Association of apoE gene polymorphisms with lipid metabolism in renal diseases

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Abstract

Background and Objectives: Apolipoprotein E (apoE) plays a central role in the metabolism and homeostasis of lipids. ApoE gene encodes three major isoforms: ε2, ε3 and ε4 forming six phenotypes: E2E2, E2E3, E2E4, E3E3, E3E3 and E4E4 . Disorders of the lipid metabolism and the homeostasis are frequently coexist in renal diseases. The association between gene polymorphisms of apoE and lipid metabolism were not consistent. This meta-analysis was performed to assess the association between gene polymorphisms of apoE and lipid metabolism in renal diseases.

Methods: A pre-defined literatures search and selection of eligible relevant investigations were performed to extract and collect data from electronic databases.

Results: Sixteen articles were enrolled for the analysis of association between apoE gene polymorphisms and lipid metabolism. Subjects with E3E4 had a higher total cholesterol (TC) than those with E3E3, and subjects with E2E3 had a lower TC than those with E3E3. Subjects with ε2 had a lower TC than those with ε3 or ε4 , and subjects with ε4 had a higher TC than those with ε3 . Subjects with E2E2, E2E3 or E4E4 had a higher triglyceride (TG) than those with E3E3. Subjects with ε4 had a higher TG than those with ε3 . Subjects with ε2 had a higher level of TG than those with non-ε2. Subjects with E3E4 had a slightly lower high-density lipoprotein (HDL) than those with E3E3. E3E4 appeared to be associated with lower levels of HDL. Subjects with E2E2, E2E3 had a notably lower low-density lipoprotein (LDL) than those with E3E3. Subjects with ε2 had a lower LDL than those with ε3 or ε4 ApoE gene polymorphisms were not associated with very low-density lipoprotein, and lipoprotein (a) [Lp(a)]. Subjects with E2E3 or E2E4 had higher apoE levels than those with E3E3, and subjects with E4E4 had lower apoE levels than those with E3E3.

Conclusion: ApoE gene polymorphisms are associated with the expression of TC, TG HDL, LDL, Lp(a) or apoE.

Keywords: Apolipoprotein E (ApoE) ; gene polymorphism; total cholesterol (TC) ;triglyceride (TG), high-density lipoprotein (HDL); low-density lipoprotein (LDL); very low-density lipoprotein (VLDL); lipoprotein (a) [Lp(a)] • Meta-analysis

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Background

Apolipoprotein E (apoE) plays a central role in lipoprotein particle metabolism and lipid homeostasis[1-4], and the regulation of metabolism involved in total cholesterol (TC) and triglyceride (TG) [5, 6]. While in circulation, apoE mediates very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) catabolism, and the de novo high-density lipoprotein (HDL) biogenesis [7], and has also been associated with expression of lipoprotein (a) (Lp(a)) [8, 9]. ApoE gene encodes a 229-amino-acid long glycoprotein, can be distinguished three major isoforms: ε2, ε3 and ε4 . According to the differences in the positions 112 and 158 of amino acids, six phenotypes were observed:E2E2, E2E3, E2E4, E3E3, E3E4 and E4E4 [10,11] ε3 and E3E3 are considered wild-type apoE, and ε2, ε4, E2E2, E2E3, E2E4, E3E4 and E4E4 ae considered mutated forms of apoE [12].

The kidney is a major organ system and plays a major role in the proper functioning of the homeostasis [13]. Disorders of the lipid metabolism and the homeostasis

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are frequently coexist in renal diseases [14], such as nephrotic syndrome (NS), most kidney diseases have been associated with the high serum/plasma level of VLDL and impaired clearance of atherosclerotic residues. Nephrotic dyslipidemia is a risk factor to develop into systemic atherosclerosis, which may aggravate glomerular sclerosis and accelerate the progression of glomerular disease [15].

Currently, a number of reports have been carried out to show the relationship between the gene polymorphisms of apoE and expression of TC, TG, HDL, LDL, VLDL, and Lp(a). However, the results were not consistent. Due to the sparseness of data, and disagreements among the reported studies, the available evidence is weak, Evidence from meta-analysis can provide more convincing evidence when compared with individual investigations [16]. There is no meta-analysis to detect the association between apoE gene polymorphisms and lipid metabolism in kidney disease. Therefore, we performed a meta-analysis to further explore the relationship between apoE gene polymorphisms with lipid metabolism in renal diseases.

Methods

Search strategy: The search term was"(ApoE OR apolipoprotein E) AND (renal OR kidney)". Studies published on Oct 1, 2017 were screened from PubMed, Embase, and Cochrane Library without language limitation. "Related articles" and the bibliographies were also screened to extend search spectrum. Only the most complete paper recruited for repetitive data.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Renal diseases were demanded. (2) ApoE gene distribution was researched in disease. (3) Studies showed the level of TC, TG, HDL, LDL, VLDL, Lp(a) or apoE.

Exclusion criteria: (1) article types such as review, editorial and meta-analysis, etc; (2) multiple duplicated data in different publications; (3) apoE was not the target gene; (4) not renal diseases.

Data extraction and synthesis

Basic information (author, year, patient, location, disease type) was extracted independtly from every study by different investigators. Outcomes included the level of TC, TG, HDL, LDL, VLDL, Lp(a) or apoE.

Statistical analysis

The relationship was analyzed between apoE gene polymorphisms and outcomes. The available values of every outcomes were entered into Cochrane Review Manager (RevMan, Version 5). Fixed effects model was tacit, unless p-value of the heterogeneity test was less than 0.1, random effect model was conducted. Results were measured by Weighted mean differences(WMD) and 95% confidence intervals(CI). $P < 0.05$ was deemed statistically significant for the overall OR. I2 was used to test the heterogeneity of included studies. The Begg adjusted rank correlation test [17] and the Egger regression asymmetry test [18] were used to detect the publication bias ($P<0.1$ was considered significant) for included studies exceeding fifteen.

