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Apo E Gene Polymorphism Affects Development of Type 2 Diabetic Nephropathy in Asian Populations, Especially in East Asians: An Updated Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1,2 Yi-jin Lin
ACD 1,2 Jin-lin Pan
BCD 1,2 Min-juan Jiang
BCD 1,2 Jun-hua Tan
AB 1,2 Wei Zhong
ACD 1,2 Tie-kai Gong
ACD 1,2 Xiao-chan Jin
ACD 1,2 Shi-hong Cai
ABDE 1,2 Yao-jun Wu

1 Department of Nephrology, Danyang People's Hospital, Danyang, Jiangsu Province, China
2 Department of Nephrology, Danyang Hospital Affiliated to Nantong University, Danyang, Jiangsu, China

Corresponding Author: Yaojun Wu, e-mail: 362228972@qq.com
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Background: Many studies have determined the correlation between the Apolipoprotein E (APO E) gene polymorphisms and diabetic nephropathy, but their results are inconclusive.

Material/Methods: With the aim to confirm this correlation, we performed a meta-analysis of 16 studies. The dichotomous data are presented as the odds ratio (OR) with a 95% confidence interval (CI).

Results: The results of our study indicate that APO ε2 allele among the pooled Asian populations were more likely to show high risk of DN development (2 allele *vs.* ε3 allele: pooled *OR* =1.629, 95% *CI*=1.010–2.628, *P*=0.045). For further analysis, the APO ε2 allele was associated with progress of DN in the group with duration >10 years, but not in the group with duration <10 years (ε2 allele *vs.* ε3 allele: pooled *OR*=1.920, 95% *CI*=1.338–2.754, *P*<0.001). The APO ε2 polymorphism increased the susceptibility to DN in Asian population compared with healthy people (ε2 allele *vs.* ε3 allele: pooled *OR*=1.629, 95% *CI*=1.010–2.628, *P*=0.045).

Conclusions: Development of DN is associated with APO E polymorphisms in Asian populations, especially in East Asians.

MeSH Keywords: Diabetic Nephropathies • Disease Susceptibility • Meta-Analysis

Abbreviations: APO E – Apolipoprotein E • DN – Diabetic nephropathy • T2D – Type 2 diabetes • SNPs – single-nucleotide polymorphisms

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Background

Diabetic nephropathy (DN) is the leading cause of chronic renal disease and a major cause of cardiovascular mortality. Diabetic nephropathy is associated with cardiovascular disease and increases mortality of diabetic patients [1]. Diabetic nephropathy has been categorized into 2 stages: microalbuminuria and macroalbuminuria. Several factors are involved in the pathophysiology of DN, including metabolic and hemodynamic alterations, oxidative stress, activation of the renin-angiotensin system, immunoregulatory cytokines [2,3] and genetic factors. The 2 main risk factors for diabetic nephropathy are hyperglycemia and arterial hypertension, but the genetic susceptibility in type 1 and type 2 diabetes is of great importance [4]. Previous studies have shown that type 2 diabetes (T2D) is a metabolic disorder characterized by hyperglycemia, developing insulin resistance, β-cell dysfunction, and impaired insulin secretion. As the incidence of type 2 diabetes continues to rise world-wide, the personal and social burdens associated with this complication are becoming increasingly serious. A familial study has provided compelling evidence that genetic factors contribute to DN susceptibility in T2D [5] as have studies aimed at identifying the causal genes responsible for its development.

The Apolipoprotein E (APO E) gene, located on chromosome 19q13.2, has 3 common alleles – 2, 3, and 4 – coding for the 3 main isoforms of the Apo E protein: ε2 (Arg→Cys), ε3 (parent isoform), and ε4 (Arg→Cys). There are 6 common Apo E polymorphisms: Apo ε3/3, Apo ε4/4, Apo ε2/2, Apo ε3/2, Apo ε4/2, and Apo ε4/3 [6].

