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Original Article

Associations of the *APOC3* rs2854116 and rs2854117 polymorphisms with plasma APOC3 and lipid levels: a meta-analysis

Shujin Li[1], Yang Yang[2], Xiaoxiao Ouyang[2], Jing Shen[3], Min Zhou[1], Yongyan Song[4]

[1]School of Continuing Education, North Sichuan Medical College, Nanchong, P. R. China; [2]School of Clinical Medicine, North Sichuan Medical College, Nanchong, P. R. China; [3]Department of Nutrition and Health Sciences, University of Nebraska-Lincoln, Lincoln, Nebraska, USA; [4]Department of Medical Biochemistry, School of Preclinical Medicine, North Sichuan Medical College, Nanchong, P. R. China

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Abstract: Studies on the associations between the apolipoprotein C3 (APOC3) gene rs2854116 and rs2854117 polymorphisms and the plasma levels of APOC3 and lipids have reported apparently conflicting findings. This meta-analysis aimed to investigate the associations of the rs2854116 and rs2854117 polymorphisms and their interaction with fasting APOC3 and lipid levels. The following information was extracted from each study: age, gender, ethnicity, health condition, sample size, genotypes, lipid assay methods, mean and standard deviation or standard error of plasma APOC3 and lipids by genotypes. There were 23 eligible studies with 17493 subjects included in this meta-analysis. A dominant model was used for this meta-analysis. The carriers of the rs2854116 variant allele (C) had higher levels of APOC3 [standardized mean difference (SMD) = 0.08, 95% confidence interval (CI) = 0.01-0.15, *P* = 0.024] and triglycerides (TG) (SMD = 0.30, 95% CI = 0.09-0.51, *P* = 0.004), and lower levels of high-density lipoprotein cholesterol (HDL-C) (SMD = -0.16, 95% CI = -0.31–0.02, *P* = 0.028) than the non-carriers. The carriers of the rs2854117 variant allele (T) had higher levels of TG (SMD = 0.24, 95% CI = 0.00-0.48, *P* = 0.047) than the non-carriers. No significant differences in plasma lipid levels between the wild-type homozygotes (rs2854116 TT and rs2854117 CC) and the carriers of one or more variant alleles (rs2854116 C and rs2854117 T) were detected under the dominant model. The rs2854116 polymorphism is significantly associated with higher levels of APOC3 and TG, and lower levels of HDL-C. The rs2854117 polymorphism is marginally significantly associated with higher levels of TG. Further studies are needed to elucidate the underlying mechanisms.

Keywords: Apolipoprotein C3, lipids, rs2854116, rs2854117, polymorphism

Introduction

Cardiovascular disease (CVD) remains the leading cause of death for both men and women in developed and some developing countries [1]. A number of CVD risk factors have been identified in the past several decades. Among these risk factors, dyslipidemia accounts for at least 50% of the population-attributable risk for CVD [2]. Dyslipidemia is currently characterized by elevated levels of triglycerides (TG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), and/or reduced levels of high-density lipoprotein cholesterol (HDL-C). In recent years, many efforts have been made by researchers to investigate the genetic polymorphisms that influence plasma lipid levels. However, it is difficult to identify the dyslipidemia-related polymorphisms and most associations have not been replicated across studies due to various reasons.

Apolipoprotein (APO) C3 gene is a member of the *APOA1/C3/A4/A5* gene cluster, which is located within chromosome 11q23. This chromosomal region has been implicated in strong linkage with plasma lipid homeostasis [3]. APOC3 is an essential component of chylomicron and very low-density lipoprotein (VLDL), to a less extent of high-density lipoprotein (HDL). The molecular function of APOC3 may be involved in the upregulation of plasma TG lev-

els. *APOC3* transgenic pigs showed significantly increased plasma TG levels as compared with nontransgenic controls [4]. In humans, heterozygous carriers of a null mutation (R19X) in *APOC3* express half the amount of APOC3 present in noncarriers. Mutation carriers also had significantly lower fasting and postprandial serum TG compared with noncarriers [5]. The results from an *in vitro* study [6] indicated that APOC3 was a noncompetitive inhibitor of lipoprotein lipase (LPL), which is the rate-limiting enzyme for TG hydrolysis. Furthermore, it interferes the clearance of the TG-rich lipoprotein remnants by displacement of APOE from VLDL particles *in vivo* [7, 8]. Except for the important role in TG metabolism, APOC3 also play roles in modulating other lipid variables such as HDL-C [9]. Given its important role in plasma lipid homeostasis, *APOC3* is generally considered as a candidate gene for dyslipidemia and atherosclerosis.

Two polymorphisms (rs2854116 and rs2854117) within the promoter of *APOC3* have been extensively explored in terms of their associations with plasma lipid levels and CVD over the past two decades. The rs2854116 polymorphism is formed by a transition from T to C, whereas the rs2854117 polymorphism is formed by a transition from C to T. A recent meta-analysis [10] demonstrated that the rs2854116, but not the rs2854117 polymorphism, is associated with the occurrence of CVD. However, whether the two polymorphisms are associated with plasma lipid levels have not been clarified yet. Although there were a number of studies investigating the associations of the two polymorphic loci with plasma APOC3 and lipid levels [11-33], the results were conflicting and inconclusive. In some of these studies, the rs2854116 polymorphism was found to be associated with higher plasma levels of APOC3 [17], TG [12, 13, 21, 22, 25, 27], TC [13] and LDL-C [13], and lower levels of HDL-C [19-22, 27]; the rs2854117 polymorphism was associated with higher plasma levels of APOC3 [25] and TG [11, 14, 23, 25], and lower levels of HDL-C [16, 20]. However, the results from other studies did not support these findings. Hence, a meta-analysis is required to clarify the relationships between the two polymorphisms and plasma lipid levels.

In 2010, a study by Petersen et al. [29] reported that the carriers of one or more variant alleles (rs2854116 C and rs2854117 T) had 30% increase in fasting plasma APOC3 and 60% increase in fasting TG concentration than the wild-type homozygotes (rs2854116 TT and rs2854117 CC). The carriers of variant alleles also had significantly higher prevalence of non-alcoholic fatty liver disease (NAFLD) than the non-carriers. These findings triggered a series of similar studies [30-33] investigating the associations between the rs2854116-rs2854117 interaction [i.e., wild-type homozygotes (rs2854116 TT and rs2854117 CC) vs. the carriers of one or more variant alleles (rs2854116 C and rs2854117 T)] and NAFLD, as well as plasma lipid levels in different populations and ethnicities, but the results among these studies were inconsistent. In this analysis, we also pooled the data from the five studies and intended to clarify the effects of the interaction of the two polymorphisms on plasma lipid levels.

In this paper, a meta-analysis was performed on previous reports to investigate the associations of rs2854116, rs2854117 and their interaction with APOC3 and fasting lipid levels. Our analysis results can provide the opportunity to elucidate the interrelationships among the rs2854116 and rs2854117 polymorphisms, dyslipidemia and CVD.