Results

Study characteristics

27 studies retrieved from PubMed, Embase, and Cochrane Library, enable to further analyze (Figure 1).

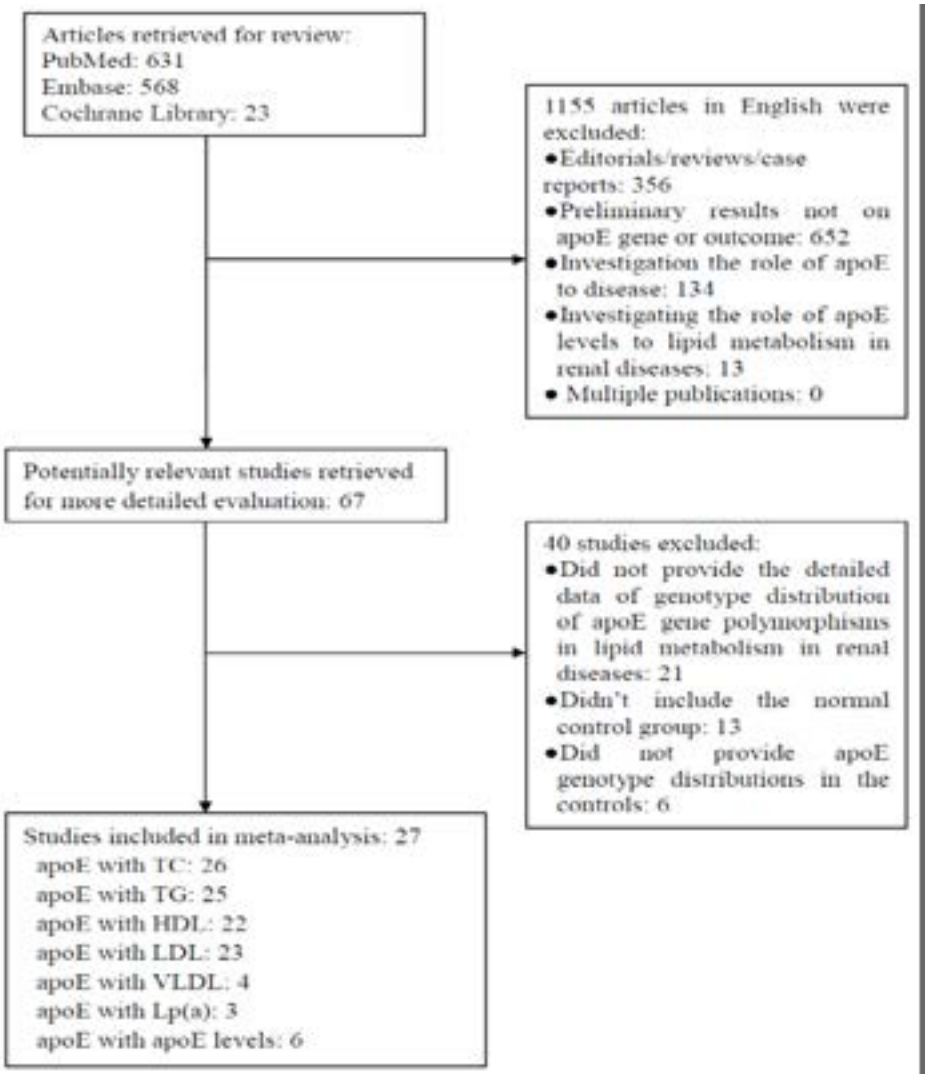

Figure 1 flowchart for including studies for this meta-analysis

Study characteristics for the association between gene polymorphisms of apoE with TC levels

Twenty-six studies were included in this meta-analysis for the association between gene polymorphisms of apoE with TC levels. Three studies [19-21] compared E2E2 with E3E3. Four kinds of gene polymorphisms comparisons were contained, they were E2E3 vs. E3E3 (13 reports[19-31]), E2E4 vs. E3E3(4 reports[19-21, 23]), E3E4 vs. E3E3 (13 reports[19-31]) and E4E4 vs. E3E3(4 reports 19-21, 23). Another five types of apoE gene polymorphisms were ε 2 vs. non-ε 2(1 report32), ε 4 with non-ε 4(4 studies[33-36]), ε 2 vs. ε 3(15 studies[20,22,24-30,37-43]),ε 4 vs. ε 3(16 studies[20,22,24-30,37-39,41-43]) and ε 2 vs. ε 4(15 studies[20,22,24-30,37-39,41-43]).

Study characteristics of the association between gene polymorphisms of apoE with TG levels

Twenty-five studies enabled to analyze the relationship between apoE gene polymorphisms with TG levels. Three studies ([19-21]) compared E2E2 vs. E3E3, 12 reports [19-30] were recruited into the study for E2E3 vs. E3E3 (including 14 comparisons), and 4 reports [19-21, 23] were recruited into the study of E2E4 vs. E3E3. Twelve reports [19-30] were recruited into the study for E3E4 vs. E3E3 (including 14 comparisons), and 4 reports [19-21, 23] were recruited into the study for E4E4 vs. E3E3. One report [32] was included for the meta-analysis of ε 2 vs. non-ε 2 (including 2 comparisons), and 4 studies [33-36] were recruited into our meta-analysis for the comparison of ε 4 with non-ε 4 (including 6 comparisons). Fifteen studies [20, 22, 24-30, 37-43] were included into the study for ε 2 vs. ε 3 (including 21 comparisons), 16 studies ([20, 22, 24-30, 37-39, 41-44]) were included into the study for ε 4 vs. ε 3 (including 21 comparisons), and 15 studies[20, 22, 24-30, 37-39, 41-43] were included into the study of ε 2 VS ε 4 (including 20 comparisons).