Many studies have investigated gene APO E polymorphism effects on susceptibility to type 2 diabetic nephropathy, and we have summarized the findings of those individual studies in the Appendix 1. Meta-analysis is a powerful method for quantitatively summarizing results from different studies. One of its advantages is to increase the sample size, which may reduce the probability that random error will result in a false-positive or false-negative association. Therefore, we performed a meta-analysis to quantitatively assess the association of APO E gene polymorphisms with DN.

Material and Methods

Literature search strategy

The Medline, PubMed, Embase, and Web of Science were searched (the last search was updated on June, 10, 2014 using the search terms: 'Diabetic Nephropathy" or "DN", "polymorphism", "APO E" or "Apolipoprotein E". All searched studies were retrieved and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant identified studies were hand-searched in addition to eligible studies. Only published studies with full-text articles were included. When more than one of the same patient populations was included in several publications, only the one with the sample size largest or the most complete study was used in this meta-analysis. A flow diagram of the study selection process is shown in Figure 1.

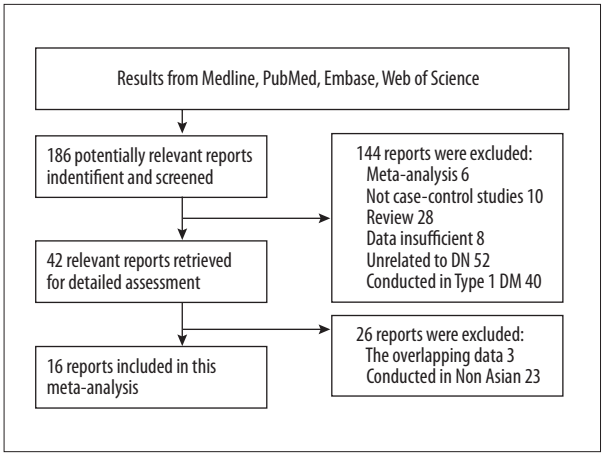

Figure 1. A flow diagram of the study selection process.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were determined by discussion. The inclusion criteria were: (1) the study aimed to examine the association between APO E polymorphisms and susceptibility to DN; (2) the design type of the study was a case-control study; (3) the study used diabetic patients without nephropathy or healthy subjects as controls; (4) the study provided the number of DN cases or controls and the frequency of APO E genotypes.

The exclusion criteria were: (1) the study did not fit the diagnosis criteria; (2) the study was conducted on animals; (3) the study was not a case-control study; (4) the study reported useless data; (5) the study focused on type 1 diabetic subjects.

Data extraction

All of the data were extracted independently by 2 reviewers (Yijin Lin and Jinlin Pan) according to the pre-specified selection criteria. Disagreement was resolved by discussion. The following data were extracted: control type, diabetic duration, study design, first author's name, publication year, and number of cases with normoalbuminuria, microalbuminuria, and macroalbuminuria, and number of healthy controls.

Statistical analysis

Allele frequencies at the APO E single-nucleotide polymorphisms (SNPs) from the studies were determined by the allele counting

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method. Statistical analysis was conducted using Stata 11.0 (StataCorp, College Station, TX) and a *P*-value ≤0.05 was considered to be statistically significant. Dichotomous data are presented as the odds ratio (OR) with a 95% confidence interval (CI). Statistical heterogeneity was measured using the *Q*-statistic (*P*≤0.10 was considered to be representative of statistically significant heterogeneity). We also quantified the effect of heterogeneity using the I^2 statistic, which measures the degree of inconsistency in the studies by calculating what percentage of the total variation across studies is due to heterogeneity rather than by chance. A fixed-effects model was used when there was no heterogeneity of the results of the trials; otherwise, the random effects model was used. For dichotomous outcomes, patients with incomplete or missing data and small-sample studies were included in the sensitivity analyses by counting them as treatment failures. To establish the effect of clinical heterogeneity between studies on the conclusions of meta-analyses, subgroup analysis was conducted on the basis of race. Several methods were used to assess the potential for publication bias. Visual inspection of asymmetry in funnel plots was conducted. Begg's rank correlation method and Egger's weighted regression method were also used to statistically assess the publication bias (*P*≤0.05 was considered to be representative of statistically significant publication bias).