Materials and methods

Identification and eligibility of relevant studies

All articles published before May 2015 on the associations of the *APOC3* rs2854116 and/or rs2854117 polymorphisms with plasma APOC3 and lipid levels were identified. The language was limited to English and Chinese. A comprehensive search of the literature was carried out by using the databases including Medline, Web of Science, Embase and Cochrane Library. The keywords used for the search were “apolipoprotein C-III or apolipoprotein CIII or apolipoprotein C3 or APOC3 or APOC-III or APO C3” concatenated with “polymorphism or variant or mutation or SNP”. The variables of this meta-analysis are limited to APOC3 and the plasma lipids including TG, TC, LDL-C and HDL-C. The studies that fulfilled the following criteria were included: (1) the studies in which mean plasma lipid levels and standard deviations (SD) or standard errors (SE) by the rs2854116 and/or rs2854117 genotypes were available; (2) data reported on

APOC3 and/or at least one of the four plasma lipid variables; (3) data reported on fasting lipid variables; (4) pre-intervention baseline data were used for interventional studies. All the references cited in the included articles were reviewed to find other published work which was not indexed by Medline, Web of Science, Embase or Cochrane Library. Reports with incomplete data, review articles, studies based on pedigree data, case reports, abstracts and animal studies were excluded from the meta-analysis.

Data extraction

The irrelevant and overlapping studies were excluded after being reviewed independently by two reviewers using a structured data collection form. In the process of data extraction, the original data were cross-checked and compared, and the disagreements were resolved by discussion. Regarding the overlapping articles, only those publications that presented the most detailed information were included. In the present meta-analysis, the data extracted from each of the included study are as followings: first author, year of publication, ethnicity, gender, health condition, age, genotyping and lipid assay methods, sample size, mean APOC3 or lipid variables and SD or SE by genotypes.

Statistical analysis

The STATA software package (Version 10, Stata Corporation, College Station, TX) was used for the meta-analysis. All data were presented as mean ± SD in this analysis. For those articles in which mean ± SE was given, the value of the SD was calculated. Since most of the included studies reported the results in a dominant way [i.e., TT vs. (TC + CC) for rs2854116; CC vs. (CT + TT) for rs2854117], a dominant model was employed in the present meta-analysis to ensure adequate statistical power. When data was presented for more than one subpopulation (e.g., female or male subjects, the subjects from different ethnicity) in one article, each subpopulation was treated as a separate comparison in this meta-analysis. Subgroup analyses were conducted according to age, gender, ethnicity and health condition. Age subgroup was defined as adults and children (less than 18 years of age). Ethnic subgroup was defined as Caucasian, Asian, and the subjects of other ethnic origins. Health condition subgroup was defined as healthy subjects, CVD patients, diabetic patients, etc. The subgroup analysis was only performed with at least three comparisons to ensure adequate statistical power.

A random effects model was used for all analyses because both between-study and within-study heterogeneity is considered in this model. The random effects model also provides a more conservative evaluation of the significance of the associations than the fixed effects model [34]. The pooled standardized mean difference (SMD) and its 95% confidence interval (CI) were used to assess the differences in APOC3 and lipids between the genotypes. Heterogeneity among studies was tested by Cochran's χ^2-based Q-statistic at a significance level of $P < 0.05$. Galbraith plots were used to detect the potential sources of heterogeneity, and the pooled SMD was recalculated after removal of the outlier studies identified by the plots. The included populations were tested for Hardy-Weinberg equilibrium (HWE) by χ^2 test if available; the significance level was defined as $\alpha < 0.05$. Publication bias was assessed by Begg's rank correlation test and Egger's linear regression test combined with funnel plots [35], and a significance level of 0.05 was used to indicate the presence of potential publication bias.

Results

Characteristics of the included studies

Initial search of the databases yielded 763 articles. Six hundred and fifty-eight studies were excluded according to titles and abstracts. Then full-text articles were retrieved and assessed on the basis of the inclusion criteria. Eighty-two papers were ineligible for the following reasons: 64 papers did not provide complete data for this meta-analysis, 12 papers presented data on other polymorphisms, 4 papers had overlapping subjects with other included publications, and 2 studies were based on pedigree data. In the end, 23 studies were selected for this meta-analysis.

The characteristics of the 23 included studies are summarized in Tables S1 and S2 of the supplementary data file. Fourteen studies [11-13, 16-22, 24-27] presented the lipid data for the rs2854116 polymorphism by genotypes. Among them, 5 studies [11, 13, 17, 25, 26], 13

Table 1. Meta-analysis of the associations between the rs2854116 polymorphism and plasma APOC3 and lipids

Groups or subgroups	Comparisons	$P_{Heterogeneity}$	SMD (95% CI)	P_{SMD}
APOC3				
All	9	0.729	0.08 (0.01-0.15)	0.024
Available studies in HWE	7	0.554	0.09 (0.01-0.16)	0.028
Healthy	6	0.628	0.11 (0.02-0.19)	0.024
Male	3	0.740	0.02 (-0.11-0.16)	0.746
Caucasian	5	0.741	0.08 (-0.01-0.17)	0.082
TG				
All	21	< 0.00001	0.30 (0.09-0.51)	0.004
Available studies in HWE	11	< 0.00001	0.49 (0.14-0.84)	0.006
Male	8	0.880	0.08 (-0.01-0.16)	0.082
Female	7	0.442	0.20 (0.11-0.28)	< 0.00001
Children	3	< 0.00001	0.65 (-0.63-1.94)	0.319
Caucasian	10	< 0.00001	0.34 (-0.02-0.70)	0.066
Asian	5	< 0.00001	0.49 (-0.04-1.02)	0.069
Other	6	0.416	0.13 (0.05-0.21)	0.002
Healthy	17	< 0.00001	0.27 (0.05-0.49)	0.016
TC				
All	13	< 0.00001	0.02 (-0.11-0.16)	0.725
Available studies in HWE	5	0.588	0.10 (0.01-0.20)	0.036
Male	6	0.622	0.03 (-0.06-0.12)	0.516
Female	5	< 0.00001	-0.01 (-0.33-0.31)	0.969
Caucasian	5	0.374	0.09 (-0.02-0.21)	0.117
Asian	4	0.889	0.07 (-0.05-0.19)	0.235
Other	4	< 0.00001	-0.04 (-0.35-0.26)	0.776
Healthy	11	< 0.00001	0.02 (-0.13-0.18)	0.778
LDL-C				
All	13	< 0.00001	-0.17 (-0.42-0.09)	0.197
Available studies in HWE	5	0.423	0.11 (0.02-0.21)	0.022
Male	6	< 0.00001	-0.40 (-1.01-0.21)	0.196
Female	5	0.107	0.02 (-0.12-0.16)	0.756
Caucasian	5	0.409	0.10 (-0.01-0.21)	0.081
Asian	4	0.193	-0.63 (-1.38-0.13)	0.561
Other	4	< 0.00001	0.05 (-0.11-0.20)	0.103
Healthy	11	< 0.00001	-0.20 (-0.50-0.09)	0.182
HDL-C				
All	18	< 0.00001	-0.16 (-0.31--0.02)	0.028
Available studies in HWE	7	< 0.00001	-0.19 (-0.47-0.10)	0.204
Male	7	0.078	0.12 (-0.26-0.01)	0.078
Female	6	< 0.00001	-0.08 (-0.28-0.12)	0.440
Caucasian	6	< 0.00001	-0.16 (-0.49-0.17)	0.333
Asian	6	< 0.00001	-0.21 (-0.45-0.02)	0.072
Other	6	< 0.00001	-0.11 (-0.32-0.10)	0.307
Healthy	15	< 0.00001	-0.16 (-0.32--0.01)	0.043

