Association of apoE gene polymorphisms with lipid metabolism in renal diseases

Tianbiao Zhou *,1, Hongyan Li *,2, Hongzhen Zhong 1, Zhiqing Zhong 1, Shujun Lin 1

1. Department of Nephrology, the Second Affiliated Hospital of Shantou University Medical College, 515041, Shantou, China.
2. Department of Nephrology, Huadu District People’s Hospital, Southern Medical University, Guangzhou, China.

*These authors contributed equally

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, E3E4 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 notably lower low-density lipoprotein (LDL) than those with E3E3. Subjects with E2E3 or E4E4 had higher total cholesterol (TC) than those with E3E3, and subjects with E2E3 had a lower triglyceride (TG) than those with E3E4. 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

DOI: https://dx.doi.org/10.4314/ahs.v20i3.43

Cite as: Zhou T, Li H, Zhong H, Zhong Z, Lin S. Association of apoE gene polymorphisms with lipid metabolism in renal diseases. Afr. Health Sci. 2020;20(3): 1368-1381. https://dx.doi.org/10.4314/ahs.v20i3.43

Background

Apolipoprotein E (apoE) plays a central role in lipoprotein particle metabolism and lipid homeostasis, and the regulation of metabolism involved in total cholesterol (TC) and triglyceride (TG). 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, and has also been associated with expression of lipoprotein (a) (Lp(a)) . 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. E3E3 and E3E4 are considered wild-type apoE, and ε2, ε4, E2E2, E2E3, E2E4, E3E4 and E4E4 are considered mutated forms of apoE. The kidney is a major organ system and plays a major role in the proper functioning of the homeostasis.

Disorders of the lipid metabolism and the homeostasis...
are frequently coexist in renal diseases\textsuperscript{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\textsuperscript{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\textsuperscript{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 independently 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. I\textsuperscript{2} was used to test the heterogeneity of included studies. The Begg adjusted rank correlation test\textsuperscript{17} and the Egger regression asymmetry test\textsuperscript{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).
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 compared E2E2 with E3E3. Four kinds of gene polymorphisms comparisons were contained, they were E2E3 vs. E3E3 (13 reports), E2E4 vs. E3E3 (4 reports), E3E4 vs. E3E3 (13 reports) and E4E4 vs. E3E3 (4 reports). Another five types of apoE gene polymorphisms were ε2 vs. non-ε2 (1 report), ε4 with non-ε4 (4 studies), ε2 vs. ε3 (15 studies), ε4 vs. ε3 (16 studies), and ε2 vs. ε4 (15 studies).

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 compared E2E2 vs. E3E3, 12 reports were recruited into the study for E2E3 vs. E3E3 (including 14 comparisons), and 4 reports were recruited into the study of E2E4 vs. E3E3. Twelve reports were recruited into the study for E3E4 vs. E3E3 (including 14 comparisons), and 4 reports were recruited into the study for E4E4 vs. E3E3. One report was included for the meta-analysis of ε2 vs. non-ε2 (including 2 comparisons), and 4 studies were recruited into our meta-analysis for the comparison of ε4 with non-ε4 (including 6 comparisons). Fifteen studies were included into the study for ε2 vs. ε3 (including 21 comparisons), 16 studies were included into the study for ε4 vs. ε3 (including 21 comparisons), and 15 studies were included into the study of ε2 vs ε4 (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 gene polymorphisms of apoE 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 \( \varepsilon \) 2 vs. non-\( \varepsilon \) 2 (including 4 comparisons), and two studies 33,36 were recruited into our meta-analysis for the comparison of \( \varepsilon \) 4 with non-\( \varepsilon \) 4. Fourteen studies 20,22, 24-29, 38-41, 43,45 were included for \( \varepsilon \) 2 vs. \( \varepsilon \) 3 (including 19 comparisons), 14 studies 20,22, 24-29, 38, 39, 41, 43-45 were included for \( \varepsilon \) 4 vs. \( \varepsilon \) 3 (including 19 comparisons), and 13 studies 20,22, 24-29, 38, 39, 41, 43,45 were included for \( \varepsilon \) 2 vs. \( \varepsilon \) 4 (including 18 comparisons).