Study characteristics for the association between gene polymorphisms of apoE with HDL levels

Twenty-two studies were included into the meta-analysis for the association between ene polymorphisms of apoE g with HDL levels. Three studies [19-21] compared E2E2 vs. E3E3, 12 reports [19-30] compared E2E3 vs. E3E3 (including 14 comparisons). Four reports [19-21, 23] were recruited into this study for E2E4 vs. E3E3, 12 reports [19-30] compared E3E4 VS E3E3 (including 14 comparisons), and 4 reports [19-21, 23] compared E4E4 vs. E3E3. One report [32] was included for the meta-analysis of ε 2 vs. non-ε 2 (including 4 comparisons), and two studies [33, 36] were recruited into our meta-analysis for the comparison of ε 4 with non-ε 4. Fourteen studies [20, 22, 24-29, 38-41, 43, 45] were included for ε 2 vs. ε 3 (including 19 comparisons), 14 studies [20, 22, 24-29, 38, 39, 41, 43-45] were included for ε 4 vs. ε 3 (including 19 comparisons), and 13 studies [20, 22, 24-29, 38, 39, 41, 43, 45] were included for ε 2 vs. ε 4 (including 18 comparisons).

Study characteristics of the association between gene polymorphisms of apoE with LDL levels

Twenty-three studies were recruited into the meta-analysis for the association between apoE gene polymorphisms with LDL levels. Three studies [19-21] compared E2E2 vs. E3E3, 12 reports [19-30] were recruited for E2E3 vs. E3E3 (including 14 comparisons), 4 reports[19-21, 23] compared E2E4 VS E3E3, and 12 reports [19-30] compared E3E4 vs. E3E3 (including 14 comparisons). Four reports [19-21, 23] were recruited into the study for E4E4 vs. E3E3. One report [32] was included for the meta-analysis of ε 2 vs. non-ε 2 (including 2 comparisons), 4 studies[33-36] were included into this meta-analysis for the comparison of ε 4 with non-ε 4 (including 6 comparisons), and 16 studies [20, 22, 24-30, 38-43, 45] were included for ε 2 vs. ε 3 (including 21 comparisons). Sixteen studies [20, 22, 24-30, 38, 39, 41-45] were included for ε 4 vs. ε 3 (including 21 comparisons), and 15 studies [20, 22, 24-30, 38, 39, 41-43, 45] were included for ε 2 vs. ε 4 (including 20 comparisons).

Study characteristics for the association between gene polymorphisms of apoE with VLDL levels

Four studies were recruited into the meta-analysis for the association between gene polymorphisms of apoE with VLDL levels. One study [19] was for the compassion of E2E2 vs. E3E3. 3 reports [19, 24, 30] were recruited into this meta-analysis of E2E3 vs. E3E3. One study [19] was recruited into this study of E2E4 vs. E3E3. 3 reports[19, 24, 30] were entered into the meta-analysis of E3E4 vs. E3E3. One study[19] was recruited into the study of E4E4 vs. E3E3. Three studies [24, 30, 38] were included into the study of ε 2 vs. ε 3 (including 4 comparisons). Three studies (24, 30, 38) were included into the investigation of ε 4 vs. ε 3 (including 4 comparisons). Three studies[24, 30, 38] were included into the study of ε 2 vs. ε 4 (including 4 comparisons).

Study characteristics for the association between gene polymorphisms of apoE with Lp(a) levels

Three studies were included into the meta-analysis for the association between gene polymorphisms of apoE with Lp(a) levels. One study[20] was for the compassion of E2E2 vs. E3E3. Two reports[20, 26] were recruited into the meta-analysis of E2E3 vs. E3E3. One study [20] was recruited into the study of E2E4 vs. E3E3. Two reports[20, 26] were recruited into the investigation of E3E4 vs. E3E3. One study [20] was recruited into the study of E4E4 vs. E3E3. Three reports [20, 26, 43] were included into the study of ε 2 vs. ε 3. Three reports [20, 26, 43] were included into the study of ε 4 vs. ε 3. Three reports [20, 26, 43] were included into the investigation of ε 2 vs. ε 4.

Study characteristics for the association between gene polymorphisms of apoE with ApoE expression

Six studies were included into the meta-analysis for the association between gene polymorphisms of apoE with TC expression. Two studies[19, 21] was for the compassion of E2E2 vs. E3E3. 3 reports [19, 21, 25] were recruited into this meta-analysis of E2E3 vs. E3E3. Two studies[19, 21] were recruited into this investigation of E2E4 vs. E3E3. 3 reports[19, 21], were recruited into our meta-analysis of E3E4 vs. E3E3. Two studies[19, 21] were recruited into the study of E4E4 vs. E3E3. Three studies [25, 39, 41, 43] were recruited into the pooled study of ε 2 vs. ε 3 (including 4 comparisons). Three studies [25, 39, 41, 43] were included into this investigation of ε 4 vs. ε 3 (including 4 comparisons). Three studies [25, 39, 41, 43] were included into the investigation of ε 2 vs. ε 4 (including 4 comparisons).

The relationship between gene polymorphisms of apoE and lipid metabolism

Relationship between gene polymorphisms of apoE and TC levels

In the current meta-analysis, we presented results separately for comparisons where the number of recruited articles was larger than ten, and where the number of recruited investigations for comparisons was no fewer than 10, since results from < 10 studies might be less robust.