APOC3: apolipoprotein C3, SMD: standardized mean difference, 95% CI: 95% confidence interval, HWE: Hardy-Weinberg equilibrium, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

studies [11-13, 17-22, 24-27], 7 studies [13, 18, 19, 22, 24-26], 7 studies [13, 18, 19, 22, 24-26] and 11 studies [13, 16, 18-22, 24-27] presented the data on APOC3, TG, TC, LDL-C and HDL-C, respectively. Twelve studies [11, 13-16, 18-20, 23, 25, 26, 28] presented the lipid data for the rs2854117 polymorphism by genotypes, and 4 studies [11, 13, 25, 26], 11 studies [11, 13-15, 18-20, 23, 25, 26, 28], 7 studies [13, 14, 18, 19, 25, 26, 28], 6 studies [13, 18, 19, 25, 26, 28] and 9 studies [13, 16, 18-20, 23, 25, 26, 28] of which presented the data on APOC3, TG, TC, LDL-C and HDL-C, respectively. Five studies [29-33] presented the lipid data for the wild-type homozygotes (rs2854116 TT and rs2854117 CC) and the carriers of one or more variant alleles (rs2854116 C and rs2854117 T). Of them, 1 study [29], 5 studies [29-33], 4 studies [29, 31-33], 4 studies [29-31, 33] and 4 studies [29-31, 33] presented the data on APOC3, TG, TC, LDL-C and HDL-C, respectively. Thirteen studies [11-15, 17, 18, 21, 23, 24, 30-32], 7 studies [16, 25-29, 33] and 2 studies [19, 20] involved Caucasians, Asians, and

Table 2. Meta-analysis of the associations between the rs2854117 polymorphism and plasma APOC3 and lipids

Groups or subgroups	Comparisons	$P_{Heterogeneity}$	SMD (95% CI)	P_{SMD}
APOC3				
All	4	0.129	0.04 (-0.14-0.22)	0.639
Available studies in HWE	3	0.098	0.09 (-0.17-0.35)	0.493
TG				
All	16	< 0.00001	0.24 (0.00-0.48)	0.047
Available studies in HWE	11	< 0.00001	0.37 (0.00-0.75)	0.05
Male	4	0.769	0.04 (-0.10-0.17)	0.585
Female	3	0.902	0.11 (-0.05-0.27)	0.182
Children	4	< 0.00001	0.66 (-0.46-1.77)	0.250
Caucasian	9	< 0.00001	0.31 (-0.07-0.69)	0.113
Asian	3	0.226	0.20 (0.04-0.36)	0.012
Other	4	0.894	0.09 (-0.05-0.23)	0.197
Healthy	12	< 0.00001	0.29 (-0.01-0.59)	0.055
TC				
All	9	0.991	0.03 (-0.05-0.11)	0.471
Available studies in HWE	4	0.756	0.03 (-0.05-0.11)	0.979
Male	3	0.924	-0.02 (-0.16-0.13)	0.835
Children	3	0.906	0.30 (-0.10-0.15)	0.671
Caucasian	4	0.674	0.03 (-0.10-0.15)	0.693
Asian	3	0.978	0.03 (-0.09-0.15)	0.643
Healthy	5	0.999	0.03 (-0.07-0.14)	0.568
LDL-C				
All	8	0.433	0.02 (-0.07-0.10)	0.691
Available studies in HWE	3	0.684	-0.10 (-0.23-0.04)	0.162
Male	3	0.349	-0.01 (-0.16-0.15)	0.933
Children	3	0.418	0.00 (-0.12-0.13)	0.974
Caucasian	3	0.181	0.01 (-0.20-0.22)	0.915
Asian	3	0.291	-0.01 (-0.15-0.13)	0.872
Healthy	4	0.516	-0.01 (-0.13-0.10)	0.823
HDL-C				
All	12	0.203	0.01 (-0.07-0.09)	0.799
Available studies in HWE	4	0.828	0.04 (-0.03-0.11)	0.304
Male	4	0.217	-0.08 (-0.25-0.09)	0.365
Female	3	0.311	0.15 (-0.03-0.32)	0.102
Children	3	0.333	0.08 (-0.05-0.22)	0.217
Caucasian	4	0.651	0.05 (-0.02-0.12)	0.196
Asian	4	0.415	-0.02 (-0.14-0.09)	0.690
Other	4	0.031	0.00 (-0.24-0.23)	0.971
Healthy	8	0.081	-0.01 (-0.11-0.10)	0.910

APOC3: apolipoprotein C3, SMD: standardized mean difference, 95% CI: 95% confidence interval, HWE: Hardy-Weinberg equilibrium, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

the subjects of other ethnic origins, respectively. One study [22] involved all the ethnicities including Caucasians, Asians and the subjects of other ethnic origins. Two studies [18, 29] only involved males, and the other 21 studies involved both males and females, among which 6 studies [12, 13, 19, 20, 22, 24] separately provided data for males and females. Three studies [11, 19, 28] involved children, and the rest of the included studies involved adults. Four studies [17, 24, 26, 27] involved both the subjects with CHD and controls, but the lipid data were not separately presented. Nine studies [12, 13, 15, 19, 20, 22, 24, 30, 33] separately provided data for more than one subpopulation, and each subpopulation was treated as a separate comparison. Nine studies [11-13, 17, 18, 21, 25-27] and 8 studies [11, 14, 15, 18, 23, 25, 26, 28] presented the detailed genotype distribution for rs2854116 and rs2854117, respectively, and none of these studies deviated from HWE except one study [26] in the rs2854117 genotype distribution. The units of APOC3 and plasma lipids used in the eligible studies included mg/dL or mmol/L. The complete plasma APOC3 and lipid data by genotypes can be found in Table S3 (rs2854116), Table S4 (rs2854117) and Table S5 (rs2854116-rs2854117 interaction) of the supplemental data file.