Results

Characteristics of studies

This meta-analysis included 16 relevant studies of APO E SNPs, with 1754 cases and 3912 controls. The characteristics of each study are presented in the Appendix 1.

Quantitative data synthesis

The aim of this study was to use the meta-analysis method to quantitatively summarize the results from the selected individual studies. In comparing DN cases versus diabetic patients without nephropathy, our was aim to evaluate the relationship between APO E polymorphisms on the progress of diabetic patients. The carriers of the APO ε2 allele were more likely to have DN than the over-all group, the East Asia group, and the Japan group, but not in the 3 other subgroups (ε2 allele *vs.* ε3 allele: over-all: pooled *OR*=1.669, 95% *CI*=1.194–2.332, *P*=0.003; East Asia group: pooled *OR*=1.667, 95% *CI*=1.150–2.417, *P*=0.007; Japan group: pooled *OR*=2.352, 95% *CI*=1.228–4.502, *P*=0.010. ε2 group *vs.* ε3 group: East Asia group: pooled *OR*=1.829, 95% *CI*=1.235–2.711, *P*=0.003; Japan group: pooled *OR*=3.085, 95% *CI*=1.852–5.140, *P*<0.001) (Table 1 and Figure 2)

To understand the influence of diabetes duration on the development of diabetes, we divided the included studies into 2 parts by duration of diabetes, comparing the group with >10 years duration versus the group with duration <10 years. As Table 1 and Figure 3 show, the carriers of the APO ε2 allele were associated with progression of DN in the duration > 10 years group, but not in the duration <10 years group (ε2 allele *vs.* ε3 allele: pooled *OR*=1.920, 95% *CI*=1.338–2.754, *P*<0.001; ε2 group *vs.* ε3 group: pooled *OR*=1.667, 95% *CI*=0.946–2.936, *P*=0.077).

The aim of comparing DN cases and healthy people was to estimate the association of the APO E polymorphisms and susceptibility to DN. The APO ε2 polymorphism increased the susceptibility to DN in the Asian population (ε2 allele *vs.* ε3 allele: pooled *OR*=1.629, 95% *CI*=1.010–2.628, *P*=0.045; ε2 group *vs.* ε3 group: pooled *OR*=1.531, 95% *CI*=0.964–2.432, *P*=0.071) (Figure 4).

To further verify the association of development of DN and APO E polymorphisms, we quantitatively summarized the results of microalbuminuria versus normoalbuminuria and macroalbuminuria versus normoalbuminuria. The meta-analysis results of these 2 comparisons supported the results above – APO ε2 allele polymorphism was associated with the progression of DN (Table 2).

There were 3 prospective studies among the papers included in this meta-analysis, and the pooled results verified the conclusion of the case-control studies – the APO ε2 allele polymorphism was a risk factor in the development of DN (Progression *vs.* Non-progression: ε2 allele *vs.* ε3 allele: pooled *RR*=1.636, 95% *CI*=1.093–2.449, *P*=0.017; ε2 group *vs.* ε3 group pooled *RR*=1.711, 95% *CI*=1.124–2.606, *P*=0.012). We found a significant difference in comparison of 'ε2 allele *vs.* ε3 allele' group among 'Progression *vs.* Non-progression', but there were no other result supporting this conclusion (Table 2).

Heterogeneity

The heterogeneity was calculated among all studies using the Q-statistic (Q>0.05) and the I^2 statistic (I=0.0%). Heterogeneity was found in some groups, and the random-effects model was used.

Sensitivity analysis

A single study was deleted each time to investigate the influence of the individual dataset on the pooled *OR*s. The corresponding pooled *OR*s were not materially altered (data not shown), indicating that our results are statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. We found no asymmetry of the funnel plot, suggesting that there was no publication bias in our meta-analysis.