When compared with those patients with E3E3, patients suffering from E3E4 had an increased level of TC (Figure 2), and persons suffering from E2E3 had a reduced TC level (Figure 3). Subjects suffering from ε 2 had a reduced TC level when compared with those persons with ε 3 or ε 4, and persons suffering from ε 4 had increased levels of TC than those persons suffering from ε 3 (Table 1). These results suggest that E3E4 and ε 4 are related to up-regulated levels of TC, and there are an association between E2/E3 or ε 2 and the reduced levels of TC. Persons suffering from ε 2 can get lower TC levels when compared peoples with non-ε 2. For these results, the sample size of number of incorporated investigations for some comparisons was larger than 10.

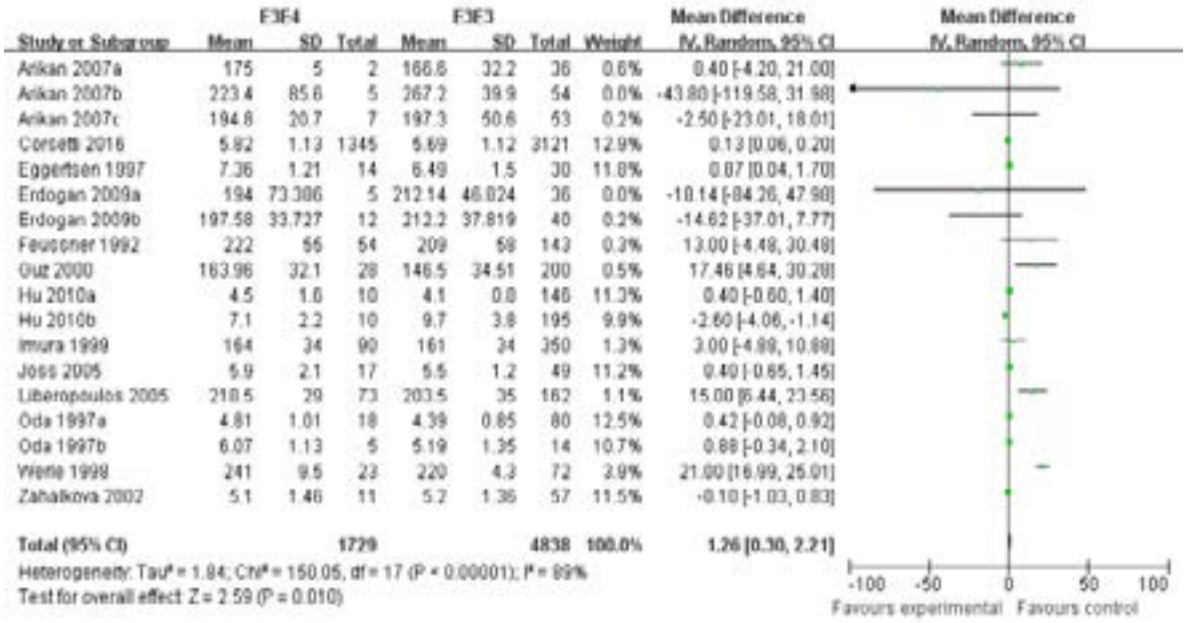

Figure 2 Association of apoE gene polymorphism with TC levels (E3E4 vs. E3E3)

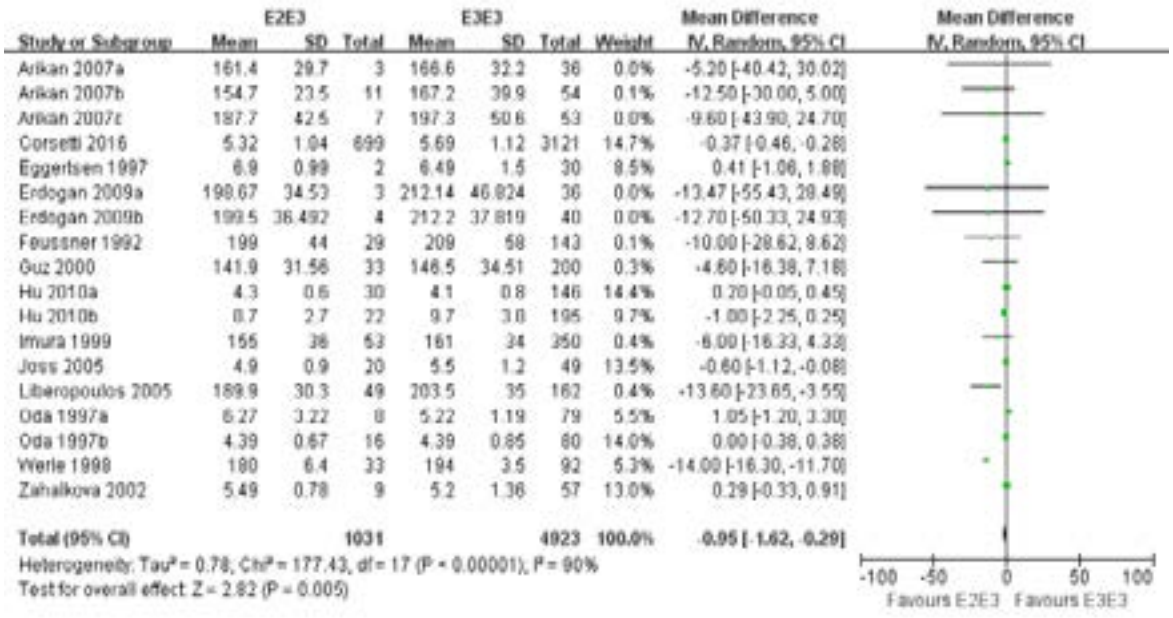

Figure 3 Association of apoE gene polymorphism with TC levels (E2E3 vs. E3E3)

Although we can't find any statistical difference between groups, subjects suffering from E2E4 tended to have lower TC levels when compared with those persons with E3E3, subjects suffering from E2E2 tended to have a slightly lower TC level when compared with those subjects with E3E3, and patients suffering from E4E4 tended to have a slightly increased TC when compared with those with E3E3. Subjects with ε 4 also tended to display a slightly increased level of TC compared to those subjects suffering from non-ε 4, although the statistical difference was no notable (Table 1), there appeared a tendency for E3E4 to be related to increased levels of TC, and E2E4 related to lower levels of TC.

