).

Results: Seven studies were identified, and all the studies were conducted in rats. Meta-analysis showed that RAAS inhibitors treatment resulted in lower levels of BUN, Scr, BP, UP/UC when compared to treatment without RAAS inhibitors, and RAAS inhibitors resulted in a longer TDRF for RD rats.

Conclusions: RAAS inhibitors treatment might achieve a protective role in RD diseases. However, more well-designed, randomized, controlled trails should be performed to confirm it in the future.

Keywords

Radiation nephropathy (RD), renin-angiotensin-aldosterone system (RAAS) inhibitors, BUN, Scr, meta-analysis

Introduction

Radiation nephropathy (RD) occurs reliably after sufficient exposure of kidneys to ionizing radiation, and single-fraction total-body irradiation (TBI) of 10 Gy will cause radiation nephropathy in humans and in rats within six months after TBI.[1] Proteinuria, azotemia and hypertension are the main characteristics of RD. RD has emerged as a significant complication of hematopoietic stem cell transplantation when TBI is used in the conditioning regimen, and after internal radionuclide cancer therapy in current medical practice, and is a potential sequela of radiological terrorism and radiation accidents.[1,2]

The renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis and progression of chronic kidney disease. Activation of the intra-renal RAAS contributes to glomerular hypertrophy, mesangial expansion and glomerulosclerosis in various renal diseases. Previous clinical and experimental studies have demonstrated that inhibition of the RAAS using angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) results in the reduction of proteinuria and retards progression of renal disease in addition to lowering blood pressure.[3]

Currently available evidence indicates that RAAS inhibitors might play a protective role in RD. However, the available evidence is weak owing to sparseness of data or disagreements among the reported investigations. The

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Table 1. The detailed characteristics of included studies.

Author, year	Age/weight of rats	Dose of radiation	RAAS inhibitors	Outcome	Reference (PMID)
Cohen, 1992[4]	26 weeks old	15–27 Gy	Captopril	BUN	1475357
Moulder, 1993[5]	7 to 9 weeks old	14–18.5 Gy	Captopril	BUN, Scr, BP, UP/UC	8278583
Juncos, 1993[6]	150–200 g	NC	Enalapril	Scr, BP	8321359
Moulder, 1993[7]	5 to 26 weeks old	17–27 Gy	Captopril, enalapril	BUN, Scr, UP/UC	8365947
Cohen, 1996[8]	5 to 7 weeks old	17 Gy	Captopril	BUN, BP, UP/UC	8804358
Moulder, 1998[9]	15 weeks old	26 Gy	Captopril	BUN, BP, UP/UC	9806595
Moulder, 2007[10]	NC	18.5 Gy	Captopril, AT1 blocker (L-158,809), AT2 blocker (PD123319)	BUN, BP, UP/UC, TDRF	17506717

BUN: blood urea nitrogen; Scr: serum creatinine; BP: blood pressure; UP/UC: ratio of urine protein to urine creatinine; TDRF: time to develop renal failure; NC: not clear.

evidence from meta-analysis might be powerful compared with individual investigations. This study was performed to assess the role of RAAS inhibitors in RD using the meta-analysis method.

Materials and methods

Search strategy

The relevant studies were screened from the search engines of PubMed, Embase, and Cochrane Library as of June 31, 2014. The search terms "(renin-angiotensin-aldosterone system OR RAAS OR angiotensin-converting enzyme inhibitor OR ACEI OR angiotensin type 1 OR AT1 OR angiotensin type 2 OR AT2) AND (radiation nephropathy)" were used in PubMed, Embase, and Cochrane Library without language limitation. We also extended the search spectrum to the "related articles" and the bibliographies of all retrieved studies. If multiple publications from the same study group occurred, we recruited only the most complete paper for analysis.

Inclusion and exclusion criteria

Inclusion criteria. The inclusion criteria for the study are given below: (1) Study type: randomized, controlled study, including RAAS inhibitors + RD group (RAAS group) vs RD group. (2) Object of the study met the diagnostic criteria for RD. (3) Interventions: using ACEI, AT1 or AT2 for treatment. (4) Baseline information: comparable.

Exclusion criteria. The exclusion criteria for the study are given below: (1) used only ACEI, AT1 or AT2 for the treatment. (2) The data were not clear.

Outcome measures

Blood urea nitrogen (BUN), serum creatinine (Scr), blood pressure (BP), ratio of urine protein to urine creatinine (UP/UC), and time to develop renal failure (TDRF) were used for the outcome measures.

Data collection

Method of agreeing on inclusion of studies was performed by two observers independently according to predetermined inclusion criteria. Titles and abstracts were scanned first to make a list of possibly related literature, and then full texts were obtained for those articles identified as either relevant or not clear; only randomized, controlled study fitting predefined inclusion criteria were included. Disagreements were resolved by other reviewers.

Statistical analysis

Statistical analysis was performed by RevMan 5.1. The pooled statistics were calculated using the fixed-effects model, but a random-effects model was conducted if the p value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data and weighted mean differences (WMD) for continuous data, and 95% confidence intervals (CI) were also counted. Heterogeneity between included studies was tested using the X^2-test.

Results

Search results

In this meta-analysis, seven studies[4–10] were included (Table 1). All the studies were conducted in rats, and there was no clinical trial.

BUN level between RAAS inhibitors group and RD group

Six reports[4,5,7–10] including 20 comparisons were included in this meta-analysis for the BUN level between the RAAS inhibitors group and the RD group. The p value of heterogeneity test was less than 0.00001 and a random-effects model was conducted. The pooled mean difference was –38.80 (95% CI: –50.43 to –27.16). The difference in

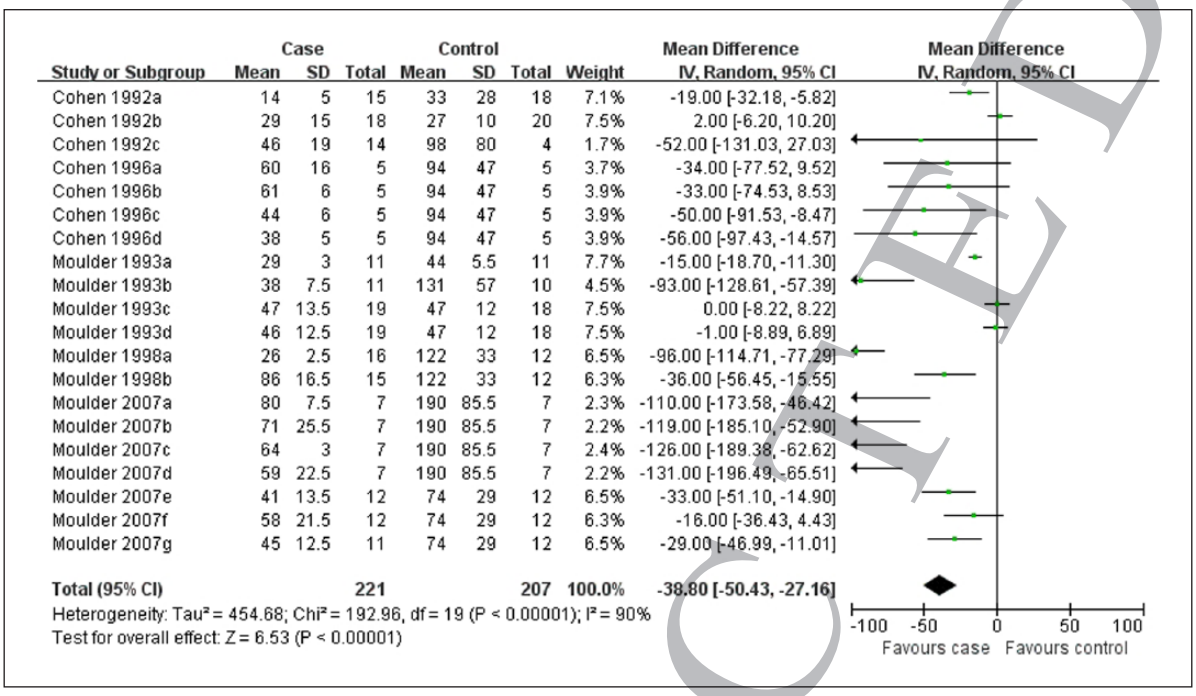

Figure 1. Blood urea nitrogen (BUN) level between the RAAS inhibitors group and the RD group.
RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

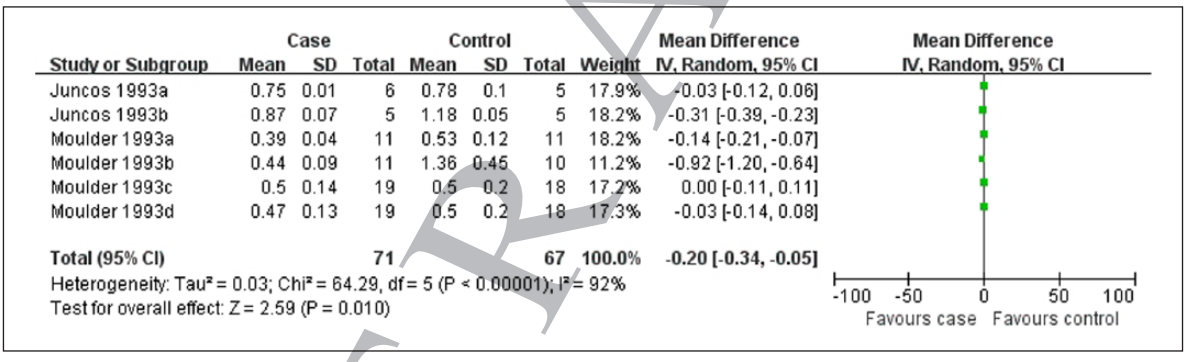

Figure 2. Serum creatinine (Scr) level between the RAAS inhibitors group and the RD group.
RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

BUN level was statistically significant between the RAAS inhibitors group and the RD group ($p < 0.00001$; Figure 1).

Scr level between RAAS inhibitors group and RD group

Three reports[5–7] including six comparisons were included in this meta-analysis of the Scr level between the RAAS inhibitors group and the RD group. The p value of heterogeneity test was less than 0.00001 and a random-effects model was conducted. The pooled mean difference was –0.20 (95% CI: –0.34 to –0.05). The difference in Scr level was statistically significant between the RAAS inhibitors group and the RD group ($p = 0.01$; Figure 2).

Ratio of UP/UC between RAAS inhibitors group and RD group

Five reports[5,7–10] including 17 comparisons were included in this meta-analysis of the UP/UC between the RAAS inhibitors group and the RD group. The p value of heterogeneity test was less than 0.00001 and a random-effects model was conducted. The pooled mean difference was –7.70 (95% CI: –11.03 to –4.36). The difference in UP/UC

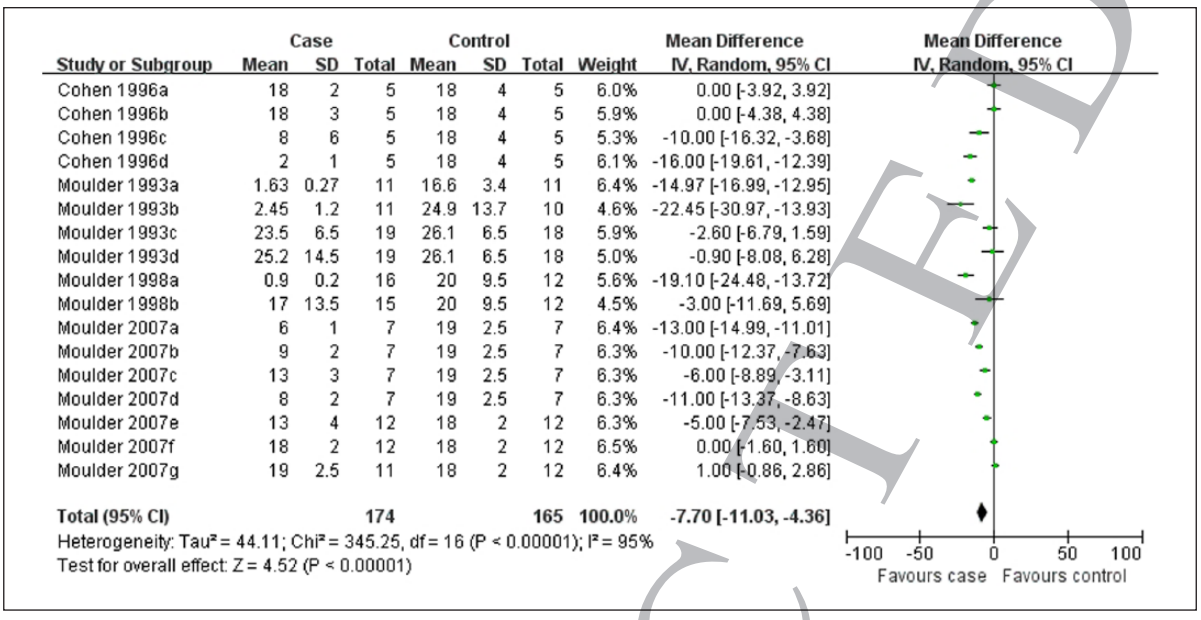

Figure 3. Ratio of urine protein to urine creatinine (UP/UC) between the RAAS inhibitors group and the RD group.
RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