Summary statistics

Twenty-four comparisons, 17 comparisons and 7 comparisons were respectively distinguished for rs2854116, rs2854117 and their interaction [Wild-type homozygotes (rs2854116 TT

Table 3. Meta-analysis of the associations between the rs2854116-rs2854117 interaction and plasma lipids

Groups or subgroups	Comparisons	$P_{Heterogeneity}$	SMD (95% CI)	P_{SMD}
TG				
All	7	0.045	0.00 (-0.14-0.14)	0.996
Caucasian	4	0.108	-0.02 (-0.19-0.15)	0.839
Asian	3	0.037	0.06 (-0.25-0.37)	0.700
TC				
All	5	0.040	-0.09 (-0.30-0.12)	0.391
Asian	3	0.309	0.03 (-0.14-0.21)	0.696
LDL-C				
All	6	0.003	-0.03 (-0.22-0.16)	0.779
Caucasian	3	0.458	-0.06 (-0.42-0.31)	0.644
Asian	3	0.000	-0.04 (-0.19-0.12)	0.763
HDL-C				
All	6	0.004	-0.06 (-0.24-0.13)	0.534
Caucasian	3	0.143	-0.06 (-0.24-0.11)	0.482
Asian	3	0.001	-0.05 (-0.49-0.38)	0.814

SMD: standardized mean difference, 95% CI: 95% confidence interval, TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

and rs2854117 CC) vs. the carriers of one or more variant alleles (rs2854116 C and rs2854117 T)] according to the categories such as age, gender, ethnicity and health condition. Nine, 21, 13, 13 and 18 comparisons were respectively included to compare the differences in APOC3, TG, TC, LDL-C and HDL-C for the rs2854116 polymorphism (**Table 1**). Four, 16, 9, 8 and 12 comparisons were respectively included to compare the differences in APOC3, TG, TC, LDL-C and HDL-C for the rs2854117 polymorphism (**Table 2**). Seven, 5, 6 and 6 comparisons were respectively included to compare the differences in TG, TC, LDL-C and HDL-C for the rs2854116-rs2854117 interaction (**Table 3**).

Totally, 17493 subjects were enrolled in this meta-analysis. Of them, 8800, 8326 and 2550 subjects were enrolled in the analysis for rs2854116, rs2854117 and the rs2854116-rs2854117 interaction, respectively. For the rs2854116 polymorphism, 33.3% of the subjects (2933 subjects) have the TT genotype, and 66.7% of them (5867 subjects) have the TC or CC genotype. For the rs2854117 polymorphism, 47.8% of the subjects (3977 subjects) have the CC genotype, and 52.2% of them (4349 subjects) have the CT or TT genotype. For the rs2854116-rs2854117 interaction, 27.5% of the subjects (700 subjects) are the wild-type homozygotes (rs2854116 TT and rs2854117 CC), and 72.5% of them are the carriers (1850 subjects) of one or more variant alleles (rs2854116 C and rs2854117 T).

Associations of the APOC3 rs2854116 polymorphism with APOC3 and lipid levels

The outcomes of the analyses on all comparisons for the rs2854116 polymorphism showed that the C carriers had higher levels of APOC3 (SMD = 0.08, 95% CI = 0.01-0.15, P = 0.024) and TG (SMD = 0.30, 95% CI = 0.09-0.51, P = 0.004), and lower levels of HDL-C (SMD = -0.16, 95% CI = -0.31--0.02, P = 0.028) than the non-carriers (**Table 1**; **Figure 1**). No statistically significant differences in the levels of TC and LDL-C were detected between the C carriers and the non-carriers (**Table 1**; **Figure 1**). In the available studies in HWE, the associations between the rs2854116 polymorphism and higher levels of APOC3 (SMD = 0.09, 95% CI: 0.01-0.16, P = 0.028) and TG (SMD = 0.49, 95% CI = 0.14-0.84, P = 0.006) were also significant (**Table 1**).

The subgroup analyses stratified by the characteristics of the subjects were performed. The associations between the *APOC3* rs2854116 polymorphism and higher levels of APOC3 (SMD = 0.11, 95% CI = 0.02-0.19, P = 0.024) and TG (SMD = 0.27, 95% CI = 0.05-0.49, P = 0.016), and lower levels of HDL-C (SMD = -0.16, 95% CI = -0.32--0.01, P = 0.043) were found to be significant in healthy subjects. The significant association between the *APOC3* rs2854116 polymorphism and higher levels of TG was detected in females (SMD = 0.20, 95% CI = 0.11-0.28, P < 0.00001) and in the subjects from other ethnic origins (SMD = 0.13, 95% CI = 0.05-0.21, P = 0.002).

Associations of the APOC3 rs2854117 polymorphism with APOC3 and lipid levels

The outcomes of the analyses on all comparisons for the rs2854117 polymorphism showed