Study characteristics for 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 \( \varepsilon \) 2 vs. non-\( \varepsilon \) 2 (including 2 comparisons), 4 studies 33,36 were included into this meta-analysis for the comparison of \( \varepsilon \) 4 with non-\( \varepsilon \) 4 (including 6 comparisons), and 16 studies 20,22, 24-30, 38-43, 45 were included for \( \varepsilon \) 2 vs. \( \varepsilon \) 3 (including 21 comparisons). Sixteen studies 20,22, 24-30, 38, 39, 41-45 were included for \( \varepsilon \) 4 vs. \( \varepsilon \) 3 (including 21 comparisons), and 15 studies 20,22, 24-30, 38, 39, 41-43,45 were included for \( \varepsilon \) 2 vs. \( \varepsilon \) 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 comparison 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 \( \varepsilon \) 2 vs. \( \varepsilon \) 3 (including 4 comparisons). Three studies (24,30,38) were included into the investigation of \( \varepsilon \) 4 vs. \( \varepsilon \) 3 (including 4 comparisons). Three studies 24,30,38 were included into the study of \( \varepsilon \) 2 vs. \( \varepsilon \) 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 comparison 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 \( \varepsilon \) 2 vs. \( \varepsilon \) 3. Three reports 20,26,43 were included into the study of \( \varepsilon \) 4 vs. \( \varepsilon \) 3. Three reports 20,26,43 were included into the investigation of \( \varepsilon \) 2 vs. \( \varepsilon \) 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 comparison 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, 25 were recruited into our meta-analysis of E3E4 vs. E3E3. Two studies 19,21 were recruited into the study of E4E4 vs. E3E3. Three reports 25,39,41,43 were recruited into the pooled study of \( \varepsilon \) 2 vs. \( \varepsilon \) 3 (including 4 comparisons). Three studies 25,39,41,43 were included into this investigation of \( \varepsilon \) 4 vs. \( \varepsilon \) 3 (including 4 comparisons). Three studies 25,39,41,43 were included into the investigation of \( \varepsilon \) 2 vs. \( \varepsilon \) 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 is 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 to people 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  | Model selected | OR          | 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      | <0.0001 | Random         | -1.04(-1.63,0.44)  | 0.0007 |
| ε4 vs. ε3                               | 21      | <0.0001 | Random         | -0.50(-0.94,-0.06) | 0.02 |
| ε2 vs. ε4                               | 20      | <0.0001 | Random         | -2.57(-3.57,-1.56) | <0.0001 |

### Relationship between gene polymorphisms of apoE and TG levels

Subjects suffering from E2E2, E2E3 or E4E4 were with increased TG levels when compared 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  | Model selected | OR          | 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) | 0.035 |
| 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 and 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 selected | 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 there 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 selected | 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 suffering from E2E3, or E2E4 got an increased level of VLDL when compared with those patients with E3E3, and persons suffering from E2E3, E4E4 had a lower Lp(a) when compared with those patients with E3E3, although no statistical difference was detected (Table 5). It indicated that e 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 |
| e2 vs. e3         | 4       | < 0.00001      | Random         | -1.60 (-12.06, 8.85) | 0.76 |
| e4 vs. e3         | 4       | 0.07           | Random         | 1.34 (-0.88, 3.56) | 0.24 |
| e2 vs. e4         | 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 e 2 had a higher Lp(a) level when compared with those patients with e 3 or e 4, and subjects with e 4 had a lower level of Lp(a) than those with e 3, although there was no statistical difference (Table 6). It indicated that e 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 |
| e2 vs. e3         | 3       | < 0.00001      | Random         | 12.57 (-7.60, 32.75) | 0.22 |
| e4 vs. e3         | 3       | < 0.00001      | Random         | -40.05 (-141.56, 59.46) | 0.42 |
| e2 vs. e4         | 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 e 2 had a higher apoE level when compared with those with e 3 or e 4. Moreover, patients with e 4 got a lower apoE level than those subjects with e 3, although there was no statistical difference (Table 7).
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=0.871), ε2 vs. ε3 (Egger P=0.567, Begg P=0.922), ε4 vs. ε2 (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 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=0.970, Begg P=0.871), ε2 vs. ε3 (Egger P=0.251, Begg P=0.315), ε4 vs. ε2 (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 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=0.970, Begg P=0.871), ε2 vs. ε3 (Egger P=0.190, Begg P=0.144), ε4 vs. ε3 (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 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=0.970, Begg P=0.871), ε2 vs. ε3 (Egger P=0.552, Begg P=0.871), ε4 vs. ε3 (Egger P=0.232, Begg P=0.624), as P values in Egger’s test and Begg’s test were larger than 0.1.