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Table 1. Summary about meta-analysis on APO E polymorphisms in Asian type 2 diabetes patients (with nephropathy *vs.* without nephropathy).

Comparisons	Stratification	Subgroups	n	OR(95% CI)			Homogeneity			Publication Bias	
				OR	CI	P value	Q	Ph	I^2 (%)	PB	PE
ε2 allele *vs.* ε3 allele	**All**		**15**	**1.669**	**1.194–2.332**	**0.003**	36.41	0.001	61.5	0.363	0.468
	Region	**East Asia**	**11**	**1.667**	**1.150–2.417**	**0.007**	28.64	0.001	65.1	0.350	0.330
		China	5	1.248	0.790–1.971	0.343	11.03	0.026	63.7	0.462	0.839
		Japan	**4**	**2.352**	**1.228–4.502**	**0.010**	6.97	0.073	56.9	0.089	0.133
		Korea	3	1.988	0.774–5.104	0.153	1.96	0.161	49.0	1.000	–
		Turkey	4	1.632	0.650–4.094	0.297	7.44	0.059	59.7	1.000	0.603
	Diabetes duration	>10 years	**9**	**1.920**	**1.338–2.754**	**<0.001**	14.73	0.251	26.8	0.348	0.199
		<10 years	4	0.793	0.480–1.310	0.366	4.10	0.065	45.7	0.734	0.982
ε4 allele *vs.* ε3 allele	All		15	1.018	0.854–1.214	0.843	11.44	0.652	0.652	0.310	0.098
	Region	East Asia	11	1.003	0.830–1.212	0.975	9.25	0.509	0.0	0.161	0.082
		China	5	1.097	0.851–1.414	0.475	1.29	0.862	0.862	0.806	0.331
		Japan	4	0.917	0.605–1.390	0.682	4.86	0.182	0.182	0.734	0.731
		Korea	2	0.698	0.289–1.683	0.423	1.63	0.201	0.201	1.000	–
		Turkey	4	1.114	0.696–1.783	0.652	2.02	0.568	0.568	0.734	0.350
	Diabetes duration	>10 years	9	0.979	0.750–1.276	0.873	9.80	0.279	18.4	0.251	0.189
		<10 years	4	0.967	0.649–1.442	0.871	1.22	0.749	0.0	0.734	0.800
ε2 group *vs.* ε3 group	All		16	1.512	0.987–2.316	0.058	49.72	< 0.001	69.8	0.760	0.138
	Region	**East Asia**	**12**	**1.829**	**1.235–2.711**	**0.003**	26.93	0.005	59.1	0.451	0.277
		China	5	1.248	0.790–1.971	0.360	8.46	0.076	52.7	1.000	0.861
		Japan	**5**	**3.085**	**1.852–5.140**	**<0.001**	4.78	0.311	16.3	1.000	0.713
		Korea	2	1.799	0.442–7.319	0.412	3.27	0.071	69.4	1.000	–
		Turkey	4	0.704	0.209–2.377	0.572	10.37	0.016	71.1	0.308	0.126
	Diabetes duration	>10 years	10	1.667	0.946–2.936	0.077	31.59	0.000	71.5	0.371	0.608
		<10 years	4	0.756	0.475–1.201	0.236	2.33	0.507	0.0	0.734	0.988
ε4 group *vs.* ε3 group	All		16	0.834	0.631–1.102	0.202	27.55	0.025	45.6	0.222	0.094
	Region	East Asia	12	0.878	0.644–1.196	0.409	21.67	0.027	49.2	0.321	0.232
		China	5	1.158	0.866–1.549	0.321	3.07	0.547	0.00	0.221	0.159
		Japan	5	0.710	0.405–1.245	0.232	10.73	0.030	62.7	0.462	0.566
		Korea	2	0.579	0.094–3.552	0.555	4.12	0.042	75.7	1.000	–
		Turkey	4	0.659	0.351–1.239	0.195	4.05	0.256	25.9	0.734	0.717
	Diabetes duration	>10 years	10	0.723	0.465–1.123	0.149	23.96	0.004	62.4	0.086	0.328
		<10 years	4	0.915	0.586–1.430	0.697	2.54	0.469	0.0	0.592	0.383

ε2 carrier (ε2/2, ε2/3 genotypes), ε3 group (ε3/3 genotype) and ε4 group (ε3/4, ε4/4 genotype).