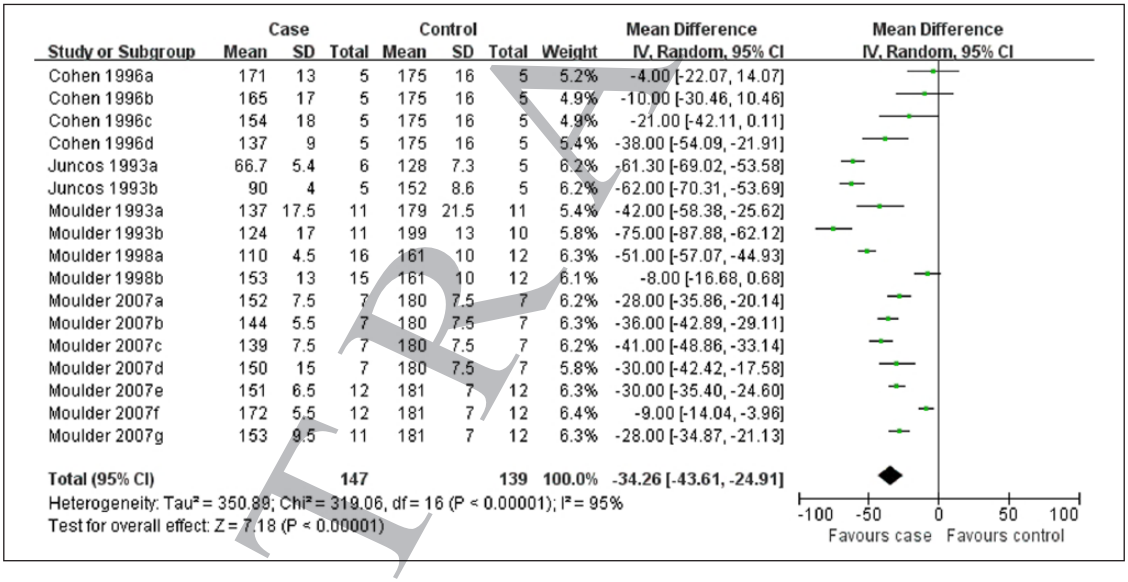

Figure 4. Blood pressure (BP) level between the RAAS inhibitors group and the RD group.
RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

level was statistically significant between the RAAS inhibitors group and the RD group ($p < 0.00001$; Figure 3).

BP level between RAAS inhibitors group and RD group

Five reports[5,6,8–10] including six comparisons were included in this meta-analysis of the BP level between the RAAS inhibitors group and the RD group. The p value of heterogeneity test was less than 0.00001 and a random-effects model was conducted. The pooled mean difference was –34.26 (95% CI: –43.61 to –24.91). The difference in BP level was statistically significant between the RAAS inhibitors group and the RD group ($p < 0.00001$; Figure 4).

TDRF between RAAS inhibitors group and RD group

One report[10] including seven comparisons were included in this meta-analysis for the TDRF between the RAAS inhibitors group and the RD group. The p value of heterogeneity test was 0.16 and a random-effects model was

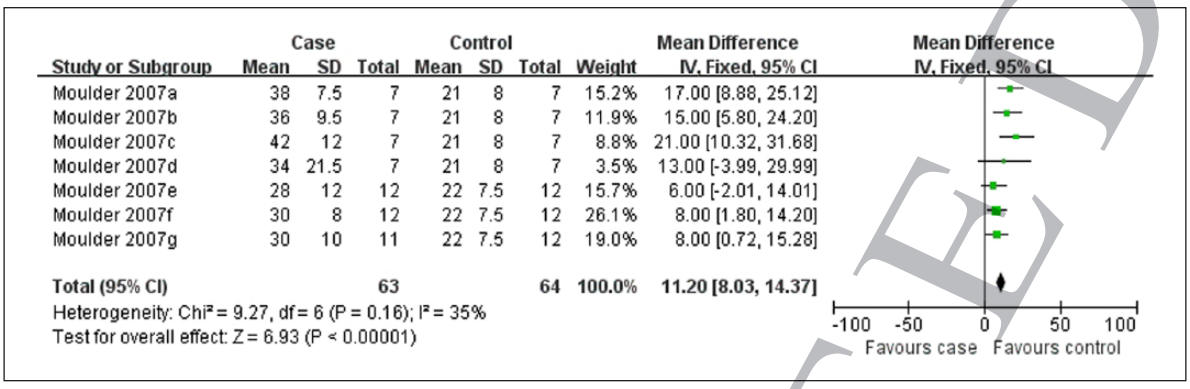

Figure 5. Time to develop renal failure (TDRF) between RAAS inhibitors group and RD group.
RAAS: renin-angiotensin-aldosterone system; RD: radiation nephropathy.

conducted. The pooled mean difference was 11.20 (95% CI: 8.03 to 14.37). The difference in TDRF was statistically significant between the RAAS inhibitors group and the RD group ($p < 0.00001$; Figure 5).

Discussion

In this meta-analysis, the difference in BUN level between the RAAS inhibitors group and the RD group was significant, and the pooled mean difference was –38.80. It indicated that the RAAS inhibitors group could achieve a lower BUN level than the RD group. When the fixed-model was chosen, we also found the result was similar to this. It indicated that using the RAAS inhibitors in rats with RD might achieve a better benefit.

The Scr level between the RAAS inhibitors group and the RD group was also assessed. In this study, we found that the pooled mean difference was –0.20. It indicated that RAAS inhibitors treatment might obtain a lower Scr than in RD rats without treatment. When the fixed-model was used to assess this relationship, it also showed that RAAS treatment might get a lower Scr level when compared with without treatment.

The ratio of UP/UC between the RAAS inhibitors group and the RD group in this meta-analysis was also detected, and we found that the pooled mean difference was –7.70. It indicated that RAAS inhibitors treatment might achieve a lower UP/UC.

Increased BP level was one of the most important risk factors for the RD patients. In this meta-analysis, we found that the RAAS inhibitors treatment could obtain a lower BP level than those without treatment, and the pooled mean difference was –34.26.

In this meta-analysis, TDRF between the RAAS inhibitors group and the RD group was also detected. The pooled mean difference was 11.20, and the difference of TDRF between the RAAS inhibitors group and RD group was significant. It indicated that the RAAS inhibitors could achieve a longer TDRF.

As those mentioned above, we might draw a conclusion that RAAS inhibitors treatment in RD rats might achieve more benefit when compared to those without treatment, such as lowers level of BUN, Scr, UP/UC, BP, and RAAS treatment could achieve a longer TDRF than without RAAS treatment.

In conclusion, the evidence in this meta-analysis indicates that RAAS inhibitors could get a protective role in rats with RD. However, more well-designed, randomized, controlled trails should be performed to confirm it in the future.

Conflict of interest

None declared.

Funding

This study was supported by the Nature Science Foundation of China (no. 81400719), the sub-item of 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation; No. 88000-3311300), Department of Social Development and Basic Research Project of Guangdong Provincial Science and Technology (2011A030400003) and Cooperative Technology Innovation Platform Project (2012B090600044).

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Retraction notice

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP18

DOI: 10.1177/1470320314563425
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SAGE

The following article has been included in a multiple retraction:

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System* (*JRAAS*) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

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Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP19–NP26

DOI: 10.1177/1470320314563425
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RETRACTED: Relationship between the *ACE* I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Tian-Biao Zhou[1], Xue-Feng Guo[2], Zongpei Jiang[1] and Hong-Yan Li[3]

Abstract

Background and objective: The relationship between the angiotensin-converting enzyme (*ACE*) insertion/deletion (I/D) gene polymorphism and type 1 diabetic nephropathy (T1DN) susceptibility/risk of type 1 diabetes mellitus (T1DM) developing into T1DN in the Caucasian population is still controversial. This study was performed to evaluate the association of the *ACE* I/D gene polymorphism with T1DN susceptibility and the risk of T1DM developing into T1DN in the Caucasian population using the meta-analysis method.

Method: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: Twenty-one articles were identified for the analysis of the association of the *ACE* I/D gene polymorphism with T1DN susceptibility and the risk of T1DM developing into T1DN in the Caucasian population. The *ACE* I/D gene polymorphism was not associated with T1DN susceptibility and the risk of patients with T1DM developing T1DN in the Caucasian population. Sensitivity analysis according to a sample size of cases (< 100 vs ≥ 100) was also performed, and the results were also similar with the non-sensitivity analysis.

Conclusions: The *ACE* I/D gene polymorphism was not associated with T1DN susceptibility and the risk of patients with T1DM developing T1DN in the Caucasian population. However, more studies should be performed in the future.

Keywords

Type 1 diabetic nephropathy (T1DN), type 1 diabetes mellitus (T1DM), angiotensin-converting enzyme (*ACE*), insertion/deletion (I/D) gene polymorphism, meta-analysis

Introduction

Diabetes mellitus is a multifactorial metabolic disease characterized by post-prandial hyperglycemia, and it is associated with significant morbidity and mortality and its prevalence is increasing worldwide.[1,2] Diabetes mellitus includes type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), and the incidence of diabetes mellitus has increased dramatically over the last several decades.[3] Diabetic nephropathy (DN) is a serious complication of diabetes mellitus, and it includes type 1 diabetic nephropathy (T1DN) due to T1DM and type-2 diabetic nephropathy (T2DN) due to T2DM.[3,4] DN as a cause of end-stage renal disease (ESRD) is associated with a poor life expectancy, causing serious socioeconomic problems.[5]

The angiotensin-converting enzyme gene (*ACE*) is directly involved in the process of cell proliferation,

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differentiation, apoptosis and angiogenesis.[6] *ACE* can convert angiotensin I into angiotensin II, and inactivate bradykinin via the kallikrein-kininogen system, and angiotensin II is the main effector molecule of the renin-angiotensin system, is pleiotropic, and is a mediator of the development and progression of diseases.[7] The *ACE* insertion/deletion (I/D) gene polymorphism is a 287-bp sequence of DNA in the intron 16 of the *ACE* gene.[8] The *ACE* gene consists of either an insertion (I) allele or a deletion (D) allele that form three possible genotypes: II, ID or DD.[9] In adults plasma *ACE* does not change with age and is only to a minor extent influenced by environmental or lifestyle factors.[8] When compared with II homozygotes, circulating *ACE* levels in plasma were nearly 30% and 60% higher in ID heterozygotes and DD homozygotes, respectively.[9] Moreover, DD homozygotes also have been associated with higher tissue levels of *ACE*. The *ACE* I/D gene polymorphism, correlating with circulating *ACE* concentration, might be implicated in the etiology of T1DN and has been investigated in numerous epidemiologic studies.

The present epidemiologic studies show that the *ACE* I/D gene polymorphism has been implicated in the etiology of T1DN and the risk of patients with T1DM developing T1DN. However, the available evidence reported to date is weak, owing to sparseness of data or disagreements among studies. We performed this meta-analysis to investigate the relation between the *ACE* I/D gene polymorphism and T1DN susceptibility and the risk of patients with T1DM developing T1DN in the Caucasian population, with the intention of providing a much more reliable finding on the significance of the association.

Materials and methods

Search strategy

The relevant studies were searched from the electronic databases of PubMed and Cochrane Library on March 1, 2014. The terms "(diabetic nephropathy) AND (angiotensin converting enzyme) AND (polymorphism OR variant)" were entered into PubMed and Cochrane Library for the search. The search in PubMed was limited to studies of humans written in the English language. We also extended the search spectrum to "related articles" and the bibliographies of all recruited studies. If multiple publications from the same study group occurred, we recruited only the most complete paper for our analysis.