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 ε2, ε3 and ε4, ε4 had a highest TC levels, while ε2 had a lowest TC levels. Thus, E3E4 and ε4 tend to have higher levels of TC, and both E2/E3 and ε2 are related to lower levels of TC. These results were evident to some extent. Toms et al. indicated that, in rheumatoid arthritis patients, the ε2 allele presented the lowest and ε4 allele presented the highest TC level \(^{89}\). 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 \(^{31}\). Smart et al. mentioned that comparing with E3E3 homozygotes as well as ε2 carriers, higher TC levels was observed in apoE ε4 carriers in 882 Greek children \(^{52}\). The outcomes from this meta-analysis are consistent with those studies.

Series of renal diseases, such as NS \(^{51}\), glomerulonephritis \(^{52}\) and chronic kidney disease with dialysis, had high serum TG levels \(^{50}\). 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 ε4 had a high-

---

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

| Genetic contrasts | Studies | Q test | 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          | -0.42 (-0.92, 0.08) | 0.10 |
| E3E4 vs. E3E3    | 4       | <0.0008 | Random         | -0.01 (-0.01, -0.01) | <0.00001|
| E4E4 vs. E3E3    | 2       | 0.34   | Fixed          | 6.15 (2.99, 9.32) | 0.0001|
| ε2 vs. ε3        | 5       | <0.00001 | Random         | -0.30 (-1.46, 0.86) | 0.61 |
| ε4 vs. ε3        | 5       | <0.00001 | Random         | 7.27 (3.81, 10.74) | <0.0001|
| ε2 vs. ε4        | 5       | <0.00001 | Random         | 7.27 (3.81, 10.74) | <0.0001|

- **OR (95%CI)**: Odds Ratio (95% Confidence Interval)
- **P**: Probability

---

African Health Sciences Vol 20 Issue 3, September, 2020 1376
er TG than those with ε 3. Subjects with ε 2 showed a higher 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. Srivastava et al. observed that in obese subjects, higher TG levels were present more in the apoE ε 4 allele than others. 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. Our results are similar.

Lower serum HDL level may be another core symbol for lots of renal diseases, including NS, glomerulonephritis, chronic kidney disease with dialysis. 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 ε 4 allele was related to lower HDL values. In a Chinese population, Tao et al. indicated that a lower level of high-density lipoprotein cholesterol was present in ε 4 subjects. In patients with colorectal cancer, Souza et al. showed that the ε 4 allele was associated with a lower level of high-density lipoprotein cholesterol fraction. Our 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, glomerulonephritis, chronic kidney disease with dialysis. 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 ε 4, ε 4 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. In healthy urban Brazilian individuals, Alvim et al. indicated that the ε 4 allele was related to higher LDL value. In sickle cell disease, Rahimi et al. discovered that ε 4 allele may induced a significant increase in LDL levels. 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. 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. Those results were similar with ours.

Increased serum VLDL level is a possible symbol for series of renal diseases, including NS, glomerulonephritis, chronic kidney disease with dialysis. 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, chronic kidney disease with dialysis. 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 E4E4 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, and is widely accepted in assisting with providing protection against mesangial cell injury. 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. ApoE deficiency in mice induces the progress of atherosclerosis and re-expression of apoE reduces the extent of the disease. 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.

Acknowledgements
None.

Funding
This study was supported by Guangzhou Medical Key Discipline Construction Project (2017-2019).

Competing interests
The authors declare that they have no competing interests.