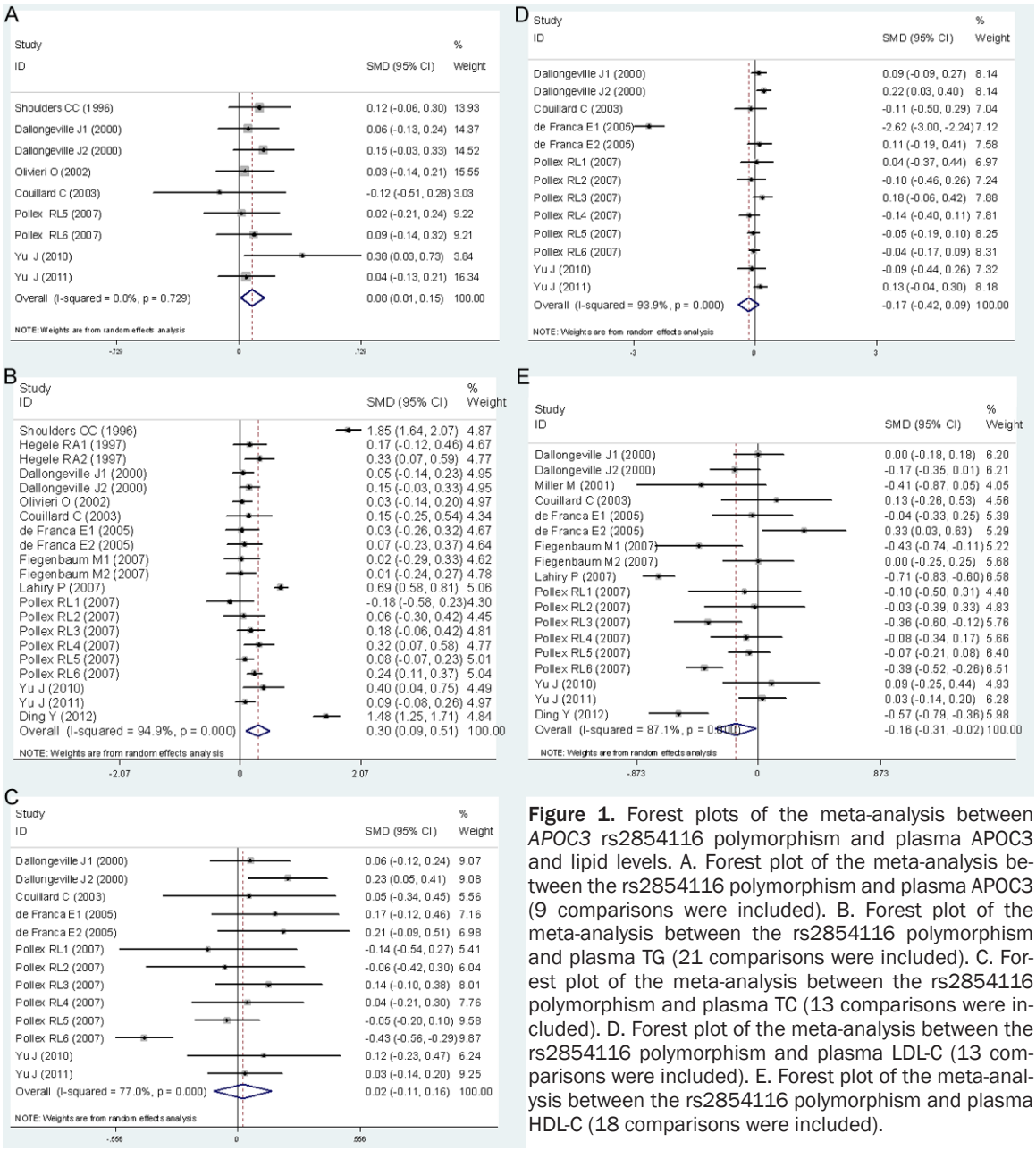

Figure 1. Forest plots of the meta-analysis between *APOC3* rs2854116 polymorphism and plasma APOC3 and lipid levels. A. Forest plot of the meta-analysis between the rs2854116 polymorphism and plasma APOC3 (9 comparisons were included). B. Forest plot of the meta-analysis between the rs2854116 polymorphism and plasma TG (21 comparisons were included). C. Forest plot of the meta-analysis between the rs2854116 polymorphism and plasma TC (13 comparisons were included). D. Forest plot of the meta-analysis between the rs2854116 polymorphism and plasma LDL-C (13 comparisons were included). E. Forest plot of the meta-analysis between the rs2854116 polymorphism and plasma HDL-C (18 comparisons were included).

that the T carriers had marginally significantly higher levels of TG (SMD = 0.24, 95% CI = 0.00-0.48, *P* = 0.047) than the non-carriers (**Table 2**; **Figure 2**). In the available studies in HWE, the association between the *APOC3* rs2854117 polymorphism and higher levels of TG (SMD = 0.37, 95% CI = 0.00-0.75, *P* = 0.05) was also marginally significant (**Table 2**). In the subgroup analyses stratified by the characteristics of the subjects, no statistically significant differences were observed for all except that the rs2854117 polymorphism was significantly associated with higher levels of TG (SMD = 0.20, 95% CI = 0.04-0.36, *P* = 0.012) in Asians.

Associations of the rs2854116-rs2854117 interaction with APOC3 and lipid levels

No statistically significant differences were detected between the wild-type homozygotes (rs2854116 TT and rs2854117 CC) and the carriers of one or more variant alleles (rs2854116 C and rs2854117 T) in either the total comparisons or the subgroup analyses strati-

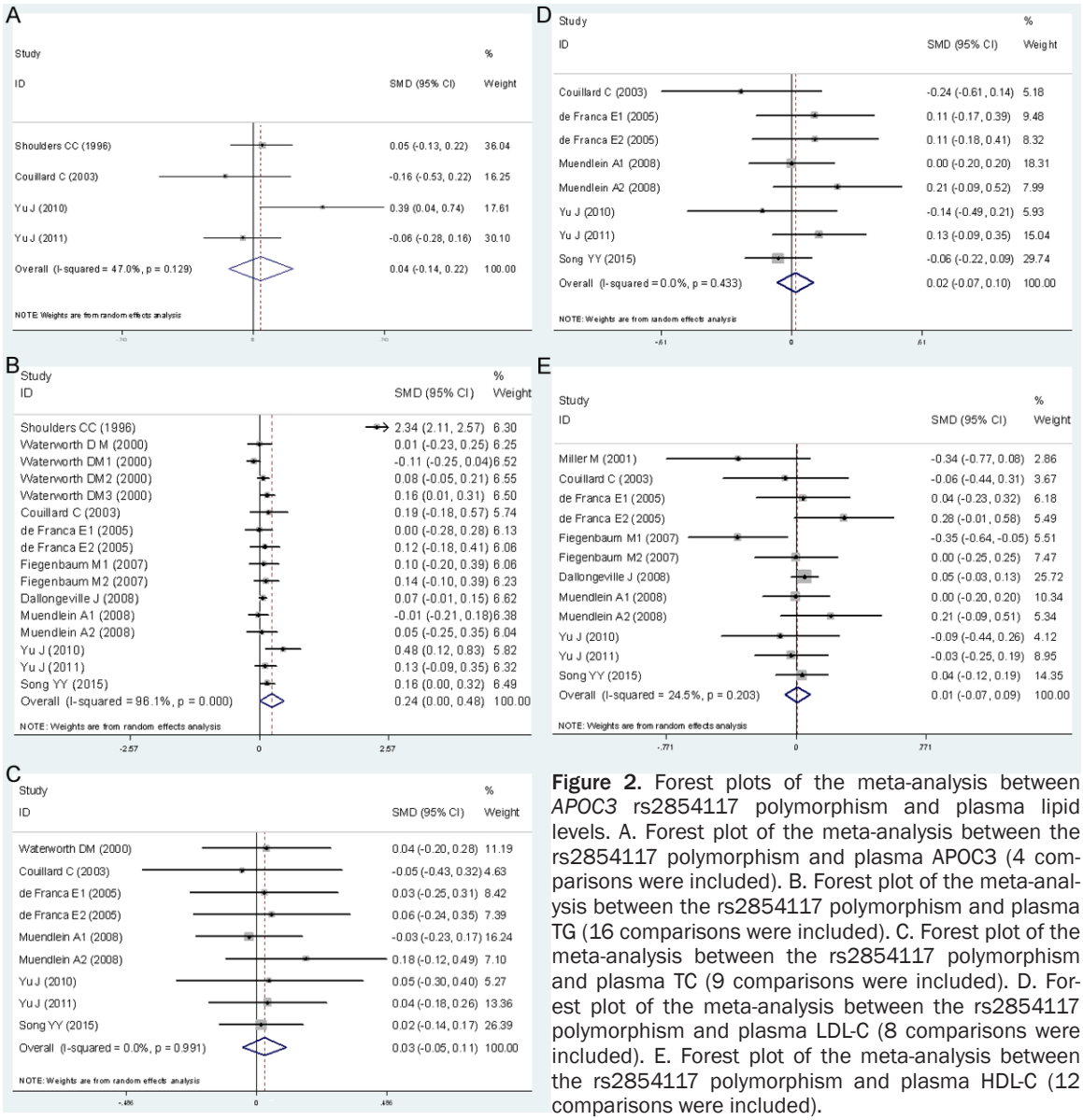

Figure 2. Forest plots of the meta-analysis between *APOC3* rs2854117 polymorphism and plasma lipid levels. A. Forest plot of the meta-analysis between the rs2854117 polymorphism and plasma APOC3 (4 comparisons were included). B. Forest plot of the meta-analysis between the rs2854117 polymorphism and plasma TG (16 comparisons were included). C. Forest plot of the meta-analysis between the rs2854117 polymorphism and plasma TC (9 comparisons were included). D. Forest plot of the meta-analysis between the rs2854117 polymorphism and plasma LDL-C (8 comparisons were included). E. Forest plot of the meta-analysis between the rs2854117 polymorphism and plasma HDL-C (12 comparisons were included).