Inclusion and exclusion criteria

Inclusion criteria. (1) A case-control study; (2) the outcome had to be T1DN; (3) there had to be at least two comparison groups (T1DN group vs control group); (4) the study should be conducted in the Caucasian population.

Exclusion criteria. (1) Review articles, editorials and case reports; (2) articles did not provide the detailed genotype data; (3) investigating the association of other genes with T1DN; (4) investigating the role of *ACE* in diseases; (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by two investigators: first author's surname, year of publication, ethnicity of the study population, and the number of cases and controls for the *ACE* I/D genotype. Frequencies of the D allele were calculated for the case group and the control group from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5, Oxford, UK) and analyzed. The pooled statistics were counted using the fixed-effects model, but a random-effects model was conducted when the p value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. $p < 0.05$ was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies. Sensitivity analysis was performed according to sample size of case (< 100 vs ≥ 100). The Begg adjusted rank correlation test[10] and the Egger regression asymmetry test[11] were used for exploring publication bias ($p < 0.1$ was considered significant).

Results

Study characteristics

The search yielded 261 references, 260 from PubMed, and one from Cochrane Library. According to the inclusion and exclusion criteria, 21 articles were identified for the analysis between the *ACE* I/D gene polymorphism and T1DN susceptibility and the risk of T1DM developing into T1DN in the Caucasian population in our review. Six studies[12–17] were conducted on the relationship between the *ACE* I/D gene polymorphism and T1DN susceptibility (Table 1), and 21 reports[12–32] were conducted on the relationship between the *ACE* I/D gene polymorphism and the susceptibility of T1DM developing into T1DN (Table 2).

Table 1. Characteristics of the studies evaluating the effects of the *ACE* I/D gene polymorphism on T1DN risk.

First author, year	T1DN						Control					
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)
Powrie, 1994	7	8	4	19	22	38	112	168	84	364	392	728
Schmidt, 1995	52	38	24	114	142	228	49	63	22	134	161	268
Chowdhury, 1996	78	124	40	242	280	484	58	91	38	187	207	374
Demurov, 1997	24	29	3	56	77	112	40	43	13	96	123	192
Pfohl, 1998	17	15	8	40	49	80	46	90	43	179	182	358
De Cosmo, 1999	73	79	23	175	225	350	86	88	26	200	260	400

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T1DN: type 1 diabetic nephropathy.

Table 2. Characteristics of the studies evaluating the effects of ACE I/D gene polymorphism on T1DM developing into T1DN.

First author, year	T1DN						T1DM					
	DD	ID	II	Total	D allele	Total (allele)	DD	ID	II	Total	D allele	Total (allele)
Powrie, 1994	7	8	4	19	22	38	24	37	24	85	85	170
Doria, 1994	78	19	51	148	175	296	87	7	60	154	181	308
Tarnow, 1995	63	95	40	198	221	396	67	77	46	190	211	380
Schmidt, 1995	52	38	24	114	142	228	55	55	23	133	165	266
Chowdhury, 1996	78	124	40	242	280	484	55	79	32	166	189	332
Hibberd, 1997	21	42	9	72	84	144	16	43	27	86	75	172
Ringel, 1997	35	68	31	134	138	268	57	130	39	226	244	452
Barnas, 1997	4	21	15	40	29	80	14	27	9	50	55	100
Marre, 1997	119	168	50	337	406	674	48	69	40	157	165	314
Demurov, 1997	24	29	3	56	77	112	24	32	20	76	80	152
Pfohl, 1998	17	15	8	40	49	80	15	18	7	40	48	80
Freire, 1998	33	32	12	77	98	154	34	45	10	89	113	178
Bouhanick, 1999	4	20	5	29	28	58	19	19	9	47	57	94
De Cosmo, 1999	73	79	23	175	225	350	65	53	18	136	183	272
Vleming, 1999	39	24	16	79	102	158	26	34	22	82	86	164
van Ittersum, 2000	40	94	66	200	174	400	26	46	28	100	98	200
Hadjadj, 2007	–	–	–	–	990	2084	–	–	–	–	1208	2246
Möllsten, 2008	16	45	12	73	77	146	48	113	36	197	209	394
Gallego, 2008	15	17	9	41	47	82	102	204	103	409	408	818
Currie, 2010	211	335	134	680	757	1360	186	392	152	730	764	1460
Ilić, 2014	10	23	13	46	43	92	10	12	11	33	32	66

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T1DM: type 1 diabetes mellitus; T1DN: type 1 diabetic nephropathy.

Association of the ACE I/D gene polymorphism with T1DN risk

In this meta-analysis, the *ACE* I/D gene polymorphism was not associated with T1DN risk in the Caucasian population (D allele: OR = 1.12, 95% CI: 0.96–1.30, $p = 0.16$; DD genotype: OR = 1.17, 95% CI: 0.94–1.45, $p = 0.16$; II genotype: OR = 0.89, 95% CI: 0.67–1.18, $p = 0.42$; Figure 1 and Table 3).

Sensitivity analysis for the relationship between the *ACE* I/D gene polymorphism and T1DN risk in the Caucasian population was also performed according to sample size of case (< 100 vs ≥ 100). We found that the results were also similar with the non-sensitivity analysis. The *ACE* I/D gene polymorphism was not associated with T1DN risk in the Caucasian population (Table 3).

Association of ACE I/D gene polymorphism with the risk of T1DM patients developing T1DN

In this meta-analysis, the *ACE* I/D gene polymorphism was also not associated with the risk of T1DM patients developing T1DN in the Caucasian population (D allele: OR =

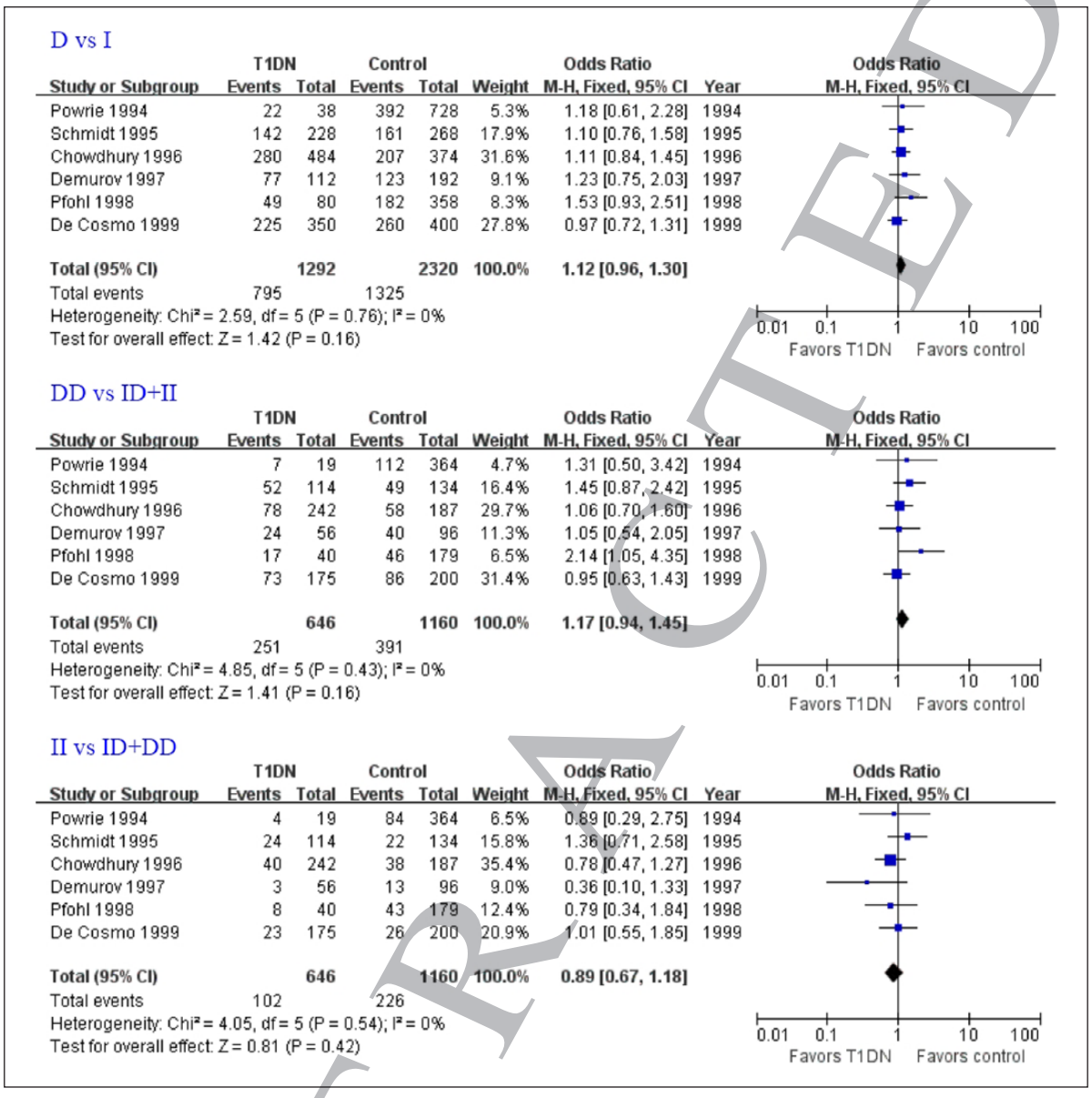

Figure 1. Association of the *ACE* I/D gene polymorphism on T1DN susceptibility (T1DN vs controls).
ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T1DN: type-1 diabetic nephropathy; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

1.04, 95% CI: 0.92–1.18, $p = 0.50$; DD genotype: OR = 1.06, 95% CI: 0.90–1.24, $p = 0.52$; II genotype: OR = 0.88, 95% CI: 0.72–1.06, $p = 0.18$; Figure 2 for D allele, Figure 3 for DD genotype and Figure 4 for II genotype; Table 3).

Sensitivity analysis for the relationship between the *ACE* I/D gene polymorphism and the risk of T1DM patients developing into T1DN in the Caucasian population was also performed according to sample size of case (< 100 vs ≥ 100). We found that the results were also similar with the non-sensitivity analysis. The *ACE* I/D gene polymorphism was not associated with the risk of T1DM patients developing T1DN in the Caucasian population (Table 3).

Evaluation of publication bias

No significant publication bias appeared in the comparison of T1DN vs T1DM (Begg $p = 0.833$, Egger $p = 0.231$; Figure 5 for Begg test).

Discussion

Dysfunction of *ACE* generation brought about by the *ACE* I/D gene polymorphism is considered the important deterioration factor associated with T1DN susceptibility and the risk for patients with T1DM developing T1DN in the Caucasian population. There was a rare genetic molecular

Table 3. Meta-analysis of the association of ACE I/D gene polymorphism with risk of T1DN and the T1DM developing into T1DN.

Genetic contrasts	Number of studies	*Q* test	Model	OR	*p*
		p value	selected	(95% CI)	
T1DN vs control					
D vs I	6	0.76	Fixed	1.12 (0.96, 1.30)	0.16
DD vs (ID+II)	6	0.43	Fixed	1.17 (0.94, 1.45)	0.16
II vs (ID+DD)	6	0.54	Fixed	0.89 (0.67, 1.18)	0.42
T1DN vs control (sensitivity analysis: ≥ 100)					
D vs I	3	0.79	Fixed	1.06 (0.88, 1.26)	0.55
DD vs (ID+II)	3	0.43	Fixed	1.10 (0.85, 1.41)	0.47
II vs (ID+DD)	3	0.39	Fixed	0.97 (0.70,1.35)	0.87
T1DN vs control (sensitivity analysis: < 100)					
D vs I	3	0.77	Fixed	1.33 (0.98, 1.81)	0.07
DD vs (ID+II)	3	0.35	Fixed	1.42 (0.92, 2.19)	0.11
II vs (ID+DD)	3	0.54	Fixed	0.68 (0.37, 1.23)	0.20
T1DN vs T1DM					
D vs I	21	<0.0001	Random	1.04 (0.92, 1.18)	0.50
DD vs (ID+II)	20	0.03	Random	1.06 (0.90, 1.24)	0.52
II vs (ID+DD)	20	0.03	Random	0.88 (0.72, 1.06)	0.18
T1DN vs T1DM (sensitivity analysis: ≥ 100)					
D vs I	10	0.002	Random	0.98 (0.86, 1.12)	0.79
DD vs (ID+II)	9	0.28	Fixed	1.06 (0.93, 1.21)	0.41
II vs (ID+DD)	9	0.15	Fixed	0.92 (0.79, 1.07)	0.26
T1DN vs T1DM (sensitivity analysis: < 100)					
D vs I	11	0.005	Random	1.14 (0.89, 1.46)	0.31
DD vs (ID+II)	10	0.02	Random	1.10 (0.77, 1.57)	0.59
II vs (ID+DD)	10	0.03	Random	0.79 (0.53, 1.18)	0.25

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T1DM: type 1 diabetes mellitus; T1DN: type 1 diabetic nephropathy; OR: odds ratio; CI: confidence interval.