References
1. Georgiadou D, Chroni A, Vezeridis A, Zannis VI, Stratikos E. Biophysical analysis of apolipoprotein E3 variants linked with development of type III hyperlipoproteinemia. PLoS One. 2011;6:e27037.
2. Annema W, Dikkers A, de Boer JF, Gautier T, Rensen PC, Rader DJ, Tietge UJ. ApoE promotes hepatic selective uptake but not RCT due to increased ABCA1-mediated cholesterol efflux to plasma. J Lipid Res. 2012;53:929-940 PubMed.
3. Zhou TB, Qin YH, Lei FY, Su LN, Zhao YJ, Huang WF. apoE expression in glomerulus and correlation with glomerulosclerosis induced by adriamycin in rats. Ren Fail. 2011;33:348-354 PubMed.
4. Shatwan IM, Weech M, Jackson KG, Lovegrove JA, Vimaleswaran KS. Apolipoprotein E gene polymorphism modifies fasting total cholesterol concentrations in response to replacement of dietary saturated with monounsaturated fatty acids in adults at moderate cardiovascular disease risk. Lipo-ids Health Dis. 2017;16:222.
5. Losonczi E, Bencsik K, Friescska Nagy Z, Honti V, Szalcerz E, Rajda C, Illes Z, Matyas K, Rozsa C, Csepany T, Fuvesi J, Vecsei L. APOE epsilon status in Hungarian patients with primary progressive multiple sclerosis. Swiss Med Wkly. 2010;140:w13119.
6. Brito DD, Fernandes AP, Gomes KB, Coelho FF, Cruz NG, Sabino AP, Cardoso JE, Figueiredo-Filho PP, Diamante R, Norton CR, Sousa MO. Apolipoprotein A5-1131T>C polymorphism, but not APOE genotypes, increases susceptibility for dyslipidemia in children and adolescents. Mol Biol Rep. 2011;38:4381-4388 PubMed.
7. Karavia EA, Papachristou DJ, Kotsikogianni I, Gi- opanou I, Kypreos KE. Deficiency in apolipoprotein E has a protective effect on diet-induced nonalcoholic fatty liver disease in mice. FEBS J. 2011;278:3119-3129 PubMed.
8. Tascilar N, Dursun A, Ankarali H, Mungan G, Sumbuloglu V, Ekem S, Bozdogan S, Baris S, Aciman E, Cabuk F. Relationship of apolipoprotein(a) levels in atherosclerotic infarct. J Neurol Sci. 2009;277:17-21 PubMed.
9. Anuuarad E, Lu G, Rubin J, Pearson TA, Berglund L. ApoE genotype affects allele-specific apo[a] levels for large apo[a] sizes in African Americans: the Harlem-Basset Study. J Lipid Res. 2007;48:693-698 PubMed.
10. De Feo E, Cefalo C, Arzani D, Amore R, Landolfi R, Grieco A, Ricciardi W, Miele L, Boccia S. A case-control study on the effects of the apolipoprotein E genotypes in nonalcoholic fatty liver disease. Mol Biol Rep. 2012;39:7381-7388 PubMed.
11. Marrzoq LF, Sharif FA, Abed AA. Relationship between ApoE gene polymorphism and coronary heart disease in Gaza Strip. J Cardiovasc Dis Res. 2011;2:29-35.
12. Hanh NT, Nhung BT, Dao DT, Tuyet LT, Hop LT, Binh TQ, Thuc VT. Association of apolipoprotein E polymorphism with plasma lipid disorders, independent of obesity-related traits in Vietnamese children. Lipids Health Dis. 2016;15:176.
13. Salem NA, Salem EA. Renoprotective effect of grape seed extract against oxidative stress induced by gentamicin and hypercholesterolemia in rats. Ren Fail. 2011;33:824-832.
14. Lee HS. Mechanisms and consequences of hypertriglyceridemia and cellular lipid accumulation in chronic kidney disease and metabolic syndrome. Histol Histopathol. 2011;26:1599-1610 PubMed.
15. Gheith O, Sheashaa H, Abdelsalam M, Shoier Z, Sobh M. Efficacy and safety of Monascus purpureus Went rice in children and young adults with secondary hyperlipidemia: a preliminary report. Eur J Intern Med. 2009;20:e57-61.
16. Zhou TB, Liu YG, Lin N, Qin YH, Huang K, Shao MB, Peng DD. Relationship between angiotensin-converting enzyme insertion/deletion gene polymorphism and systemic lupus erythematosus/lupus nephritis: a systematic review and metaanalysis. J Rheumatol. 2012;39:686-693 PubMed.
17. Egger M, Davey Smith G, Schneider M, Minder
C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-634 PubMed.