fied by the characteristics of the subjects (**Table 3**; **Figure 3**).

Heterogeneity analysis

In the analyses for the rs2854116 polymorphism, there was significant heterogeneity among the total comparisons for TG, TC, LDL-C, and HDL-C. Seven comparisons (Shoulders CC, 1996, Dallongeville J1, 2000, Olivieri O, 2002, Lahiry P, 2007, Pollex RL5, 2007, Yu J, 2011, Ding Y, 2012), 2 comparisons (Dallongeville J2, 2000, Pollex RL6, 2007), 2 comparisons (Dallongeville J1, 2000, de França E1, 2005) and 6 comparisons (Dallongeville J1, 2000, de França E2, 2005, Lahiry P, 2007, Pollex RL6, 2007, Yu J, 2011, Ding Y, 2012) were respectively identified as the main contributors to the heterogeneity for TG, TC, LDL-C and HDL-C by using Galbraith plots (Figures S1, S2, S3, S4 of the supplemental data file). The heterogeneity was effectively removed or decreased after exclusion of these outlier studies, but the SMD values and their 95% CIs did not change substantially (TG: SMD = 0.17, 95% CI = 0.10-0.24, P_{SMD} < 0.00001, $P_{Heterogeneity}$ = 0.49; TC: SMD = 0.04, 95% CI = -0.03-0.11, P_{SMD} = 0.244, $P_{Heterogeneity}$ = 0.875; LDL-C: SMD = 0.03, 95% CI = -0.04-0.11, P_{SMD} = 0.427, $P_{Heterogeneity}$ = 0.266; HDL-C: SMD = -0.12, 95% CI = -0.21--0.03, P = 0.008, $P_{Heterogeneity}$ = 0.223).

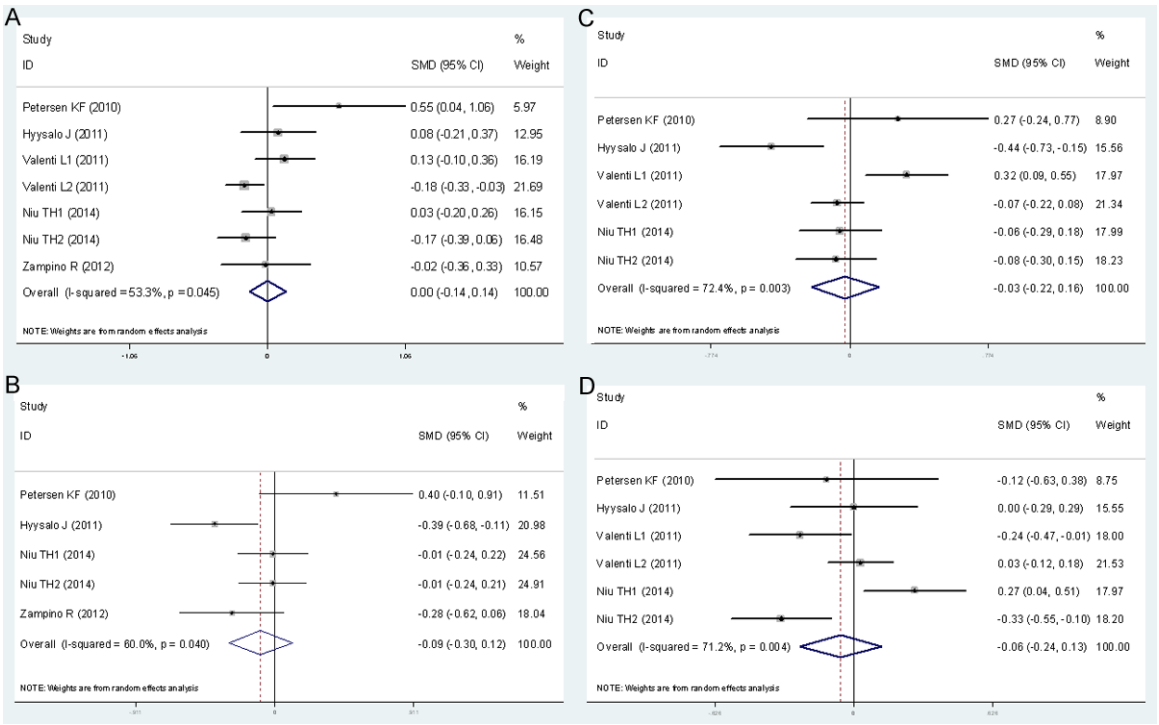

Figure 3. Forest plots of the meta-analysis between the APOC3 rs2854116-rs2854117 interaction and plasma lipid levels. A. Forest plot of the meta-analysis between the rs2854116-rs2854117 interaction and plasma TG (7 comparisons were included). B. Forest plot of the meta-analysis between the rs2854116-rs2854117 interaction and plasma TC (5 comparisons were included). C. Forest plot of the meta-analysis between the rs2854116-rs2854117 interaction and plasma LDL-C (6 comparisons were included). D. Forest plot of the meta-analysis between the rs2854116-rs2854117 interaction and plasma HDL-C (6 comparisons were included).

In the analyses for the rs2854117 polymorphism, there was significant heterogeneity in the total comparison for TG, and 2 comparisons (Shoulders CC, 1996, Waterworth DM2, 2000) were identified as the main contributors to the heterogeneity by using Galbraith plot (Figure S5 of the supplemental data file). The heterogeneity was effectively removed after exclusion of the two studies, but the SMD value and its 95% CI did not change significantly (SMD = 0.10, 95% CI = 0.05-0.14, P_{SMD} < 0.00001, $P_{Heterogeneity}$ = 0.775). No significant heterogeneity was found among the total comparisons or the subgroup analyses for APOC3, TC, LDL-C and HDL-C.