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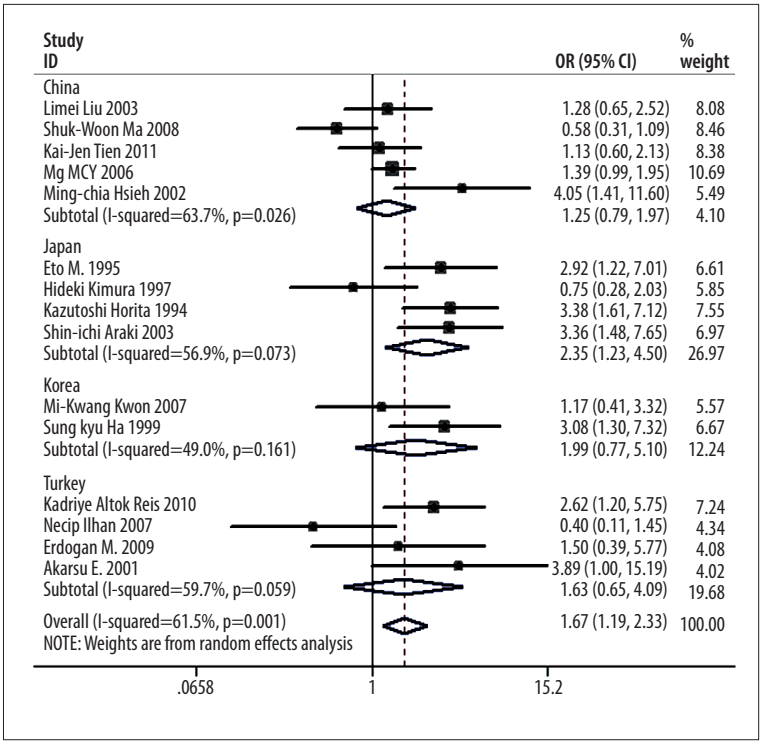

Figure 2. Forest plot of the APO E polymorphism and DN stratified by region(ε2 allele *vs.* ε3 allele).