19. Feussner G, Wey S, Bommer J, Deppermann D, Grutzmacher P, Ziegler R. Apolipoprotein E phenotypes and hyperlipidemia in patients under maintenance hemodialysis. Hum Genet. 1992;88:307-312 PubMed.

20. Hu P, Qin YH, Lu L, Hu B, Jing CX, Lei FY, Li MF. Genetic variation of apolipoprotein E does not contribute to the lipid abnormalities secondary to childhood minimal change nephrotic syndrome. Int Urol Nephrol. 2010;42:453-460 PubMed.

21. Corsetti JP, Gansevoort RT, Bakker SJL, Dullaart RPF. Apolipoprotein E phenotypes and levels and apolipoprotein E genotypes in incident cardiovascular disease risk in subjects of the Prevention of Renal and Vascular End-stage disease study. J Clin Lipidol. 2016;10:842-850 PubMed.

22. Oda H, Yorioka N, Ueda C, Nishida Y, Yamakido M. Apolipoprotein E phenotype and renal disease. Contrib Nephrol. 1997;120:22-29 PubMed.

23. Eggertsen G, Heimburger O, Stenvinkel P, Berglund L. Influence of variation at the apolipoprotein E locus on lipid and lipoprotein levels in CAPD patients. Nephrol Dial Transplant. 1997;12:141-144.

24. Werle E, Fiehn W, Hasslacher C. Apolipoprotein E polymorphism and renal function in German type 1 and type 2 diabetic patients. Diabetes Care. 1998;21:994-998 PubMed.

25. Imura T, Kimura H, Gejyo F. Apolipoprotein E phenotypes in hemodialysis patients. Kidney Int Suppl. 1999;71:S245-247.

26. Guz G, Nurhan Ozdemir F, Sezer S, Isiklar I, Arat Z, Turan M, Haberal M. Effect of apolipoprotein E polymorphism on serum lipid, lipoproteins, and atherosclerosis in hemodialysis patients. Am J Kidney Dis. 2000;36:826-836 PubMed.

27. Erdogan M, Eroglu Z, Biray C, Karadeniz M, Cetinkalp S, Kosova B, Gunduz C, Topcuoglu S, Ozgen G, Yilmaz C. The relationship of apolipoprotein E gene polymorphism Turkish Type 2 diabetic patients with and without nephropathy. J Endocrinol Invest. 2009;32:219-222 PubMed.

28. Zahalkova J, Vaverkova H, Novotny D, Kosatikova Z. Impaired triglyceride tolerance in hemodialysis patients with different apolipoprotein E (apo E) isoforms. Biomed Pap Med Fac Univ Palacky Olomouc Czeb Repub. 2002;146:73-76.

29. Arikhan H, Koc M, Sari H, Tuglular S, Ozener C, Akoglu E. Associations between apolipoprotein E gene polymorphism and plasminogen activator inhibitor-1 and atherogenic lipid profile in dialysis patients. Ren Fail. 2007;29:713-719 PubMed.

30. Joss N, Jardine A, Gaffney D, Boulton-Jones JM. Influence of apolipoprotein E genotype on progression of diabetic nephropathy. Nephron Exp Nephrol. 2005;101:e127-133.

31. Liberopoulos EN, Miliadou GA, Athyros VG, Ganotakis M, Cariolou M, Bairaktari E, Elisaf MS. Effect of apolipoprotein E polymorphism on serum uric acid levels in healthy subjects. Journal of investigative medicine : the official publication of the American Federation for Clinical Research. 2005;53:116-122.

32. Ma SW, Benzie IF, Yeung VT. Type 2 diabetes mellitus and its renal complications in relation to apolipoprotein E gene polymorphism. Transl Res. 2008;152:134-142 PubMed.

33. Lim PS, Liu CS, Hong CJ, Wei YH. Prevalence of apolipoprotein E genotypes in ischaemic cerebrovascular disease in end-stage renal disease patients. Nephrol Dial Transplant. 1997;12:1916-1920.

34. Kimura H, Suzuki Y, Gejyo F, Karasawa R, Miyazaki K, Suzuki S, Arakawa M. Apolipoprotein E4 reduces risk of diabetic nephropathy in patients with NIDDM. Am J Kidney Dis. 1998;31:666-673 PubMed.