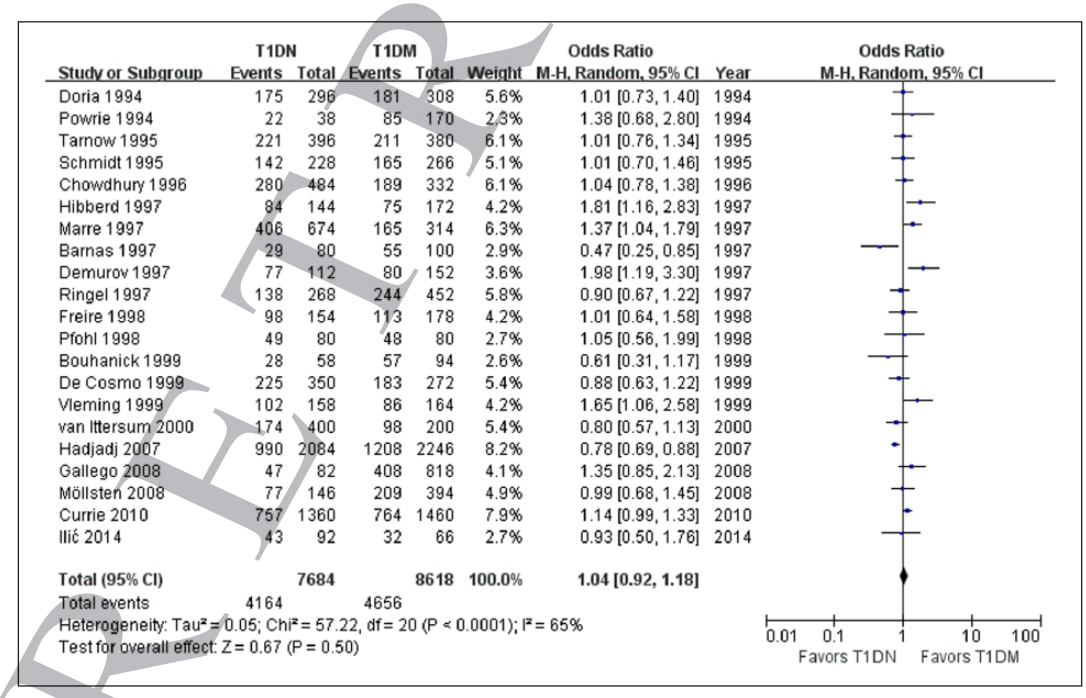

Figure 2. Association of *ACE* D allele on the risk of T1DM developing into T1DN (T1DN vs T1DM).
ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T1DN: type-1 diabetic nephropathy; T1DM: type-1 diabetes mellitus; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

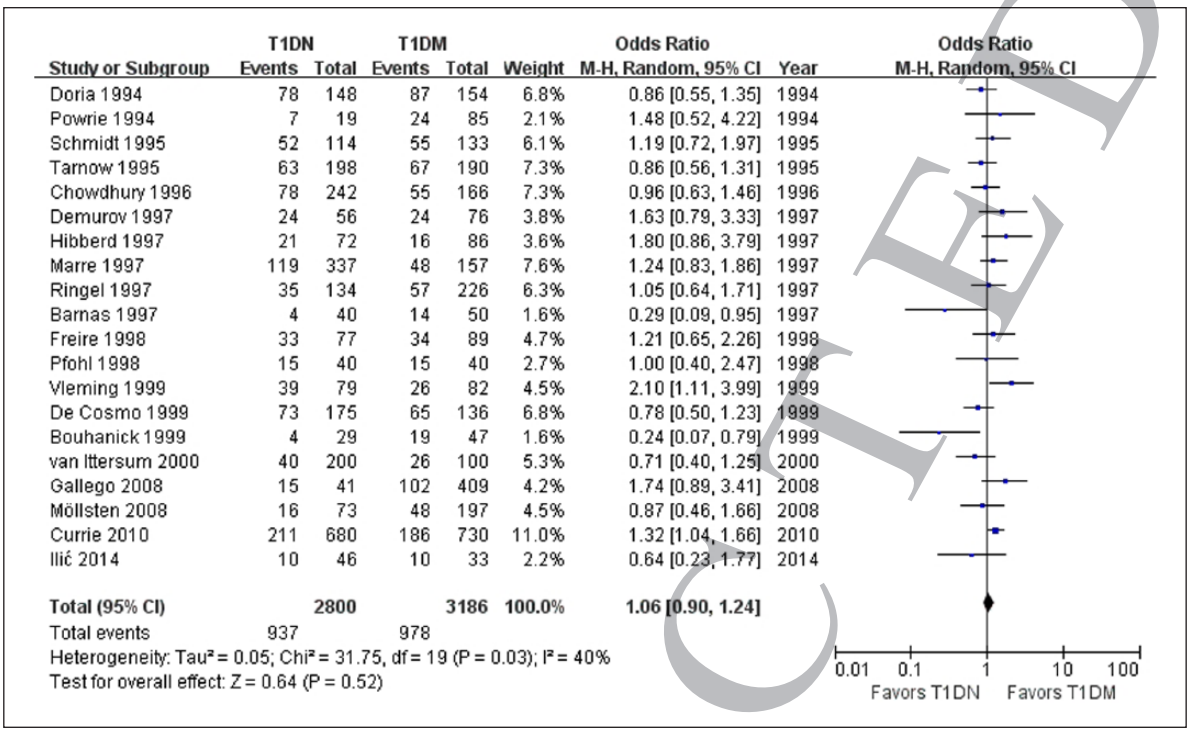

Figure 3. Association of *ACE* DD genotype on the risk of T1DM developing into T1DN (T1DN vs T1DM).
ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T1DN: type-1 diabetic nephropathy; T1DM: type-1 diabetes mellitus; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

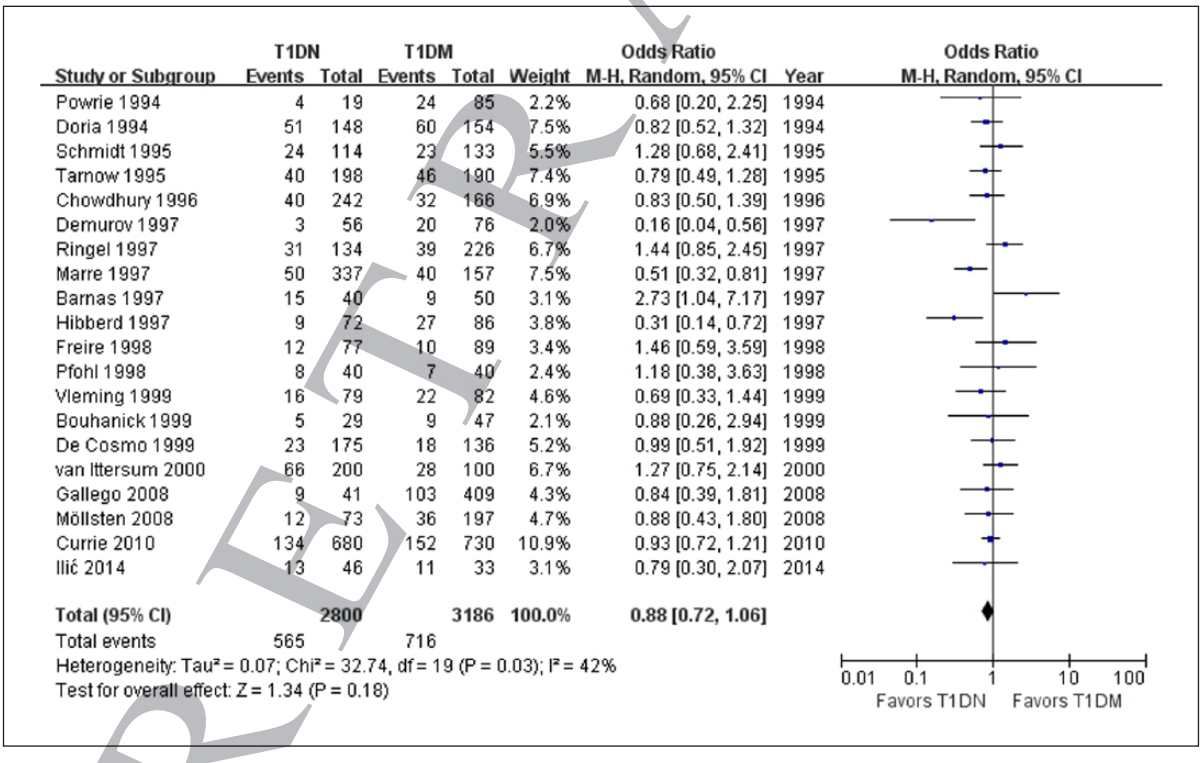

Figure 4. Association of *ACE* II genotype on the risk of T1DM developing into T1DN (T1DN vs T1DM).
ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T1DN: type-1 diabetic nephropathy; T1DM: type-1 diabetes mellitus; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

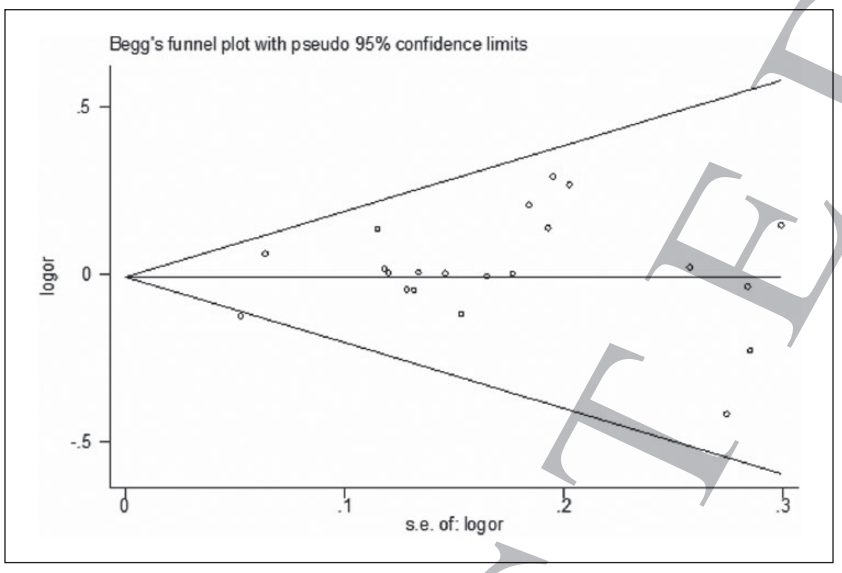

Figure 5. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of *ACE* I/D gene polymorphism with the risk of T1DM developing into T1DN.
ACE: angiotensin-converting enzyme; I/D: insertion/deletion; T1DN: type-1 diabetic nephropathy; T1DM: type-1 diabetes mellitus.

marker to predict the onset of T1DN and the risk of patients with T1DM developing T1DN in Caucasian population. This study using the meta-analysis method was performed to explore whether the *ACE* I/D gene polymorphism could predict the susceptibility of T1DN susceptibility and the risk of patients with T1DM developing T1DN in Caucasian population.

In this study, the relationship between the *ACE* I/D gene polymorphism and T1DN susceptibility in the Caucasian population was assessed using the meta-analysis method. We found that the *ACE* I/D gene polymorphism was not associated with T1DN susceptibility in the Caucasian population. Furthermore, sensitivity analysis was performed according to sample size of case (< 100 vs ≥ 100), and the results from the sensitivity analysis were similar to those from the non-sensitivity analysis. However, the number of included studies was small (only six included studies for meta-analysis), and the evidence was less robust. More studies should be performed in the future.