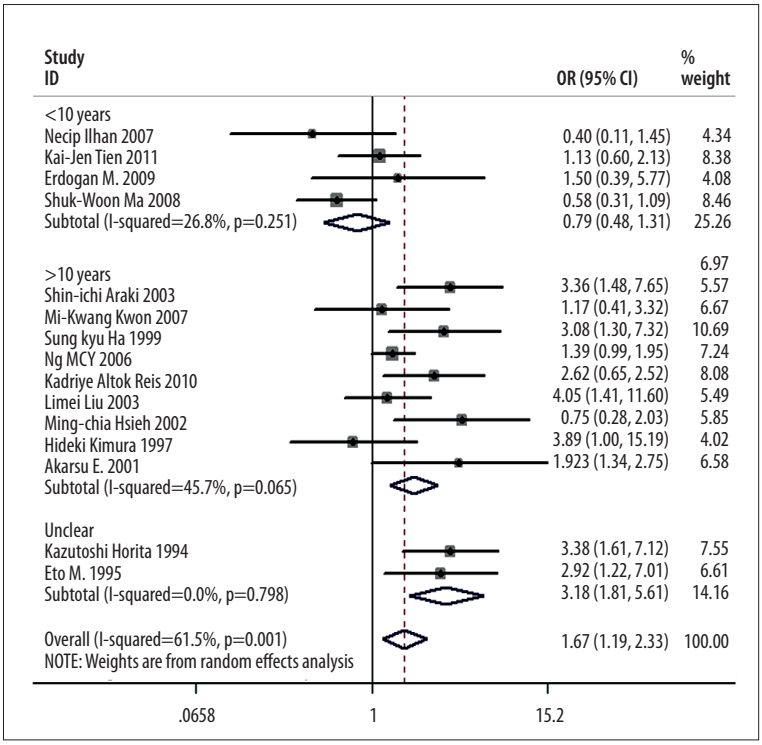

Figure 3. Forest plot of the APO E polymorphism and DN stratified by diabetic duration (ε2 allele *vs.* ε3 allele).

Discussion

Diabetic nephropathy (DN) is a major contributor to the high mortality of patients with DM [23]. Several acquired risk factors, such as abnormal lipoprotein metabolism, hypertension, and hyperglycemia, have been identified for the development of DN [24]. Genetic susceptibility is thought to contribute to the pathogenesis of this complication. Studies of patients with type 2 DM have shown either that the ε2 allele is a risk factor for DN or no association between Apo E polymorphism and DN

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Table 2. Summary about meta-analysis on APOE polymorphisms in Asian type 2 diabetes patients with nephropathy (DN *vs.* with nephropathy; microalbuminuria *vs.* normoalbuminuria; macroalbuminuria *vs.* normoalbuminuria; progress *vs.* non-progress).

Comparisons	Stratification	n	OR/RR(95% CI)			Homogeneity			Publication Bias	
			OR/RR	CI	P value	Q	Ph	I^2 (%)	P_B	P_E
ε2 allele *vs.* ε3 allele	**DN *vs.* healthy**	**7**	**1.629**	**1.010–2.628**	**0.045**	12.88	0.045	53.4	0.230	0.255
	Microalbuminuria *vs.* normoalbuminuria	**4**	**1.619**	**1.087–2.414**	**0.018**	1.13	0.770	0.0	1.000	0.870
	Macroalbuminuria *vs.* normoalbuminuria	3	1.808	0.980–3.337	0.058	4.42	0.110	54.7	1.000	0.469
	Progress *vs.* non-progress	**3**	***RR*=1.636**	**1.093–2.449**	**0.017**	4.18	0.124	52.2	0.602	0.527
ε4 allele *vs.* ε3 allele	DN vs. healthy	7	0.929	0.566–1.522	0.769	20.38	0.002	70.6	1.000	0.658
	Microalbuminuria *vs.* normoalbuminuria	4	0.792	0.541–1.160	0.231	2.75	0.431	0.0	0.308	0.553
	Macroalbuminuria *vs.* normoalbuminuria	3	0.992	0.601–1.639	0.976	1.01	0.605	0.0	1.000	0.208
	Progress *vs.* non-progress	**3**	***RR*=1.597**	**1.025–2.486**	**0.038**	2.21	0.331	9.5	1.000	0.132
ε2 group *vs.* ε3 group	DN *vs.* healthy	7	1.531	0.964–2.432	0.071	9.76	0.135	38.6	0.548	0.352
	Microalbuminuria *vs.* normoalbuminuria	4	1.382	0.874–2.187	0.167	1.13	0.771	0.0	0.806	0.291
	Macroalbuminuria *vs.* normoalbuminuria	**3**	**2.081**	**1.080–4.010**	**0.028**	2.81	0.245	28.8	0.734	0.649
	Progress *vs.* non-progress	**3**	***RR*=1.711**	**1.124–2.606**	**0.012**	3.08	0.215	35.0	1.000	0.786
ε4 group *vs.* ε3 group	DN *vs.* healthy	7	0.927	0.486–1.769	0.819	26.81	<0.01	77.6	1.000	0.831
	Microalbuminuria *vs.* normoalbuminuria	4	0.687	0.443–1.065	0.093	3.96	0.266	24.3	0.806	0.436
	Macroalbuminuria *vs.* normoalbuminuria	3	1.153	0.663–2.003	0.614	0.62	0.734	0.0	0.308	0.278
	Progress *vs.* non-progress	3	RR=1.533	0.952–2.468	0.087	2.15	0.342	6.8	0.296	0.127

ε2 carrier (ε2/2, ε2/3 genotypes), ε3 group (ε3/3 genotype) and ε4 group (ε3/4, ε4/4 genotype). The progressors on DN were defined as the subjects who shifted to a higher stage of DN from that at the baseline.