35. Lehtinen S, Rantalaaho V, Wirta O, Pasternack A, Laippala P, Koivula T, Lehtimaki T. Apolipoprotein E gene polymorphism, hypercholesterolemia and glomerular filtration rate in type 2 diabetic subjects: a 9-year follow-up study. J Biomed Sci. 2003;10:260-265 PubMed.

36. Marrocos MS, Teixeira AA, Quinto BM, Carmo Sde M, Kuniyoshi M, Rodrigues CJ, Dalboni MA, Manfredi S, Canziani ME, Batista MC. Apolipoprotein E polymorphism modulation of asymmetric dimethylarginine in hypertensive patients is determined by renal function. Lipids Health Dis. 2016;15:14.

37. Kwon MK, Rhee SY, Chon S, Oh S, Woo JT, Kim SW, Kim JW, Kim YS, Jeong KH, Lee SH, Lee TW, Ihm CJ. Association between apolipoprotein E genetic polymorphism and the development of diabetic nephropathy in type 2 diabetic patients. Diabetes Res Clin Pract. 2007;77 Suppl 1:S228-232.

38. Kahraman S, Kiykim AA, Altun B, Genetoy G, Arici M, Gulsun M, Erdem Y, Yasavul U, Turgan C, Caglar S. Apolipoprotein E gene polymorphism in renal transplant recipients: effects on lipid metabolism, atherosclerosis and allograft function. Clin Transplant. 2004;18:288-294 PubMed.

39. Liberopoulos EN, Miliadou GA, Cariolou M, Tselepis AD, Siamopoulos KC, Elisaf MS. The influence of serum apolipoprotein E concentration and polymorphism on serum lipid parameters in hemodialysis patients. Am J Kidney Dis. 2004;44:300-308 PubMed.

40. Xiang G, Xia B, He Y. The relationship of Apo E2
and renal insufficiency lipid levels in NIDDM. *Zhonghua Yi Xue Za Zhi*. 1999;79:339-341.

41. Li HF, Han CF, Wang YX, Lu YS, Zou HQ, Xu QQ. Effect of apolipoprotein E gene polymorphism on serum lipid level before and after renal transplantation. *Transplant Proc*. 2010;42:2513-2517 PubMed.

42. Maluf DG, Mas VR, Archer KJ, Yanek K, King A, Ferreira-Gonzalez A, Fisher RA, Posner M. Apolipoprotein E genotypes as predictors of high-risk groups for developing hyperlipidemia in kidney transplant recipients undergoing sirolimus treatment. *Transplantation*. 2005;80:1705-1711 PubMed.

43. Lahrach H, Essiarab F, Timinouni M, Hatim B, El Khayat S, Er-Rachdi L, Jarir J, Kettani A, Ghalim N, Taki H, Lebrazi H, Ramdani B, Saile R. Association of apolipoprotein E gene polymorphism with end-stage renal disease and hyperlipidemia in patients on long-term hemodialysis. *Ren Fail*. 2014;36:1504-1509 PubMed.

44. Leiva E, Mujica V, Elematore I, Orrego R, Diaz G, Prieto M, Arredondo M. Relationship between Apolipoprotein E gene polymorphism and nephropathy in type-2 diabetic patients. *Diabetes Res Clin Pract*. 2007;78:196-201.

45. Winkler K, Hoffmann MM, Krane V, Marz W, Drechsler C, Wanner C. Apolipoprotein E genotype predicts cardiovascular endpoints in dialysis patients with type 2 diabetes mellitus. Atherosclerosis. 2010;208:197-2 PubMed 02.

46. Stoycheff N, Stevens LA, Schmid CH, Tighiouart H, Lewis J, Atkins RC, Levey AS. Nephrotic syndrome in diabetic kidney disease: an evaluation and update of the definition. *Am J Kidney Dis*. 2009;54:840-849 PubMed.

47. Zhou TB, Qin YH, Lei FY, Su LN, Zhao YJ, Huang WF. All-trans retinoic acid regulates the expression of apolipoprotein E in rats with glomerulosclerosis induced by Adriamycin. *Exp Mol Pathol*. 2011;90:287-294.