The relationship between the *ACE* I/D gene polymorphism and the risk of patients with T1DM developing T1DN in the Caucasian population was also assessed in this meta-analysis. The results indicated that the *ACE* I/D gene polymorphism was not associated with T1DN susceptibility. Furthermore, sensitivity analysis was performed according to sample size of case (< 100 vs ≥ 100), and the results from the sensitivity analysis were similar to those from the non-sensitivity analysis, and there was no significant publication bias. The number of included studies was large, and the evidence might be robust to some extent.

In this meta-analysis, we found that the *ACE* I/D gene polymorphism was not associated with T1DN susceptibility and the risk of patients with T1DM developing T1DN. However, these findings should be regarded cautiously because many other factors, such as heterogeneity of enrolled cases, limited statistical power, variable study designs and different interventions, were closely related to affect the results. Undoubtedly, the limitations mentioned above might affect our final conclusions.

In conclusion, the results in our study support that the *ACE* I/D gene polymorphism was not associated with T1DN susceptibility and the risk of patients with T1DM developing T1DN in the Caucasian population. However, more association investigations on larger, stratified populations are required to further clarify the role of the *ACE* I/D gene polymorphism in T1DN susceptibility and the risk of patients with T1DM developing T1DN in the Caucasian population.

Conflict of interest

None declared.

Funding

This study was supported by the sub-item of 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation, no. 88000-3311300), and the Guangzhou Medical Key Subject Construction Project (2013–2015).

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Retraction notice

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP27

DOI: 10.1177/1470320314563426
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SAGE

This article has been included in a multiple retraction:

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

This article has been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System* (*JRAAS*) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563424, first published on December 18, 2014 doi:10.1177/1470320314563424

Weiqiang Zhong, Zongpei Jiang, and Tian-Biao Zhou

Association between the ACE I/D gene polymorphism and T2DN susceptibility: The risk of T2DM developing into T2DN in the Asian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314566019, first published on January 26, 2015 doi:10.1177/1470320314566019

Tian-Biao Zhou, Xue-Feng Guo, Zongpei Jiang, and Hong-Yan Li

Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

Journal of Renin-Angiotensin-Aldosterone System 1470320314563425, first published on February 1, 2015 doi:10.1177/1470320314563425

Chun-Hua Yang and Tian-Biao Zhou

Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

Chun-Hua Yang and Tian-Biao Zhou

Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

Guohui Liu, Tian-Biao Zhou, Zongpei Jiang, and Dongwen Zheng

Association of ACE I/D gene polymorphism with T2DN susceptibility and the risk of T2DM developing into T2DN in a Caucasian population

Journal of Renin-Angiotensin-Aldosterone System March 2015 16: 165-171, first published on November 14, 2014 doi:10.1177/1470320314557849

Weiqiang Zhong, Zhongliang Huang, Yong Wu, Zongpei Jiang, and Tian-Biao Zhou

Association of aldosterone synthase (CYP11B2) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Journal of Renin-Angiotensin-Aldosterone System September 2015 16: 660-665, first published on August 20, 2014 doi:10.1177/1470320314524011

jraas

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP28–NP34

DOI: 10.1177/1470320314563426
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RETRACTED: Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Wenzhuang Tang[1], Tian-Biao Zhou[2] and Zongpei Jiang[2]

Abstract

Aim: The association between angiotensinogen (*AGT*) M235T gene polymorphism and the risk of diabetes mellitus (DM) developing into diabetic nephropathy (DN) is still controversial. This meta-analysis was performed to evaluate the association of *AGT* M235T gene polymorphism with the susceptibility of DM developing into DN.

Methods: A predefined literature search and selection of eligible relevant studies were performed to collect data from electronic databases.

Results: Nineteen articles were identified for analysis of the association of the *AGT* M235T gene polymorphism with the susceptibility of DM developing into DN. The *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN in overall populations, in Asians and in the Caucasian population. Furthermore, the *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN in the T1DM population and T2DM population.

Conclusions: The *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN. However, more studies should be performed in the future.

Keywords

Diabetes mellitus (DM), diabetic nephropathy (DN), angiotensinogen, M235T, gene polymorphism, meta-analysis

Introduction

Diabetes mellitus (DM) is a major public health problem worldwide.[1] It is associated with endothelial dysfunction, reducing nitric oxide (NO)-dependent vasodilation and increasing production of pro-inflammatory factors, leading to increased long-term cardiovascular and kidney risk.[2] Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes and the leading cause of end-stage renal disease.[3] DN includes type 1 diabetic nephropathy (T1DN) due to type 1 DM and type 2 diabetic nephropathy (T2DN) due to type 2 DM.[4,5] Some investigations suggested that genetic factors might play a key role in the risk of DM developing into DN.

The angiotensinogen (*AGT*) gene is located on chromosome 1q41-qter, and regulates the expression of angiotensinogen, a glycoprotein produced by the liver. Its cleavage by renin liberates angiotensin I, which is converted into angiotensin II by the angiotensin-converting enzyme.[6–8] The M235T variant of the *AGT* gene has been associated with higher plasma AGT levels in patients homozygous for the T allele and occurs among various ethnic populations.[9] The *AGT* M235T gene polymorphism, correlating with circulating and cellular AGT concentration, has been implicated in the etiology of DM developing into DN and has been investigated in numerous epidemiologic studies at present. However, the available evidence reported to date is

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weak, due to sparseness of data or disagreements among studies. There was rare meta-analysis to explore the association of *AGT* M235T gene polymorphism with risk of DM developing into DN. We performed this meta-analysis to investigate the relation between AGT M235T gene polymorphism and risk of DM developing into DN.

Materials and methods

Search strategy

The relevant studies were screened from the search engines of PubMed, Cochrane Library on August 1, 2014. The terms "(angiotensinogen OR AGT) AND (diabetic nephropathy)" were used in PubMed and Cochrane Library to complete the search. We also extended the search spectrum to the "related articles" and the bibliographies of all retrieved studies. If multiple publications of the same data from the same study group occurred, we recruited only the later paper for analysis.

Inclusion criteria. (1) A case-control study; (2) the outcome had to be DN; (3) there had to be at least two comparison groups (DN group vs DM group).

Exclusion criteria. (1) Review articles, editorials and case reports; (2) articles did not provide the detail genotype data; (3) investigating the association of other genes with DN; (4) investigating the role of drugs on diseases; (5) multiple publications of the same data from the same study group.

Data extraction and synthesis

The following information was extracted from each study independently by at least two investigators: first author's surname, year of publication, ethnicity of study population, and the number of cases and controls for the M235T genotype. Frequencies of T allele were calculated for case group and control group, from the corresponding genotype distribution. The results were compared and disagreements were resolved by discussion.

Statistical analysis

Available data were entered into Cochrane Review Manager (RevMan, version 5) and analyzed. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the *p* value of heterogeneity test was less than 0.1. Results were expressed with odds ratios (OR) for dichotomous data, and 95% confidence intervals (CI) were also calculated. $p < 0.05$ was required for the overall OR to be deemed statistically significant. I^2 was used to test the heterogeneity between the included studies. We classified the investigations into studies for Asians, Caucasians and African populations because genotype frequencies and prevalence of DN were different among ethnic groups. The Begg adjusted rank correlation test[10] and the Egger regression asymmetry test[11] were used for exploring publication bias ($p < 0.1$ was considered significant) when the sample number was more than five.

Results

Study characteristics

The search yielded 162 references: 162 from PubMed, and 0 from Cochrane Library. According to the inclusion and exclusion criteria, nineteen articles[12–30] were identified for the analysis of the between the *AGT* M/T gene polymorphism and the susceptibility of DM developing into DN in our review (Table 1).

Association of AGT M/T gene polymorphism with the risk of DM patients developing into DN

In this meta-analysis, the *AGT* M/T gene polymorphism was not associated with the susceptibility of DM developing into DN in the overall population (T allele: OR = 1.26, 95% CI: 0.96–1.65, $p = 0.10$; TT genotype: OR = 1.42, 95% CI: 0.97–2.08, $p = 0.07$; MM genotype: OR = 0.81, 95% CI: 0.56–1.18, $p = 0.28$; Figure 1 for T allele, and Figure 2 for TT genotype and Figure 3 for MM genotype; Table 2). Furthermore, the *AGT* M/T gene polymorphism was not associated with the susceptibility of DM developing into DN in Asians and the Caucasian population (Table 2).

Sensitivity analysis for the relationship between the *AGT* M/T gene polymorphism and the susceptibility of DM developing into DN was also performed according to types of DM. In the sensitivity analysis, the *AGT* M/T gene polymorphism was not associated with the susceptibility of T1DM developing into T1DN in the overall population (T allele: OR = 1.26, 95% CI: 0.94–1.70, $p = 0.12$; TT genotype: OR = 1.41, 95% CI: 0.76–2.63, $p = 0.28$; MM genotype: OR = 0.76, 95% CI: 0.55–1.04, $p = 0.09$; Table 2). Furthermore, the *AGT* M/T gene polymorphism was not associated with the susceptibility of T2DM developing into T2DN in the overall population (T allele: OR = 1.17, 95% CI: 0.78–1.76, $p = 0.45$; TT genotype: OR = 1.31, 95% CI: 0.79–2.15, $p = 0.29$; MM genotype: OR = 0.89, 95% CI: 0.54–1.47, $p = 0.65$; Table 2).

Evaluation of publication bias

No significant publication bias was shown in this meta-analysis (Begg P=0.596, Egger P=0.416; Figure 4 for Begg test).

Discussion

In this investigation, 19 studies were included into this meta-analysis, and we found that the *AGT* M/T gene polymorphism was not associated with the susceptibility of

Table 1. Characteristics of the studies evaluating the effects of the *ATG M235T* gene polymorphism on DM developing into DN.

First author, year	Ethnicity	Type of DM	DN						DM					
			TT	MT	MM	Total	T allele	Total (allele)	TT	MT	MM	Total	T allele	Total (allele)
Rogus, 1998	Caucasian	T1DM	–	–	–	–	76	143	–	–	–	–	32	70
Miura, 1999	Asian	T1DM	61	34	3	98	156	196	69	32	2	103	170	206
Tomino, 1999	Asian	T2DM	507	–	–	745	–	–	277	–	–	407	–	–
van Ittersum, 2000	Caucasian	T1DM	13	37	19	69	63	138	21	96	71	188	138	376
Zychma, 2000	Caucasian	T2DM	106	228	116	450	440	900	64	116	63	243	244	486
Lovati, 2001	Caucasian	T1DM	5	18	9	32	28	64	1	16	20	37	18	74
Fradin, 2002	Caucasian	T2DM	25	44	49	118	94	236	19	59	40	118	97	236
Prasad, 2006	Asian	T2DM	86	86	24	196	258	392	45	85	95	225	175	450
Osawa, 2007	Asian	T2DM	22	209	504	735	253	1470	15	195	341	551	225	1102
Eroglu, 2008	Caucasian	T2DM	10	24	12	46	44	92	9	32	15	56	50	112
Möllsten, 2008	Caucasian	T1DM	7	40	26	73	54	146	35	104	58	197	174	394
Gallego, 2008	Caucasian	T1DM	10	23	8	41	43	82	77	231	136	444	385	888
Tien, 2009	Asian	T2DM	17	–	–	93	–	–	97	–	–	432	–	–
Ahluwalia, 2009	Asian	T2DM	82	104	54	240	268	480	27	120	108	255	174	510
Manea, 2011	Caucasian	T2DM	17	60	30	107	94	214	41	92	10	143	174	286
Mtiraoui, 2011	Caucasian	T2DM	73	138	118	329	284	658	20	176	209	405	216	810
Reis, 2011	Caucasian	T2DM	17	68	23	108	102	216	41	51	19	111	133	222
Shaikh, 2014	Asian	NC	62	47	1	110	171	220	35	77	3	115	147	230
Ilić, 2014	Caucasian	T1DM	15	23	8	46	53	92	3	23	7	33	29	66

DM: diabetes mellitus; DN: diabetic nephropathy; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; NC: Not clear.