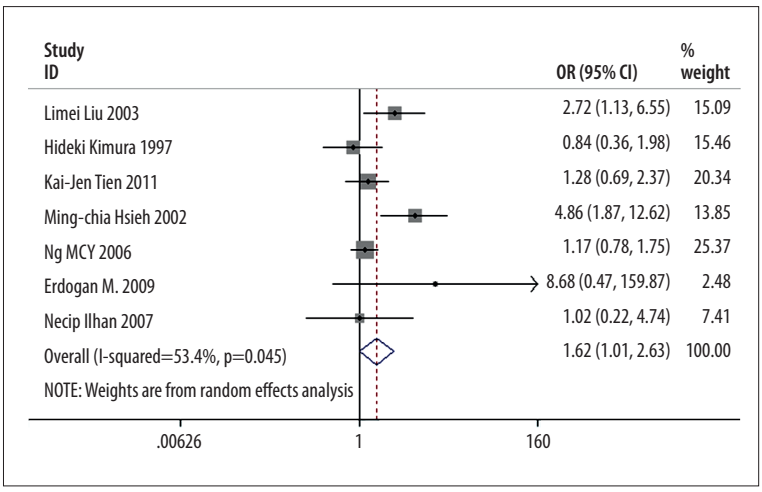

Figure 4. Forest plot of the APO E polymorphism and DN (DN *vs.* Healthy controls; ε2 allele *vs.* ε3 allele).

exists in Asian populations. A study conducted in Korean patients with type 2 DM found that the Apo ε2 allele was significantly more frequent in the macroalbuminuria group compared with the normoalbuminuria group [13]. A Japanese study involving 158 patients with long-term type 2 DM obtained similar results, showing that the ε2 allele could increase the risk

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Appendix 1. Findings of the studies included in this meta-analysis.