48. Makowka A, Dryja P, Chwatkow G, Balc E, Nowicki M. Treatment of chronic hemodialysis patients with low-dose fenofibrate effectively reduces plasma lipids and affects plasma redox status. *Lipids Health Dis*. 2012;11:47.

49. Toms TE, Smith JP, Panoulas VF, Blackmore H, Douglas KM, Kitas GD. Apolipoprotein E gene polymorphisms are strong predictors of inflammation and dyslipidemia in rheumatoid arthritis. *J Rheumatol*. 2012;39:218-225 PubMed.

50. Alvim RO, Freitas SR, Ferreira NE, Santos PC, Cunha RS, Mill JG, Krieger JE, Pereira AC. APOE polymorphism is associated with lipid profile, but not with arterial stiffness in the general population. *Lipids Health Dis*. 2010;9:128.

51. Rahimi Z, Vaisi-Raygani A, Pourmortabbed T. Association between apolipoprotein epsilon4 allele, factor V Leiden, and plasma lipid and lipoprotein levels with sickle cell disease in Southern Iran. *Mol Biol Rep*. 2011;38:703-710 PubMed.

52. Smart MC, Dedoussis G, Louizou E, Yannakoulia M, Drenos F, Papoutsakis C, Maniatis N, Humphries SE, Talmud PJ. APOE, CETP and LPL genes show strong association with lipid levels in Greek children. *Nutr Metab Cardiovasc Dis*. 2010;20:26-33.

53. Klosterman ES, Moore GE, de Brito Galvao JF, DiBartola SP, Groman RP, Whittemore JC, Vaden SL, Harris TL, Byron JK, Dowling SR, Grant DC, Grauer GF, Pressler BM. Comparison of signalment, clinicopathologic findings, histologic diagnosis, and prognosis in dogs with glomerular disease with or without nephrotic syndrome. *J Vet Intern Med*. 2011;25:206-214 PubMed.

54. Marques de Mattos A, Marino LV, Ovidio PP, Jordan AA, Almeida CC, Chiarello PG. Protein oxidative stress and dyslipidemia in dialysis patients. *Ther Apher Dial*. 2012;16:68-74 PubMed.

55. Stiefel P, Miranda ML, Bellido LM, Luna J, Jimenez L, Pamies E, de Frutos PG, Villar J. Genotype of the CYBA promoter -930A/G, polymorphism C677T of the MTHFR and APOE genotype in patients with hypertensive disorders of pregnancy: an observational study. *Med Clin (Barc).* 2009;133:657-661.

56. Srivastava N, Achyut BR, Prakash J, Agarwal CG, Pant DC, Mittal B. Association of cholesterol ester transfer protein (TaqIB) and apolipoprotein E (HhaI) gene variants with obesity. *Mol Cell Biochem*. 2008;314:171-177 PubMed.

57. Ouyang T, Song JN, Miao Y, Lin Q, Niu XH, Jin H, Chen B. Study on relationship between polymorphism of apolipoprotein (TaqIB) and apolipoprotein E (HhaI) gene variants with obesity. *Mol Cell Biochem*. 2010;320:26-33.

58. Krikken JA, Waanders F, Dallinga-Thie GM, Dikkeschei LD, Vogt I, Navis GJ, Dullaart RP. Antiproteinuric therapy decreases LDL-cholesterol as well as HDL-cholesterol in non-diabetic proteinuric patients: relationships with choleseryl ester transfer protein mass and adiponectin. *Expert Opin Ther Targets*. 2009;13:497-504 PubMed.

59. Mattana J, Chaplia L, Singhal PC, Wagner JD, Valderrama E. Possible role of high density lipopro-
tein in the progression of glomerulosclerosis. *J Med.* 2003;34:81-86 PubMed.

60. Cacciagiu LD, Gonzalez AI, Gomez Rosso L, Merono T, De Marziani G, Elbert A, Berg G, Brites F, Schreier L. HDL-associated enzymes and proteins in hemodialysis patients. *Clin Biochem.* 2012;45:243-248 PubMed.