In the analyses for the rs2854116-rs2854117 interaction, there was significant heterogeneity among the total comparisons for TG, TC, LDL-C and HDL-C. One comparison (Petersen KF, 2010), 1 comparison (Hyysalo J, 2012), 2 comparisons (Hyysalo J, 2012, Valenti L1, 2011) and 2 comparisons (Niu TH1, 2014, Niu TH2, 2014) were respectively identified as the main contributors to the heterogeneity for TG, TC, LDL-C and HDL-C by using Galbraith plots (Figures S6, S7, S8, S9 of the supplemental data file). The heterogeneity was effectively removed or decreased after exclusion of these outlier studies, but the SMD values and their 95% CIs did not change significantly (TG: SMD = -0.04, 95% CI = -0.16-0.07, P_{SMD} = 0.457, $P_{Heterogeneity}$ = 0.186; TC: SMD = -0.02, 95% CI: -0.21-0.17, P_{SMD} = 0.846, $P_{Heterogeneity}$ = 0.180; LDL-C: SMD = -0.05, 95% CI = -0.16-0.05, P_{SMD} = 0.318, $P_{Heterogeneity}$ = 0.644; HDL-C: SMD = -0.06, 95% CI = -0.20-0.08, P_{SMD} = 0.396, $P_{Heterogeneity}$ = 0.264).

Publication bias test

In the present study, Begg's and Egger's tests did not find any publication bias in the association analyses for the rs2854116 and rs2854117 polymorphisms, and their interaction. For the rs2854116 polymorphism, no publication bias was detected for the analyses regarding APOC3, TG, TC and LDL-C. However,

Egger's test showed that there might be a publication bias in the pooling analysis for HDL-C (t = -0.85, P = 0.045), although the Begg's test could not demonstrate the presence of publication bias (z = 1.17, P = 0.244). To clarify this problem, a trim-and-fill method was employed to adjust the results, and no trimming was performed and the results were unchanged. It indicated that there was no publication bias for HDL-C analysis. The significant P value of Egger's test was originated from other factors, e.g., heterogeneity.

Discussion

The polymorphisms in or near *APOC3* have been suggested to be the strongest genetic determinants of plasma lipid concentrations [36]. A substantial body of literature has investigated the associations of rs2854116, rs2854117, and their interaction with plasma APOC3 and/or lipid levels [11-33]. Associations of these polymorphisms with increased levels of APOC3, TG, TC and LDL-C, and/or decreased levels of HDL-C have been reported in some, but not all studies. The lack of consistency across the studies reflects some existed limitations such as small sample size and differences in ethnicity and research methodology. In the present meta-analysis, the associations of the *APOC3* rs2854116 and rs2854117 polymorphisms and their interaction with plasma APOC3 and lipid levels were investigated to clarify these discrepancies.

A dominant model was adopted in most of the included studies, i.e., TT vs. TC + CC for the rs2854116 polymorphism; CC vs. CT + TT for the rs2854117 polymorphism. Therefore, a dominant model was employed for both the polymorphic loci in this meta-analysis to ensure adequate statistical power. Regarding the interaction of the rs2854116 and rs2854117 polymorphisms, all the five included studies stratified the subjects as the wild-type homozygotes (rs2854116 TT and rs2854117 CC) and the carriers of one or more variant alleles (rs2854116 C and rs2854117 T), so the two groups were compared in the meta-analysis. Our results suggested that the rs2854116 polymorphism was significantly associated with higher levels of APOC3 and TG, and lower levels of HDL-C. A meta-analysis [10] demonstrated that the rs2854116 polymorphism is associated with the risk of CVD, and which was replicated by another recent case-control and meta-analysis study [37]. Taken our results together, it is possible that the association between the rs2854116 polymorphism and CVD is mediated by the increase of TG levels and decrease of HDL-C levels caused by the C allele of the rs2854116 polymorphism, since both Hypertriglyceridemia (HTG) and hypo HDL cholesterolemia are recognized risk factors for CVD [38]. The present meta-analysis also demonstrated a marginally significant association between the rs2854117 polymorphism and higher levels of TG, which indicates that the rs2854117 polymorphism may have mild effects on the expression of *APOC3* since this gene has profound effects on plasma levels of TG [39].

In the present meta-analysis, we also examined whether the interaction of the two polymorphisms had any effects on plasma lipid levels since a recent meta-analysis [40] has clarified its relationship with NAFLD. Our analysis did not find any significant associations between the interaction of the two polymorphisms [i.e., the wild-type homozygotes (rs2854116 TT and rs2854117 CC) vs. the carriers of one or more variant alleles (rs2854116 C and rs2854117 T)] and plasma lipid levels. One of the reasons could be that the significant effects of the rs2854116 polymorphism on lipids have been counteracted by the rs2854117 polymorphism which only had a weak association with TG as our analyses demonstrated.

Subgroup analyses by gender, age, ethnicity and health condition were performed since they might be important variables in determining associative risk with dyslipidemia. For example, the present analyses indicated that gender might modulate the association between the rs2854116 polymorphism and TG levels since the significant association especially exists in females, but not in males (**Table 1**). Ethnicity might modulate the associations of the two polymorphic loci with TG levels, i.e., the significant effect of the rs2854116 polymorphism on TG exists in the subjects with other ethnic origins, but not in Caucasians and Asians (**Table 1**), and the significant effect of the rs2854117 polymorphism on TG exists in Asians, but not in Caucasians and the subjects with other ethnic origins (**Table 2**). Further stud-

ies are needed to examine the associations of two polymorphisms with TG levels in terms of the different effects by gender and ethnicity. The associations of the rs2854116 polymorphism with plasma levels of APOC3 and TG were very robust, which did not vary appreciably when the analyses were performed only with the available studies in HWE. The significant associations of the *APOC3* rs2854116 polymorphism with plasma TC and LDL-C levels were not detected in this meta-analysis. However, they became significant when the analyses were limited to the studies in HWE, which might be due to the small sample size enrolled in the analyses performed only with the available studies in HWE.

The possible mechanism under which the rs2854116 polymorphism modulates the plasma levels of APOC3, TG and HDL-C has not been clarified yet. One explanation could be that the C allele enhances the transcriptional activity of *APOC3* and leads to a higher plasma APOC3 level since the rs2854116 polymorphism is located in the promoter of this gene. Peter et al. [41] demonstrated that the carriers of the C allele tended to have higher hepatic *APOC3* mRNA expression. In the present analysis, significant higher levels of APOC3 were observed in C carriers compared with the TT genotype subjects. Previous studies have shown that APOC3 could increase plasma TG levels [4, 5]. Three mechanisms were considered to be involved in the elevation of TG levels by APOC3. Firstly, APOC3 promotes the assembly and secretion of VLDL in liver [42]. Secondly, APOC3 inhibits LPL, which is located on the inner side of capillaries and is the key enzyme to hydrolyze TG-rich particles [6]. Thirdly, APOC3 inhibits hepatic lipase. Hepatic lipase is located on the endothelial side of liver sinusoids, and its main function is to remove the remnants of chylomicron and VLDL. The present meta-analysis also suggested the significant association of the rs2854116 polymorphism with lower levels of HDL-C. There is a profound interrelationship between the plasma levels of TG and that of HDL-C. Generally, a higher plasma level of TG correlates with a lower level of HDL-C [38].