Table 1. Meta-analysis of the association of ApoE gene polymorphisms with TC levels

Genetic contrasts	Studies	Q test *P*-value	Model selected	OR (95%CI)	P	
E2E2 vs. E3E3	3	0.31	Fixed	-0.37 (-0.97, 0.23)	0.22	
E2E3 vs. E3E3	13	< 0.00001	Random	-0.95 (-1.62, -0.29)	0.005	
E2E4 vs. E3E3	4	0.07	Random	-0.74 (-2.10, 0.61)	0.28	
E3E4 vs. E3E3	13	< 0.00001	Random	1.26 (0.30, 2.21)	0.01	
E4E4 vs. E3E3	4	0.02	Random	0.23 (-0.72, 1.18)	0.64	
ε2 vs. non–ε2	2	0.16	Fixed	-0.16 (-0.31, -0.01)	0.04	
ε4 vs. non–ε4	5	< 0.0001	Random	0.20 (-0.40, 0.79)	0.52	
ε2 vs. ε3	21	< 0.00001	Random	-1.04 (-1.63, -0.44)	0.0007	
ε4 vs. ε3	21	< 0.00001	Random	-0.50 (-0.94, -0.06)	0.02	
ε2 vs. ε4	20	< 0.00001	Random	-2.57 (-3.57, -1.56)	< 0.00001	

Relationship between gene polymorphisms of apoE and TG levels

Subjects suffering from E2E2, E2E3 or E4E4 were with increased TG levels when comared with those persons with E3E3 genotype. Persons suffering from ε 4 suffered from higher TG levels when compared with those subjects with ε 3. Patients with ε 2 got an up-regulated TG level than subjects with non-ε 2 (Table 2). These results suggest that E3E4 or E2E3 is associated with increased levels of TG, and ε 2 and ε 4 are related to the increased TG levels.

Similarly, although the tendencies were similar, no statistical difference for TG was found between subjects with E2E4 vs. E3E3, and ε subjects with E3E4 vs. E3E3. Subjects with ε 4 vs. non-ε 4, and subjects with ε 2 vs. ε 3 (Table 2). Furthermore, no statistical difference was found between subjects with ε 2 vs. ε 4 (Table 2). Thus, there were trends suggesting E2E2, E2E3, E4E4, ε 2 and ε 4 are associated with increased TG levels, whereas E2E4 is associated with reduced levels of TG.

Table 2. Meta-analysis of the association of ApoE gene polymorphisms with TG levels

Genetic contrasts	Studies	Q test *P*-value	Model selected	OR (95%CI)	P	
E2E2 vs. E3E3	3	0.33	Fixed	0.31 (0.09, 0.53)	0.005	
E2E3 vs. E3E3	14	0.007	Random	0.16 (0.02, 0.31)	0.03	
E2E4 vs. E3E3	4	< 0.00001	Random	-0.09 (-0.55, 0.37)	0.69	
E3E4 vs. E3E3	14	< 0.00001	Random	0.33 (-0.04, 0.70)	0.08	
E4E4 vs. E3E3	4	< 0.00001	Random	0.68 (0.01, 1.34)	0.05	
ε2 vs. non–ε2	2	0.73	Fixed	0.21 (0.03, 0.39)	0.02	
ε4 vs. non–ε4	2	0.24	Fixed	0.19 (-0.03, 0.42)	0.09	
ε2 vs. ε3	21	< 0.00001	Random	0.25 (-0.07, 0.57)	0.12	
ε4 vs. ε3	21	< 0.00001	Random	0.32 (0.05, 0.60)	0.02	
ε2 vs. ε4	20	< 0.00001	Random	-0.29 (-0.84, 0.26)	0.30	

Relationship between gene polymorphisms of apoE and HDL levels

Subjects suffering from E3E4 got a slightly lower HDL when compared with those persons with E3E3 genotype (Table 3). It indicated that E3E4 genotype was associated with the reduced levels of HDL.

No significant differences in HDL were found for subjects with E2E2 vs. those subjects suffering from E3E3, Patients with E2E4, E2E3 or E4E4 vs. those with E3E3, or subjects with ε 2 and ε 4vs. non-ε 2 and non-ε 4, respectively. Interestingly, subjects with ε 4 tended to get a slightly reduced level of HDL when compared with those persons with ε 2, and ε 3, and subjects with ε 2 tended to have a slightly lower level of HDL than those with ε 3, although the statistical difference was no notable (Table 3). In these studies, ε 4 tended to be associated with lower level of HDL.