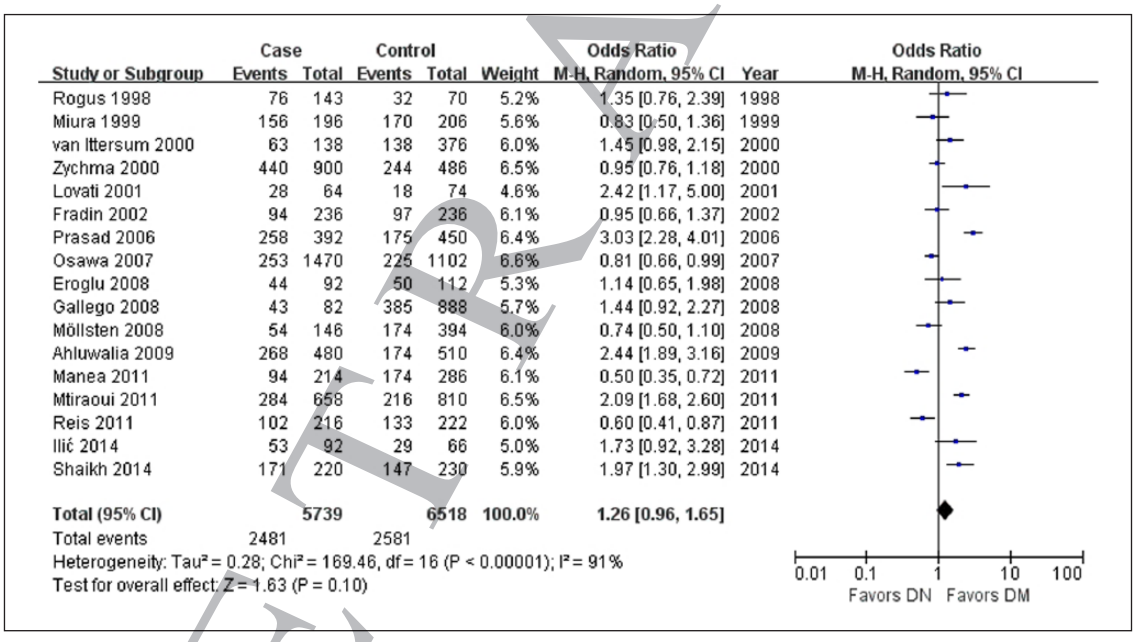

Figure 1. Association of *AGT* T allele on the risk of DM developing into DN.
AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

DM developing into DN in the overall population. Furthermore, the *AGT* M/T gene polymorphism was not associated with the susceptibility of DM developing into DN in Asians and the Caucasian population. There was no publication bias in this meta-analysis, and the results might be robust to some extent.

In the sensitivity analysis, the relationship between the *AGT* M/T gene polymorphism and the susceptibility of DM developing into DN was also performed according to types of DM. We found that the *AGT* M/T gene polymorphism was not associated with the susceptibility of T1DM developing into T1DN in the overall population.

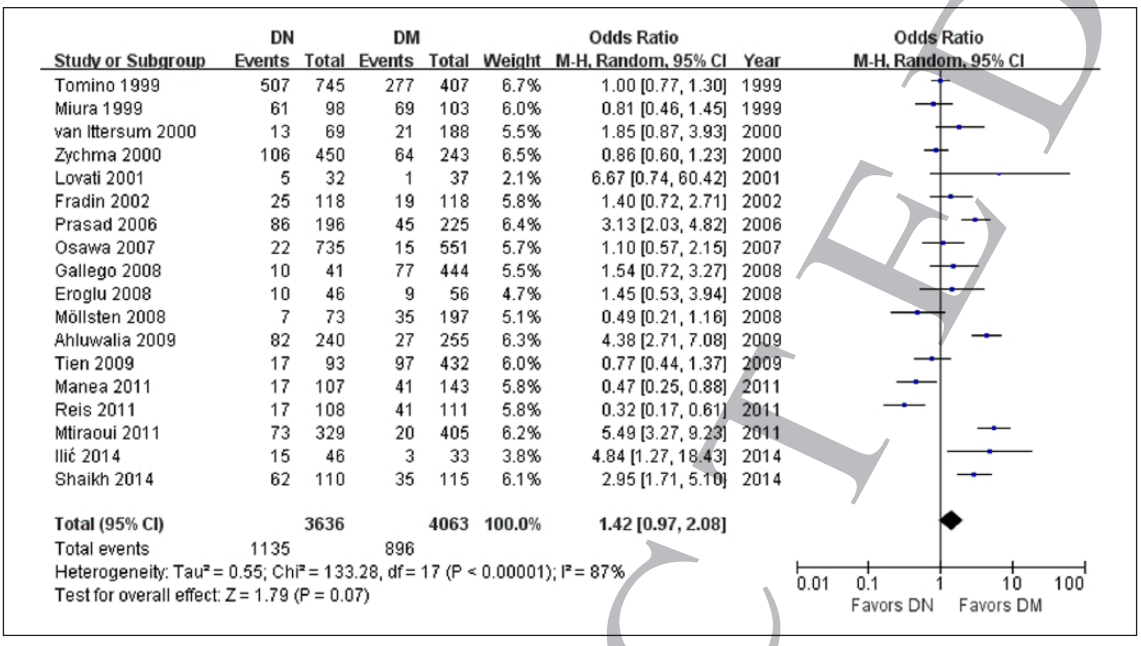

Figure 2. Association of *AGT* TT genotype on the risk of DM developing into DN.
AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

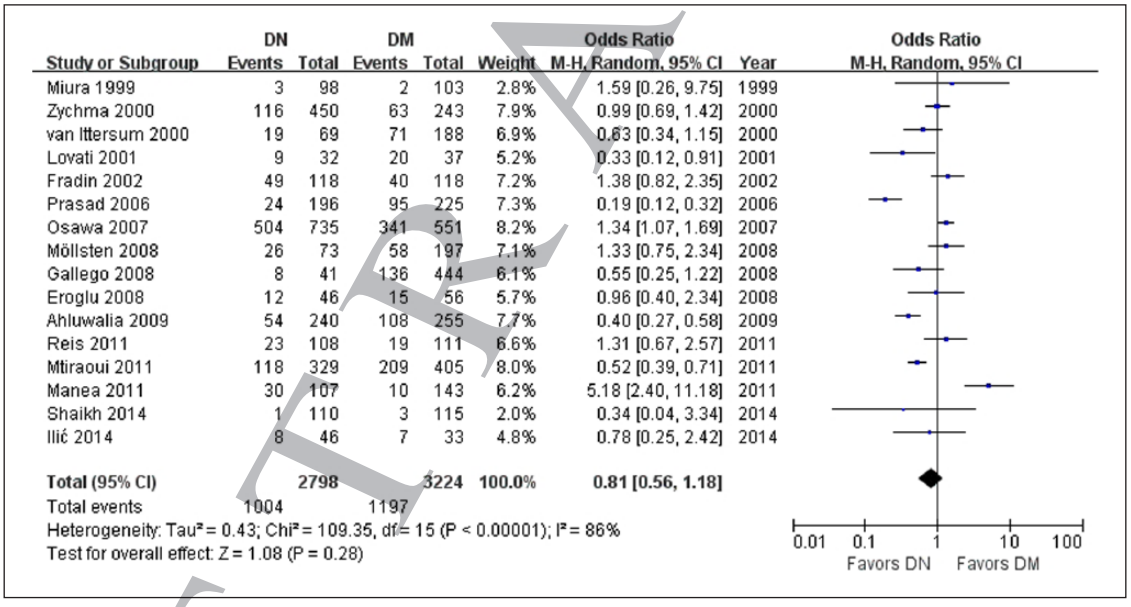

Figure 3. Association of *AGT* MM genotype on the risk of DM developing into DN.
AGT: angiotensinogen; DM: diabetes mellitus; DN: diabetic nephropathy; OR: odds ratio; CI: confidence interval; df: degree of freedom; M-H: Mantel-Haenszel.

Furthermore, the *AGT* M/T gene polymorphism was not associated with the susceptibility of T2DM developing into T2DN in the overall population.

As those mentioned above, this study indicated that the *AGT* M/T gene polymorphism might not be associated with the susceptibility of DM developing into DN. However, more studies should be conducted in further to confirm it. However, when the fixed model was used for this meta-analysis, we found that the *AGT* M/T gene polymorphism was associated with the susceptibility of DM developing into DN (data not shown).

In our investigation, we found that the *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN in overall populations, in

Table 2. Meta-analysis of the association of the *ATG M235T* gene polymorphism with risk of DM developing into DN.

Genetic contrasts	Group and subgroups	Studies	Q test	Model	OR	*p*
			p value	Selected	(95% CI)	
T vs M	Overall	17	<0.00001	Random	1.26 (0.96, 1.65)	0.10
	Asian	5	<0.00001	Random	1.59 (0.87,2.90)	0.13
	Caucasian	12	<0.00001	Random	1.13 (0.84, 1.51)	0.43
TT vs (TM+MM)	Overall	18	<0.00001	Random	1.42 (0.97, 2.08)	0.07
	Asian	7	<0.00001	Random	1.62 (0.94, 2.79)	0.08
	Caucasian	11	<0.00001	Random	1.31 (0.73, 2.34)	0.37
MM vs (TM+TT)	Overall	16	<0.00001	Random	0.81 (0.56, 1.18)	0.28
	Asian	5	<0.00001	Random	0.54 (0.20, 1.46)	0.23
	Caucasian	11	<0.00001	Random	0.96 (0.66, 1.41)	0.84
T1DN						
T vs M	Overall	7	0.02	Random	1.26 (0.94, 1.70)	0.12
TT vs (TM+MM)	Overall	6	0.02	Random	1.41 (0.76, 2.63)	0.28
MM vs (TM+TT)	Overall	6	0.16	Fixed	0.76 (0.55, 1.04)	0.09
T2DN						
T vs M	Overall	9	<0.00001	Random	1.17 (0.78, 1.76)	0.45
TT vs (TM+MM)	Overall	11	<0.00001	Random	1.31 (0.79, 2.15)	0.29
MM vs (TM+TT)	Overall	9	<0.00001	Random	0.89 (0.54, 1.47)	0.65

DM: diabetes mellitus; DN: diabetic nephropathy.

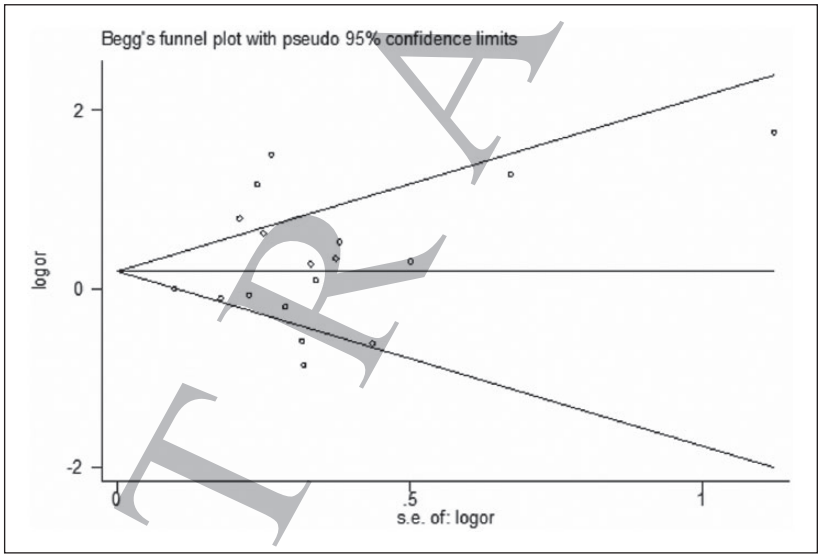

Figure 4. Begg's funnel plots with pseudo 95% confidence limits. Evaluation of publication bias for the association of the *AGT* M/T gene polymorphism with the risk of DM developing into DN.
DM: diabetes mellitus; DN: diabetic nephropathy.

Asians and in the Caucasian population. Furthermore, the *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN in the T1DM population and T2DM populations. However, these findings should be regarded cautiously because many other factors, such as heterogeneity of enrolled cases, limited statistical power, variable study designs and different interventions, were closely related to affect the results. Furthermore, whether the **AGT** M235T polymorphism is just linked with other discrete loci involved in the susceptibility of DM developing into DN is not clear at the moment.

Conclusions

In conclusion, the results in our study support that the *AGT* M235T gene polymorphism was not associated with the susceptibility of DM developing into DN. However, more

case-control association investigations on larger, stratified populations are required to further clarify the role of this *AGT* M235T gene polymorphism in the susceptibility of DM developing into DN.

Conflict of interest

None declared.

Funding

This study was supported by the sub-item of 985 Project Foundation of Sun Yat-Sen (The Hundred Talents Program Foundation, no. 88000-3311300).