Studies	Year	Country	Number			Conclusion
			DN	Non-DN	Control	
Necip I'lhan [7]	2007	Turkey	37	71	46	In conclusion, the present prospective study indicates that thee4 allele of the Apo E polymorphism is one of the prognostic risk factors involved in the development of DN with type 2 diabetes mellitus
Shin-ichi Araki [8]	2003	Japan	31	398	–	Our follow-up study indicates that the2 allele of the APO E polymorphism is a prognostic risk factor for both the onset and the progression of diabetic nephropathy in Japanese type 2 diabetes
Masaaki Eto [9]	2001	Japan	99	59	–	Apo E2 is a positive factor and apo E4 is a negative factor for diabetic nephropathy. Apo E2 TG-rich lipoproteins, including remnant lipoproteins, affected HMCs. Remnant lipoproteins may have an important role in the progression of diabetic nephropathy
Kai-Jen Tien [10]	2011	China	136	382	576	Our study suggests the apo E4 carrier might serve as a predictor of DN progression in Taiwan
Kazutoshi Horita [11]	1994	Japan	57	398	–	It is concluded that apo E2 is associated with renal insuffkiency in NIDDM and that apo E2 may be a factor that aggravates lipid abnormalities in NIDDM with renal failure
Mi-Kwang Kwon [12]	2007	Korea	36	58	–	These data suggest that E4 carrier might be associated with the protection for the development of diabetic nephropathy in type 2 diabetic patients without respect to dyslipidemia
Sung kyu Ha [13]	1999	Korea	74	93	–	Apo E2 allele and E2 carrier frequencies were significantly higher in macroalbuminuria group. These results suggest that E2 allele may be associated with the development of clinical albuminuria in Korean Patients with NIDDM
Ng MCY [14]	2006	China	366	386	200	Our findings suggest the importance of interactions among lipid genes in modulating the risk of DN
Kadriye Altok Reis [15]	2010	Turkey	106	110	–	Our study has shown that AGT M235T TT genotype and APO E ε2/3 genotype may be linked to a risk for DN among Turkish population
Limei Liu [16]	2003	China	218	80	81	These results suggest that the HSPG T allele is a risk factor for the development of severe diabetic nephropathy in type 2 diabetic patients, and that the Apo E E2 allele is a risk factor for the occurrence of type 2 diabetes mellitus in Chinese general population. In addition, we find that co-inheritance of T/E2 confers a higher risk of type 2 diabetes mellitus progression to diabetic nephropathy in Chinese
Ming-chia Hsieh [17]	2002	China	215	100	150	These findings imply that apo E polymorphism is apparently related to the development of DN in type 2 diabetes in Taiwan
Eto M. [18]	1995	Japan	146	135	–	It is concluded that is a possibility that the ε2 allele is associated with nephropathy in NINNM
Hideki Kimura [19]	1997	Japan	81	96	251	Results indicate that apolipoprotein E polymorphism is associated with the progression of diabetic nephropathy. Presence of the apolipoprotein E4 allele is a protective factor, and other alleles are risk factors
M. Erdogan [20]	2009	Turkey	46	56	35	We conclude that the Apo E gene polymorphism is not associated with the development of diabetic nephropathy in Turkish Type 2 diabetic patients. Lack of association between Apo E gene polymorphism and Type 2 diabetic nephropathy might be due to ethnic differences
Shuk-Woon Ma [21]	2008	China	112	169	–	The APOE ε2 allele does not seem to be associated with increased risk of renal impairment in Chinese type 2 diabetic patients. Plasma lipid-standardized α-tocopherol may play a role in determining risk of renal dysfunction in type 2 diabetes
Akarsu E. [22]	2001	Turkey	24	22	–	As a result,we concluded that the ε2 allele of apo E may play a role in the mechanism of nephropathy in type 2 diabetes mellitus

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of DN, and ε4 was a protective factor [9]. Conversely, there are conflicting results regarding the impact of allele ε2 and ε4 on the development of DN. The APO ε2 allele did not appear to be associated with increased risk of renal impairment in Chinese type 2 diabetic patients [21] and a study indicated that the ε4 allele of the Apo E polymorphism is one of the prognostic risk factors involved in the development of DN with type 2 diabetes mellitus [7].

The results of this study suggest that APO ε2 allele is more likely to increase the risk of DN, while APO ε4 allele is not associated with the DN development and susceptibility in an East Asia population. Specifically, the OR value of most included studies (3/15) were larger than 1 when the ε2 allele and APO ε3 was compared (Figure 2). This finding indicates that the negative results of those studies might be due to inadequate sample size. In addition to the sample size, another reason for this inconsistency is the duration of diabetes in the DN and non-DN groups. This meta-analysis shows that, in most individual studies in patients with diabetes duration >10 years group, there is a significant correlation between DN and APO ε2, but none of the studies had positive results in subgroups of patients with diabetes duration <10 years (Figure 3). The defective ability of the APO ε2 isoform to bind to Apo E receptors may increase the risk of DN.

There are some limitations to this study. Firstly, because only published studies were included in the meta-analysis, publication bias may have occurred, even though it was not found by statistical tests. Secondly, a meta-analysis essentially retains the methodological deficiencies of the included studies. Finally, this meta-analysis is based on unadjusted estimates, while a more precise analysis could be performed if individual data were available.

Conclusions

In conclusion, in spite of several limitations mentioned above, this meta-analysis suggests that APO ε2 mutation increased the development of DN, especially in East Asian populations.

Conflicts of interest

None.

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