Table 3. Meta-analysis of the association of ApoE gene polymorphisms with HDL levels

Genetic contrasts	Studies	Q test *P*-value	Model selected	OR (95%CI)	P	
E2E2 vs. E3E3	3	0.47	Fixed	0.04 (-0.09, 0.16)	0.56	
E2E3 vs. E3E3	14	< 0.00001	Random	-0.08 (-0.27, 0.10)	0.38	
E2E4 vs. E3E3	4	0.002	Random	-0.23 (-0.68, 0.23)	0.33	
E3E4 vs. E3E3	14	0.58	Fixed	-0.03 (-0.06, -0.01)	0.007	
E4E4 vs. E3E3	4	0.45	Fixed	-0.03 (-0.09, 0.03)	0.37	
ε2 vs. non–ε2	2	0.65	Fixed	-0.02 (-0.08, 0.04)	0.46	
ε4 vs. non–ε4	2	< 0.00001	Random	-0.34 (-0.74, 0.05)	0.09	
ε2 vs. ε3	19	< 0.00001	Random	0.02 (-0.15, 0.19)	0.82	
ε4 vs. ε3	19	< 0.00001	Random	-0.09 (-0.22, 0.04)	0.16	
ε2 vs. ε4	18	< 0.00001	Random	0.18 (-0.04, 0.40)	0.11	

Relationship between gene polymorphisms of apoE and LDL levels

Persons suffering from E2E3 or E2E2 had a notably reduced LDL when compared with those patients with E3E3 genotype. Patients suffering from ε 2 had a decreased LDL compared to those patients suffering from ε 3 or ε 4 (Table 4), suggesting that E2E2, E2E3 and ε 2 are associated with lower levels of LDL. No statistical difference was found between subjects with E2E4, E4E4 and E3E3, nor between subjects with E3E4 and E3E3. Subjects with ε 2 tended to have a reduced LDL level than those with non-ε 2, and subjects with ε 4 also tended to have a down-regulated level of LDL than the patients with non-ε 4, (Table 4), and patients with ε 4 have tended toward increased LDL levels than those with ε 3, but again tere were no statistical differences.

Table 4. Meta-analysis of the association of ApoE gene polymorphisms with LDL levels

Genetic contrasts	Studies	Q test *P*-value	Model selected	OR (95%CI)	P	
E2E2 vs. E3E3	3	0.74	Fixed	-0.73 (-1.19, -0.26)	0.002	
E2E3 vs. E3E3	14	< 0.00001	Random	-1.21 (-1.87, -0.56)	0.0003	
E2E4 vs. E3E3	4	0.002	Random	-0.96 (-2.13, 0.21)	0.11	
E3E4 vs. E3E3	14	< 0.00001	Random	0.51 (-0.04, 1.11)	0.10	
E4E4 vs. E3E3	4	< 0.00001	Random	-0.25 (-1.12, -0.61)	0.57	
ε2 vs. non–ε2	2	0.009	Random	-0.24 (-0.52, 0.04)	0.09	
ε4 vs. non–ε4	2	< 0.00001	Random	-0.99 (-2.10, 0.12)	0.08	
ε2 vs. ε3	21	< 0.00001	Random	-1.35 (-1.98, -0.73)	< 0.0001	
ε4 vs. ε3	21	< 0.00001	Random	0.28 (-0.09, 0.65)	0.13	
ε2 vs. ε4	20	< 0.00001	Random	-2.74 (-3.65, -1.83)	< 0.00001	

Relationship between gene polymorphisms of apoE and VLDL levels

For VLDL, no statistical difference was found between subjects with E2E2, E2E3, E2E4, E3E4 or E4E4 when compared with those patients with E3E3. Subjects suffering from E2E2 genotype got a lower VLDL when compared with those patients with the genotype of E3E3, although no statistical difference was observed. Patients with ε 2 had a lower VLDL level when compared with those patients with the genotype of ε 3 or ε 4, although no statistical difference was found. Moreover, patients with ε 4 got a increased level of VLDL than the patients with ε 3, although no statistical difference was detected (Table 5). It indicated that ε 4 was related to a increased level of VLDL.

Table 5. Meta analysis of the association of ApoE gene polymorphisms with VLDL levels

Genetic contrasts	Studies	Q test *P*-value	Model selected	OR (95%CI)	P
E2E2 vs. E3E3	1	-	Fixed	119.00 (-23.36, 261.36)	0.10
E2E3 vs. E3E3	3	< 0.00001	Random	4.58 (-7.86, 17.03)	0.47
E2E4 vs. E3E3	1	-	Fixed	21.00 (-21.68, 63.68)	0.33
E3E4 vs. E3E3	3	0.92	Fixed	0.52 (-0.32, 1.37)	0.23
E4E4 vs. E3E3	1	-	Fixed	18.00 (-32.33, 68.33)	0.48
ε2 vs. ε3	4	< 0.00001	Random	-1.60 (-12.06, 8.85)	0.76
ε4 vs. ε3	4	0.07	Random	1.34 (-0.88, 3.56)	0.24
ε2 vs. ε4	4	< 0.00001	Random	-5.64 (-17.52, 6.24)	0.35

Relationship between gene polymorphisms of apoE and Lp(a) levels

Patients suffering from E2E2, E2E4 or E3E4 genotype had a lower Lp(a) when compared with those patients with E3E3, and persons suffering from E2E3, E4E4 got a increased level of Lp(a) compared to the patients with E3E3 genotype, although no statistical difference was found. Patients with ε 2 got a higher Lp(a) levewhen compared with those with ε 4, ε 3, and subjects with ε 4 had a lower level of Lp(a) than those with ε 3, although there was no statistical difference (Table 6). It indicated that ε 2 was related to a higher Lp(a) level.