61. Tao MH, Liu JW, LaMonte MJ, Liu J, Wang L, He Y, Li XY, Wang LN, Ye L. Different associations of apo-lipoprotein E polymorphism with metabolic syndrome by sex in an elderly Chinese population. *Metabolism.* 2011;60:1488-1496 PubMed.

62. Souza DR, Nakazone MA, Pinhel MA, Alvares RM, Monaco AC, Pinheiro A, Barros CF, Cury PM, Cunrath GS, Netinho JG. Association between apolipoprotein E genotype, serum lipids, and colorectal cancer in Brazilian individuals. *Braz J Med Biol Res.* 2009;42:397-403 PubMed.

63. Akoglu H, Agbaht K, Piskinpasa S, Falay MY, Dede F, Ozet G, Odabas AR. High frequency of aspirin resistance in patients with nephrotic syndrome. *Nephrol Dial Transplant.* 2012;27:1460-1466.

64. Oto J, Suga K, Matsuura S, Kondo S, Ohnishi Y, Inui D, Imanaka H, Kagami S, Nishimura M. Low-density lipoprotein apheresis in a pediatric patient with refractory nephrotic syndrome due to focal segmental glomerulosclerosis. *J Anesth.* 2009;23:284-287 PubMed.

65. Lobo JC, Farage NE, Abdalla DS, Velarde LG, Torres JP, Mafra D. Association between circulating electronegative low-density lipoproteins and serum ferritin in hemodialysis patients: a pilot study. *J Ren Nutr.* 2012;22:350-356 PubMed.

66. Zhang J, Xuemei Z, Fan P, Liu R, Huang Y, Liang S, Liu Y, Wu Y, Bai H. Distribution and effect of apo E genotype on plasma lipid and apolipoprotein profiles in overweight/obese and nonobese Chinese subjects. *J Clin Lab Anal.* 2012;26:200-205 PubMed.

67. Fuzikawa AK, Peixoto SV, Tauer M, Moriguchi EH, Lima-Costa MF. Association of ApoE polymorphisms with prevalent hypertension in 1406 older adults: the Bambui Health Aging Study (BHAS). *Braz J Med Biol Res.* 2008;41:89-94.

68. Newman JW, Kaysen GA, Hammock BD, Shearer GC. Proteinuria increases oxylipid concentrations in VLDL and HDL but not LDL particles in the rat. *J Lipid Res.* 2007;48:1792-1800 PubMed.

69. Rodriguez-Iturbe B, Sato T, Quiroz Y, Vaziri ND. AT-1 receptor blockade prevents proteinuria, renal failure, hyperlipidemia, and glomerulosclerosis in the Imai rat. *Kidney Int.* 2004;66:668-675 PubMed.

70. Hirowatari Y, Yoshida H, Fueki Y, Ito M, Ogura Y, Sakurai N, Miida T. Measurement of cholesterol concentrations of major serum lipoprotein classes in haemodialysis patients by anion-exchange chromatography. *Ann Clin Biochem.* 2008;45:571-574 PubMed.

71. Li HQ, Wu J, Niu DM, Shi YH, Zhang CN, Wang JJ. The level of native and oxidized lipoprotein(a) in children with nephrotic syndrome. *Clin Biochem.* 2012;45:101-105 PubMed.

72. Tao J, Sun Y, Li X, Li H, Liu S, Wen Y, Duan L, Li Y. Conventional versus ultrapure dialysate for lowering serum lipoprotein(a) levels in patients on long-term hemodialysis: a randomized trial. *Int J Artif Organs.* 2010;33:290-296.

73. Jofre-Monseny L, Minihane AM, Rimbach G. Impact of apoE genotype on oxidative stress, inflammation and disease risk. *Mol Nutr Food Res.* 2008;52:131-145 PubMed.

74. Arora S, Husain M, Kumar D, Patni H, Pathak S, Mehrotra D, Reddy VK, Reddy LR, Salhan D, Yadav A, Mathieson PW, Saleem MA, Chander PN, Singhal PC. Human immunodeficiency virus downregulates podocyte apoE expression. *Am J Physiol Renal Physiol.* 2009;297:F653-661.

75. Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science.* 1988;240:622-630 PubMed.

76. Greenow K, Pearce NJ, Ramji DP. The key role of apolipoprotein E in atherosclerosis. *J Mol Med* (Berl). 2005;83:329-342.