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Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) NP10

DOI: 10.1177/1470320315623881
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Retraction notice

The following articles have been retracted at the request of the Editors and the Publisher.

After conducting a thorough investigation, SAGE found that the submitting authors of a number of papers published in the *Journal of the Renin-Angiotensin Aldosterone System* (*JRAAS*) (listed below) had supplied fabricated contact details for their nominated reviewers. The Editors accepted these papers based on the reports supplied by the individuals using these fake reviewer email accounts. After concluding that the peer review process was therefore seriously compromised, SAGE and the journal Editors have decided to retract all affected articles.

Online First articles (these articles will not be published in an issue)

Wenzhuang Tang, Tian-Biao Zhou, and Zongpei Jiang

Association of the angiotensinogen M235T gene polymorphism with risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314563426, first published on December 18, 2014 doi:10.1177/1470320314563426

Tian-Biao Zhou, Hong-Yan Li, Zong-Pei Jiang, Jia-Fan Zhou, Miao-Fang Huang, and Zhi-Yang Zhou

Role of renin-angiotensin-aldosterone system inhibitors in radiation nephropathy

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Relationship between the ACE I/D gene polymorphism and T1DN susceptibility/risk of T1DM developing into T1DN in the Caucasian population

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Relationship between the angiotensinogen A1166C gene polymorphism and the risk of diabetes mellitus developing into diabetic nephropathy

Journal of Renin-Angiotensin-Aldosterone System 1470320314566221, first published on February 1, 2015 doi:10.1177/1470320314566221

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Association of the ACE I/D gene polymorphism with sepsis susceptibility and sepsis progression

Journal of Renin-Angiotensin-Aldosterone System 1470320314568521, first published on February 3, 2015 doi:10.1177/1470320314568521

Articles published in an issue

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Journal of the Renin-Angiotensin-Aldosterone System
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Online First articles (these articles will not be published in an issue)

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jraas

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(3) 660–665

DOI: 10.1177/1470320314524011
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RETRACTED: Association of aldosterone synthase (*CYP11B2*) gene polymorphism with IgA nephropathy risk and progression of IgA nephropathy

Weiqiang Zhong[1], Zhongliang Huang[1], Yong Wu[1], Zongpei Jiang[2] and Tian-Biao Zhou[2]

Abstract

Objective: This meta-analysis was conducted to assess the association of aldosterone synthase (*CYP11B2*) gene polymorphism with the risk of immunoglobulin A (IgA) nephropathy (IgAN) and the progression of IgAN.

Methods: The literature on associations was identified from PubMed and the Cochrane Library on 1 October 2013, and eligible reports were synthesized.

Results: Eligible reports were recruited into this meta-analysis for the association of *CYP11B2*-344C/T (rs1799998) gene polymorphism with IgAN risk, and the progression of IgAN. In this meta-analysis, the association of *CYP11B2*-344C/T (rs1799998) gene polymorphism with IgAN risk was not found in overall populations and in Asians. Interestingly, the C allele and CC genotype were associated with the risk of IgAN in Caucasians, but the TT genotype was not.

Conclusion: *CYP11B2*-344C/T gene polymorphism is not associated with IgAN risk and IgAN progression in overall populations and in Asians, but *CYP11B2* C allele and CC genotype were associated with the risk of IgAN in Caucasians. However, more studies should be performed in the future to confirm this association.

Keywords

IgA nephropathy, aldosterone synthase, *CYP11B2*, gene polymorphism, meta-analysis

Date received: 9 November 2013; accepted: 15 January 2014

Introduction

Immunoglobulin A (IgA) nephropathy (IgAN), the most prevalent glomerular disease in the world and characterized by predominant IgA deposition in the mesangium, requires a renal biopsy for diagnosis.[1] It is initially regarded as a disease with a favorable prognosis but data from long-term follow-up studies have revealed that IgAN may progress to end-stage renal failure in up to 30% of patients with a follow up period of 20 years.[2,3] There is a lack of a well-documented diagnostic approach for IgAN risk; and reliable biomarkers are needed for the non-invasive diagnosis of this disease and to more fully delineate its natural history and risk for progression. Current evidence indicates that gene polymorphism of some genes is associated with the susceptibility of IgAN.[4–6]

Aldosterone, one of the main effectors of the renin-angiotensin system, has classically been thought to act as a regulator for the absorption of sodium and water, as well as the excretion of potassium in normal physiology, and as a mediator of edema in numerous disease states.[7] Aldosterone secretion is regulated largely by the expression level of the final enzyme required for its biosynthesis, aldosterone synthase (CYP11B2). Expression of CYP11B2 is regulated by angiotensin II through cyclic adenosine monophosphate (cAMP) dependent modulation of the gene promoter region, which contains a variety of control factors.[7] Therefore, genetic variants in CYP11B2, which may be associated with the biosynthesis of aldosterone in local tissue, may also affect the progression of renal dysfunction in primary glomerulonephritis. Aldosterone, via its

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binding to and activation of the mineralocorticoid receptors, is a main regulator of blood pressure by controlling renal sodium reabsorption.[8]

Gene polymorphism is one of the most important factors taking part in the etiology of some diseases. The evidence from meta-analysis might be powerful compared with the individual investigation. There was no meta-analysis to evaluate the association of the *CYP11B2*-344C/T gene polymorphism with the risk of IgAN and progression of IgAN. This meta-analysis was conducted to investigate whether the *CYP11B2*-344C/T gene polymorphism was associated with the risk of IgAN and the progression of IgAN, by widely collecting reported studies.

Materials and methods

Search strategy

The relevant studies were sought from the electronic databases of PubMed and the Cochrane Library on 1 October 2013. The retrieval strategy of '(IgA nephropathy OR IgA renal disease OR IgAN) AND (aldosterone synthase OR *CYP11B2*) AND (polymorphism OR variant)' was entered into these databases. Additional reports were identified through references cited in recruited articles.

Inclusion and exclusion criteria

Inclusion criteria: (a) The outcome had to be IgAN; (b) there had to be at least two comparison groups (case group vs control group); (c) investigation should provide data on *CYP11B2* genotype distribution.

Exclusion criteria: (a) Review articles and editorials; (b) case reports; (c) preliminary result not on *CYP11B2*-344C/T gene polymorphism or outcome; (d) investigating the role *CYP11B2* gene expression in disease; (e) if multiple publications for the same data from the same study group occurred, we only recruited the later paper into our final analysis.

Data extraction and synthesis

The following information from each eligible study was extracted independently by two investigators: first author's surname, year of publication, ethnicity, genotyping methods, control source of the control group, and the number of cases and controls for *CYP11B2*-344C/T genotypes. The results were compared and disagreement was resolved by discussion.

Statistical analysis

Cochrane Review Manager Version 5 (Cochrane Library, UK) was used to calculate the available data from each study. The pooled statistic was counted using the fixed effects model, but a random effects model was conducted when the p value of heterogeneity test was less than 0.1.[9–11] Results were expressed with odds ratios (ORs) for dichotomous data, and 95% confidence intervals (CIs) were also calculated.[12,13] The value of $p<0.05$ was required for the pooled OR to be statistically significant.[14] I^2 was used to test the heterogeneity among the included studies. Sensitivity analysis was also performed according to source of the controls (healthy vs hospital) and sample size of case (<100 vs ≥100).

Results

Study characteristics

Four studies[15–18] reporting the relationship between *CYP11B2*-344C/T gene polymorphism and IgAN susceptibility/IgAN progression were included into this meta-analysis. Four investigations[15–18] were conducted for the association of *CYP11B2*-344C/T gene polymorphism and IgAN risk, and two studies[15,16] were performed for the relationship between *CYP11B2*-344C/T gene polymorphism and IgAN progression (Table 1). Those four investigations contained 542 IgAN patients and 707 controls. The average distribution frequency of C allele of *CYP11B2*-344C/T in the IgAN group was 32.57% and the average frequency in the control group was 39%. The average distribution frequency of the case group for C allele was lower than that in the control group (case/control=0.84).

Table 1. General characteristics of the included studies in this meta-analysis.

Authors, year	Country/ District	Ethnicity	Genotyping methods	Source of control	Case				Control			
					CC	CT	TT	total	CC	CT	TT	Total
IgAN risk												
Kim et al., 2009[15]	Asian	Korea	TaqMan	Healthy	26	90	122	238	31	124	145	300
Huang et al., 2010[16]	Asian	Chinese	PCR-RFLP	Healthy	14	52	64	130	13	52	55	120
Bantis et al., 2011[17]	Caucasian	Germany	PCR-RFLP	Healthy	–	–	48	143	–	–	31	100
Pawlik et al., 2013[18]	Caucasian	Poland	PCR-RFLP	Healthy	4	15	12	31	48	104	35	187
IgAN progression												
Kim et al., 2009[15]	Asian	Korea	TaqMan	Healthy	–	–	34	66	–	–	88	172
Huang et al., 2010[16]	Asian	Chinese	PCR-RFLP	Healthy	5	17	25	47	9	35	39	83

IGAN: IgA nephropathy; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

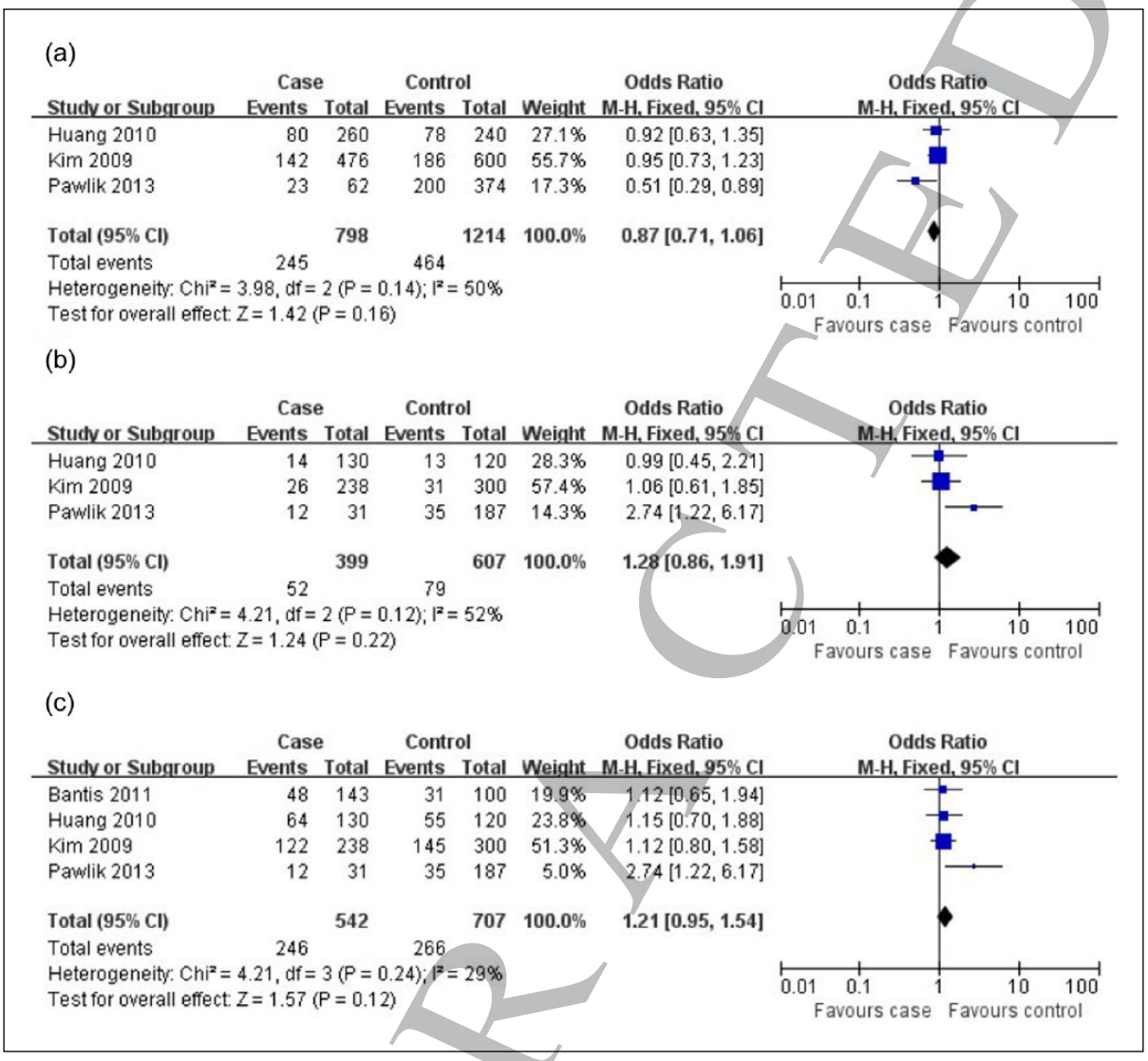

Figure 1. Association of aldosterone synthase *CYP11B2*-344C/T gene polymorphism with IgA nephropathy (IgAN) risk in overall populations. (a) C vs T; (b) CC vs CT + TT; (c) TT vs CT + CC.