Table 6. Meta analysis of the association of ApoE gene polymorphisms with LP(a) levels

Genetic contrasts	Studies	Q test *P*-value	Model selected	OR (95%CI)	P
E2E2 vs. E3E3	1	-	Fixed	-56.40 (-93.45, -19.35)	0.003
E2E3 vs. E3E3	2	< 0.00001	Random	20.02 (-22.19, 62.23)	0.35
E2E4 vs. E3E3	1	< 0.00001	Random	-34.96 (-247.70, 177.78)	0.75
E3E4 vs. E3E3	2	< 0.00001	Random	-60.20 (-222.29, 101.90)	0.47
E4E4 vs. E3E3	1	< 0.00001	Random	42.59 (-178.10, 263.28)	0.71
ε2 vs. ε3	3	< 0.00001	Random	12.57 (-7.60, 32.75)	0.22
ε4 vs. ε3	3	< 0.00001	Random	-40.05 (-141.56, 59.46)	0.42
ε2 vs. ε4	3	< 0.00001	Random	54.17 (-17.44, 125.79)	0.14

Relationship between gene polymorphisms of apoE and apoE levels

Patients suffering from E2E3, or E2E4 got an increased apoE levels when compared with those patients with E3E3 genotype, and patients with E4E4 had a reduced apoE level than those subjects suffering from E3E3. Furthermore, patients suffering from E2E2 got a higher apoE levels when compared with those patients with E3E3 and subjects suffering from E3E4 got lower apoE levels compared to the patients with E3E3, although no statistical difference was found. Patients suffering from ε 2 had a higher apoE level when compared with those with ε 3 or ε 4. Moreover, patients with ε 4 got a lower apoE level than those subjects with ε 3, although there was no statistical difference (Table 7).

Table 7. Meta-analysis of the association of ApoE gene polymorphisms with ApoE levels

Genetic contrasts	Studies	Q test *P*-value	Model selected	OR (95%CI)	P
E2E2 vs. E3E3	2	0.03	Random	3.55 (-4.92, 12.03)	0.41
E2E3 vs. E3E3	3	< 0.00001	Random	3.15 (1.02, 5.27)	0.004
E2E4 vs. E3E3	2	0.13	Fixed	0.01 (0.01, 0.01)	< 0.00001
E3E4 vs. E3E3	4	< 0.0008	Random	-0.42 (-0.92, 0.08)	0.10
E4E4 vs. E3E3	2	0.34	Fixed	-0.01 (-0.01, -0.01)	< 0.00001
ε2 vs. ε3	5	< 0.00001	Random	6.15 (2.99, 9.32)	0.0001
ε4 vs. ε3	5	< 0.00001	Random	-0.30 (-1.46, 0.86)	0.61
ε2 vs. ε4	5	< 0.00001	Random	7.27 (3.81, 10.74)	< 0.0001

Evaluation of publication bias

apoE gene polymorphisms with TC levels

A significant publication bias was not observed in the analysis for apoE gene polymorphisms with TC levels for the comparisons of E2E3 vs. E3E3 (Egger P=0.936, Begg P=0.951), E3E4 vs, E3E3 (Egger P=0.710, Begg P=0.951), ε2 vs, ε3 (Egger P=0.970, Begg P=0.871)ε4 vs, ε 3 (Egger P=0.251, Begg P=0.315)ε2 vs, ε4 Egger P=0.495, Begg P=0.294), as P values in Egger's test and Begg's test were larger than 0.1.

apoE gene polymorphisms with TG levels

A significant publication bias was not found in the analysis for apoE gene polymorphisms with TG levels for the comparisons of E2E3 vs. E3E3 (Egger P=0.215, Begg P=0.300), E3E4 vs. E3E3 (Egger P=0.269, Begg P=0.300), ε2 vs, ε3 (Egger P=0.190, Begg P=0.144) ε4 vs, ε 3 (Egger P=0.567, Begg P=0.922)ε2 vs, ε4 Egger P=0.823, Begg P=0.780), as P values in Egger's test and Begg's test were larger than 0.1.

apoE gene polymorphism with HDL levels

A significant publication bias was not observed in the analysis for apoE gene polymorphisms with HDL levels for the comparisons of E2E3 vs. E3E3 (Egger P=0.996, Begg P=0.760), E3E4 vs. E3E3 (Egger P=0.766, Begg P=0.951), ε2 vs, ε3 (Egger P=0.451, Begg P=0.596) ε4 vs, ε 3 (Egger P=0.628, Begg P=0.449)ε2 vs, ε4 Egger P=0.204, Begg P=0.967), as P values in Egger's test and Begg's test were larger than 0.1.

apoE gene polymorphisms with LDL levels

A significant publication bias was not found in the analysis for apoE gene polymorphisms with LDL levels for the comparisons of E2E3 vs E3E3 (Egger P=0.816, Begg P=0.760), E3E4 vs E3E3 (Egger P=0.675, Begg P=0.669), ε2 vs, ε3 (Egger P=0.552, Begg P=0.871) ε4 vs, ε 3 (Egger P=0.274, Begg P=0.456)ε2 vs, ε4 Egger P=0.232, Begg P=0.624), as P values

Discussion

This meta-analysis was conducted to identify correlations between apoE isoforms and lipid metabolites. No publication bias was observed for any of the comparisons. Lots of renal diseases, including NS[46], glomerulonephritis[47] and chronic kidney disease with dialysis[48], usually manifested high serum TC levels. Increased level of TC might be a crucial symbol for the onset of renal diseases. Our meta-analysis showed the TC levels in subjects with E3E3 were higher than E2E3 but lower than E3E4. Among subjects with ε 2, ε 3 and ε 4, ε 4 had a highest TC levels, while ε 2 had a lowest TC levels. Thus, E3E4 and ε 4 tend to have higher levels of TC, and both E2/E3 and ε 2 are related to lower levels of TC. These results were evident to some extent. Toms et al. indicated that, in rheumatoid arthritis patients, the ε 2 allele presented the lowest and ε 4 allele presented the highest TC level[49]. In healthy urban Brazilian individuals, Alvim et al. also found that the ε4 allele had an apparent relationship with higher TC value[50]. Rahimi et al. proved that the ε4 allele inducing an upward trend in TC levels in sickle cell disease[51]. Smart et al. mentioned that comparing with E3E3 homozygotes as well as ε 2 carriers, higher TC levels was observed in apoE ε 4 carriers in 882 Greek children[52]. The outcomes from this meta-analysis are consistent with those studies.

Series of renal diseases, such as NS[53], glomerulonephritis[54] and chronic kidney disease with dialysis, had high serum TG levels[55]. Increasing levels of TG might be a core sign for the onset susceptibility of renal diseases. This meta-analysis found that subjects with E2E2, E2E3 or E4E4 manifested significantly higher TG levels than those with E3E3. Subjects with ε 4 had a high-

er TG than those with ε 3. Subjects with ε 2 showed a highr level of TG than those with non-ε 2. This suggests that E2E3 or E3E4, and ε 2 and ε 4 are related to higher levels of TG. These outcomes were credible to some extent. Stiefel et al. indicated that apoE E3E4 and E4E4 genotypes had a worse lipoprotein profile characterized by higher plasma values for TG [56]. Srivastava et al. observed that in obese subjects, higher TG levels were present more in the apoE ε 4 allele than others[57]. Tao et al. discovered that in coronary heart disease patients, the TG levels in patients with ε 4 are higher than those without ε 4 [58]. Our results are similar.

Lower serum HDL level may be another core symbol for lots of renal diseases, including NS [59, 60], glomerulonephritis [60], chronic kidney disease with dialysis [61]. Our study put forward subjects with E3E4 had a slightly lower HDL than those with E3E3. This would suggest that E3E4 is related to lower levels of HDL. In healthy urban Brazilian individuals, Alvim et al. put forward that the ε4 allele was related to lower HDL values 50. In a Chinese population, Tao et al. indicated that a lower level of high-density lipoprotein cholesterol was present in ε 4 subjects [62]. In patients with colorectal cancer, Souza et al. showed the ε 4 allele was associated with a lower level of high-density lipoprotein cholesterol fraction [63]. Ours results support the above studies robustly by showing that the ε 4 had a close relationship with lower levels of HDL.

Increased serum LDL level is a widely accepted signal for series of renal diseases, including NS [64], glomerulonephritis [65], chronic kidney disease with dialysis[66]. In our study, a notably lower LDL can be found in subjects with E2E2 and E2E3 rather than in E3E3. Among subjects with ε 2, ε 3 and ε4, ε4 had a highest LDL levels, while ε 2 had a lowest LDL levels. This indicates that E2E2, E2E3 or ε 2 is related to lower levels of LDL, and ε 4 is related to higher levels of LDL. In rheumatoid arthritis patients, Toms et al. put forward that the ε 2 allele was related to the lowest and ε 4 allele had the highest level of LDL [49]. In healthy urban Brazilian individuals, Alvim et al. indicated that the ε4 allele was related to higher LDL value[50]. In sickle cell disease, Rahimi et al. discovered that ε4 allele may induced a significant increase in LDL levels[51]. Zhang et al. indicated that both ε 4 and ε 3 allele carriers had the higher serum LDL than those with ε 2 carriers in the healthy subjects [67]. Fuzikawa et al. found that LDL cholesterol level presented lower in the ε 2 allele carriers but higher in the ε 4 carriers in a large unselected population of older adults[68]. Those results were similar with ours.

Increased serum VLDL level is a possible symbol for series of renal diseases, including NS [69], glomerulonephritis [70], chronic kidney disease with dialysis [71]. Whether it play a role in the pathogenesis of renal diseases is not well elucidated. Our study did not showed association between apoE gene polymorphisms and VLDL expression in patients with renal diseases. However, the results might be less robust because less than ten studies was included.

Increased serum Lp(a) level might be an core symbol for lots of renal diseases, including NS [72], chronic kidney disease with dialysis [73]. Whether it plays a role in the pathogenesis of renal diseases, it is not well elucidated. In our study, both subjects with E2E2 and E2E4 had a lower Lp(a) than those with E3E3. Moreover, Lp(a) levels of subjects with E4E4 were higher than those with E3E3. However, the results might be less evident because less than ten studies was included.

Whether apoE gene polymorphisms are associated with apoE expression, and whether low/high levels of apoE are associated with renal diseases are not well elucidated at present. Among subjects with E2E3, E2E4, E3E3, and E4E4, E2E3 and E2E4 had higher apoE levels than others, while E4E4 had a lowest apoE levels. Subjects with ε 2 had a higher level of apoE when compared with those with ε 3 or ε 4. E2E2, or E2E3 might be a protective factor in fighting against renal diseases, while E3/E4 could be a risk factor. Our data also suggest that increased apoE has a protective role in renal diseases, and lower apoE is a risk factor for renal diseases.

It is complicated to assess the roles of apoE in diseases. Lots of studies indicated that apoE is a positive factor when against diseases. apoE has antioxidant activity [74], and is widely accepted in assisting with providing protection against mesangial cell injury [75]. ApoE also took part in the repairment of tissue injury; for incidence, increased amounts of apoE levels are discovered in sites of peripheral nerve injury and regeneration[76]. ApoE deficency in mice induces the progress of atherosclerosis and re-expression of apoE reduces the extent of the disease [77]. Thus, increased apoE appears to be a protective factor against disease.

Conclusion

ApoE gene polymorphisms are associated with the expression of TC, TG HDL, LDL, Lp(a) or apoE.

List of abbreviations

apoE: apolipoprotein E; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Lp(a): lipoprotein (a); NS: nephrotic syndrome.

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Competing interests

The authors declare that they have no competing interests.

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