Association of CYP11B2*-344C/T gene polymorphism with IgAN susceptibility*

The *CYP11B2*-344C/T gene polymorphism was not associated with IgAN risk for overall populations and Asians in this meta-analysis, (overall populations: C allele: OR=0.87, 95% CI: 0.71–1.06, p=0.16; CC: OR=1.28, 95% CI: 0.86–1.91, p=0.22; TT: OR=1.21, 95% CI: 0.95–1.54, p=0.12; Asians: C allele: OR=0.94, 95% CI: 0.76–1.16, p=0.56; CC: OR=1.04, 95% CI: 0.66–1.64, p=0.86; TT: OR=1.13, 95% CI: 0.85–1.50, p=0.39; Figure 1 for overall populations, Table 2). Interestingly, C allele and CC genotype were associated with the risk of IgAN in Caucasians, but not the TT genotype (C allele: OR=0.51, 95% CI: 0.29–0.89, p=0.02; CC: OR=2.74, 95% CI: 1.22–6.17, p=0.01; TT: OR=1.67, 95% CI: 0.70–3.98, p=0.25; Table 2).

Association of CYP11B2*-344C/T gene polymorphism with IgAN progression*

In this meta-analysis, all the included studies were from the Asian population, and *CYP11B2*-344C/T gene polymorphism was not associated with IgAN progression in overall populations and Asians (overall populations: C allele: OR=0.86, 95% CI: 0.49–1.49, p=0.59; CC: OR=0.98, 95% CI: 0.31–3.11, p=0.97; TT: OR=1.11, 95% CI: 0.71–1.73, p=0.65; Asians: C allele: OR=0.86, 95% CI: 0.49–1.49, p=0.59; CC: OR=0.98, 95% CI: 0.31–3.11, p=0.97; TT: OR=1.11, 95% CI: 0.71–1.73, p=0.65; Figure 2 and Table 2).

Sensitivity analysis

Sensitivity analysis for the relationship between *CYP11B2* -344C/T gene polymorphism and IgAN risk was also

Table 2. Meta-analysis of the association of *CYP11B2*-344C/T gene polymorphism with IgA nephropathy (IgAN) risk and IgAN progression.

Genetic contrasts	Group and subgroups	Studies number	Q test *p* value	Model selected	OR (95% CI)	*p*
IgAN risk						
C vs T	Overall	3	0.14	Fixed	0.87(0.71–1.06)	0.16
	Asian	2	0.92	Fixed	0.94(0.76–1.16)	0.56
	Caucasian	1	–	Fixed	0.51(0.29–0.89)	0.02
CC vs CT+TT	Overall	3	0.12	Fixed	1.28(0.86–1.91)	0.22
	Asian	2	0.89	Fixed	1.04(0.66–1.64)	0.86
	Caucasian	1	–	Fixed	2.74(1.22–6.17)	0.01
TT vs CT+CC	Overall	4	0.24	Fixed	1.21(0.95–1.54)	0.12
	Asian	2	0.95	Fixed	1.13(0.85–1.50)	0.39
	Caucasian	2	0.07	Random	1.67(0.70–3.98)	0.25
IgAN progression						
C vs T	Overall	1	–	Fixed	0.86(0.49–1.49)	0.59
	Asian	1	–	Fixed	0.86(0.49–1.49)	0.59
CC vs CT+TT	Overall	1	–	Fixed	0.98(0.31–3.11)	0.97
	Asian	1	–	Fixed	0.98(0.31–3.11)	0.97
TT vs CT+CC	Overall	2	0.62	Fixed	1.11(0.71–1.73)	0.65
	Asian	2	0.62	Fixed	1.11(0.71–1.73)	0.65

CI: confidence interval; OR: odds ratio.

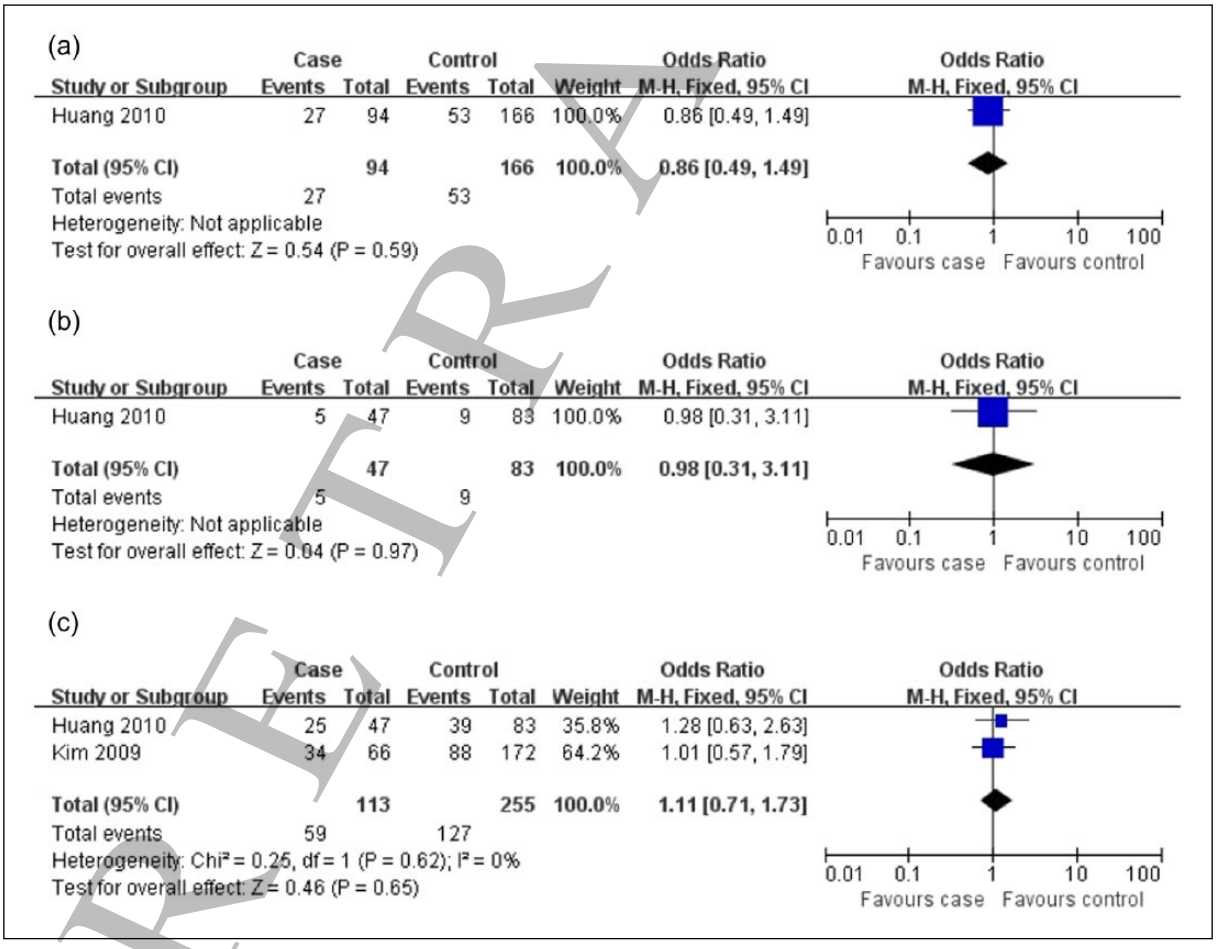

Figure 2. Association of aldosterone synthase *CYP11B2*-344C/T gene polymorphism with IgA nephropathy (IgAN) progression in overall populations. (a) C vs T; (b) CC vs CT + TT; (c) TT vs CT + CC.

performed according to according to the source of the controls (healthy vs hospital). The controls of all the included studies for *CYP11B2*-344C/T were from healthy sources, and the results were the same as in the non-sensitivity analysis.

Sensitivity analysis for the relationship between *CYP11B2*-344C/T gene polymorphism and IgAN risk was also performed according to sample size of case (<100 vs ≥100). We found that the results were also similar to the non-sensitivity analysis, but the *CYP11B2*-344C/T gene polymorphism was not associated with IgAN risk in the sensitivity analysis according to sample size of less than 100 (data not shown).

Discussion

Gene polymorphism, one of the most important factors, takes part in the etiology of IgAN disease. There were some interesting studies performed to assess the association of the polymorphism of some genes with IgAN risk or IgAN progression. Zhou et al.[2] performed a meta-analysis to evaluate the association between angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism and end-stage renal disease (ESRD) susceptibility in IgAN patients, and reported that the DD homozygote was a significant genetic molecular marker for the onset of ESRD in IgAN patients. Qin et al.[3] performed a meta-analysis to evaluate the association of ACE gene polymorphism with IgAN in different ethnic groups, and showed that the D allele or DD genotype was associated with IgAN risk in the Asian population, but not in the Caucasian population; there was no significant association between the D allele or DD gene and IgAN progression for Asians and Caucasians. In this meta-analysis, we also performed a meta-analysis to assess the association of *CYP11B2*-344C/T gene polymorphism and IgAN risk or IgAN progression.

In this study, the average distribution frequency of *CYP11B2*-344C/T C allele in the IgAN group was 0.84-fold increased when compared with that in control group. The average distribution frequency data indicated that the *CYP11B2*-344C/T C allele in IgAN group was lower when compared with that in control group. However, there were only three studies for this calculation, and this result might be less robust.

There was no meta-analysis performed to investigate the association of *CYP11B2*-344C/T gene polymorphism and the risk of IgAN in the past. This study was conducted firstly to assess the relationship between *CYP11B2*-344C/T gene polymorphism and the risk of IgAN and the progression of IgAN.

Four studies were included in this meta-analysis. We found that most of them reported that *CYP11B2*-344C/T gene polymorphism was not associated with the risk of IgAN. Kim et al.[15] included a total of 238 IgAN and 300 healthy cohorts in their study, and showed that the genotype distributions of the polymorphisms were similar between patients and controls, and the individual genotypes taken alone were not associated with the progression of renal dysfunction. Huang et al.[16] included 130 Chinese patients with IgAN and 120 healthy Chinese subjects, and reported that the *CYP11B2*-344C/T genotype distributions were similar in patients with IgAN and in controls, and the *CYP11B2*-344C/T gene polymorphism was not associated with ESRD progression in IgAN-ESRD patients. Bantis et al.[17] conducted a study in 143 patients with biopsy-proven IgAN and 100 healthy controls, and indicated that aldosterone synthase gene C-344T polymorphism was a risk factor for accelerated progression in Caucasian patients with IgAN. Pawlik et al.[18] included 31 IgAN patients and 187 controls, and reported that the CYP11B2-344C/T gene polymorphism might be an independent risk factor for IgAN. These two studies from the Caucasian population might get a more positive result than in the Asian population.

Our meta-analysis indicated that the *CYP11B2*-344C/T gene polymorphism was not associated with IgAN risk for overall populations and Asians in this meta-analysis. Interestingly, the C allele and CC genotype were associated with the risk of IgAN in Caucasians, but the TT genotype not. The outcome might be robust to some extent. However, those findings should be regarded cautiously because many other ingredients, such as small sample size of the included report, limited statistical power, heterogeneity of enrolled cases, variable study designs and different interventions, were closely related to affect the results. Since the number of included studies is rather small, more studies should be performed to evaluate the relationship in the future.

In conclusion, the results in our study support that *CYP11B2*-344C/T gene polymorphism was not associated with IgAN risk for overall populations and Asians in this meta-analysis. Interestingly, C allele and CC genotype were associated with the risk of IgAN in Caucasians, but not the TT genotype. However, more association investigations are required to further clarify the role of the *CYP11B2*-344C/T gene polymorphism in predicting the risk of IgAN and the progression of IgAN.

Declaration of Conflicting Interests

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

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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