Significant heterogeneity was found across the analyses for rs2854116 (TG, TC, LDL-C and HDL-C), rs2854117 (TG) and their interaction (TG, TC, LDL-C and HDL-C). Subgroup analyses stratified by the characteristics of the subjects were performed to explore the potential sources of the observed heterogeneity, and the results showed that the main sources of heterogeneity were from ethnic origin, gender and health condition of the subjects, etc. Galbraith plots were employed to further evaluate the sources of heterogeneity. Outlier studies were identified by using the plots, and the heterogeneity was effectively removed or decreased after exclusion of these outlier studies. No significant changes in SMD values and 95% CIs were found after excluding the outlier studies.

The associations of the *APOC3* rs2854116 and rs2854117 polymorphisms with plasma lipids were not likely to be type I errors (false-positive results). Firstly, the results from this meta-analysis were based on the random effects model. Comparing with fixed effects model, the random effects model is a more conservative method and less likely to produce false-positive results. Secondly, 8800 subjects and 8326 subjects were respectively included in the analyses for the rs2854116 and rs2854117 polymorphisms. Among the subjects, 65.7% (rs2854116) and 52.2% (rs2854117) of the subjects were respectively the carriers of the variant allele. Since the incidence of the variant allele carriers was sufficiently high, type I error may have been prevented for both polymorphic loci.

The present meta-analysis has several limitations. Firstly, dyslipidemia is involved in a group of genes as well as some environmental factors. However, the interactions of the rs2854116 and rs2854117 polymorphisms with the polymorphic loci on other related genes or with environmental factors on plasma APOC3 and lipid levels have not been investigated in this analysis due to the lack of the original data from the included studies. In other words, the more precise results could have been gained if more detailed individual data were available or the stratification analyses based on the environmental factors such as diet, exercise, smoking status, etc., were performed. Secondly, a relatively small number of subjects were included for the association analysis between the rs2854116-rs2854117 interaction and plasma lipid levels due to the limited available studies, which may reduce the statistic power and even cause the type II errors

(false-negative results). Studies with larger sample size are required to further investigate these associations. Thirdly, this meta-analysis only included the studies published in English and Chinese as it was very difficult to get the full papers published in various languages.

Conclusions

In conclusion, the significant associations between the *APOC3* rs2854116 polymorphism and higher levels of APOC3 and TG, and lower levels of HDL-C were found in the present meta-analysis. In addition, a marginally significant association between *APOC3* rs2854117 polymorphism and higher levels of TG were also detected.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yongyan Song, Department of Medical Biochemistry, School of Preclinical Medicine, North Sichuan Medical College, Nanchong 637000, P. R. China. Tel: +86 817 3352032; E-mail: songyongyan2014@foxmail.com

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Table S1. Characteristics of the studies included in the meta-analysis for the rs2854116 and rs2854117 polymorphisms

First author, reference	Polymorphisms	Year	Ethnicity	Gender	Study population	Outcomes
Shoulders CC [11]	rs2854116 and rs2854117	1996	Caucasian	M/F	Healthy children	APOC3, TG
Hegele RA1 [12]	rs2854116	1997	Caucasian	M	Healthy subjects	TG
Hegele RA2 [12]	rs2854116	1997	Caucasian	F	Healthy subjects	TG
Dallongeville J1 [13]	rs2854116 and rs2854117	2000	Caucasian	M	Healthy subjects	APOC3, TG, TC, LDL-C, HDL-C
Dallongeville J2 [13]	rs2854116 and rs2854117	2000	Caucasian	F	Healthy subjects	APOC3, TG, TC, LDL-C, HDL-C
Waterworth DM [14]	rs2854117	2000	Caucasian	M/F	Healthy subjects	TG, TC
Waterworth DM1 [15]	rs2854117	2000	Caucasian	M/F	Never smokers	TG
Waterworth DM2 [15]	rs2854117	2000	Caucasian	M/F	Exsmokers	TG
Waterworth DM3 [15]	rs2854117	2000	Caucasian	M/F	Current smokers	TG
Miller M [16]	rs2854116 and rs2854117	2001	Asian	M/F	Healthy subjects	HDL-C
Olivieri O [17]	rs2854116	2002	Caucasian	M/F	Subjects with CHD and controls	APOC3, TG
Couillard C [18]	rs2854116 and rs2854117	2003	Caucasian	M	Obese subjects	TG, TC, LDL-C, HDL-C
de França E1 [19]	rs2854116 and rs2854117	2005	Other	M	Healthy children	TG, TC, LDL-C, HDL-C
de França E2 [19]	rs2854116 and rs2854117	2005	Other	F	Healthy children	TG, TC, LDL-C, HDL-C
Fiegenbaum M1 [20]	rs2854116 and rs2854117	2007	Other	M	Healthy subjects	TG, HDL-C
Fiegenbaum M2 [20]	rs2854116 and rs2854117	2007	Other	F	Healthy subjects	TG, HDL-C
Lahiry P [21]	rs2854116	2007	Caucasian	M/F	Healthy subjects	TG, HDL-C
Pollex RL1 [22]	rs2854116	2007	Caucasian	M	Healthy subjects	TG, TC, LDL-C, HDL-C
Pollex RL2 [22]	rs2854116	2007	Caucasian	F	Healthy subjects	TG, TC, LDL-C, HDL-C
Pollex RL3 [22]	rs2854116	2007	Asian	M	Healthy subjects	TG, TC, LDL-C, HDL-C
Pollex RL4 [22]	rs2854116	2007	Asian	F	Healthy subjects	TG, TC, LDL-C, HDL-C
Pollex RL5 [22]	rs2854116	2007	Other	M	Healthy subjects	TG, TC, LDL-C, HDL-C
Pollex RL6 [22]	rs2854116	2007	Other	F	Healthy subjects	TG, TC, LDL-C, HDL-C
Dallongeville J [23]	rs2854117	2008	Caucasian	M/F	Subjects without metabolic syndrome	TG, HDL-C
Muendlein A1 [24]	rs2854116	2008	Caucasian	M	Subjects with CHD and controls	TG, TC, LDL-C, HDL-C
Muendlein A2 [24]	rs2854116	2008	Caucasian	F	Subjects with CHD and controls	TG, TC, LDL-C, HDL-C
Yu J [25]	rs2854116 and rs2854117	2010	Asian	M/F	Healthy subjects	APOC3, TG, TC, LDL-C, HDL-C
Yu J [26]	rs2854116 and rs2854117	2011	Asian	M/F	Subjects with CHD and controls	APOC3, TG, TC, LDL-C, HDL-C
Ding Y [27]	rs2854116	2012	Asian	M/F	Subjects with CHD can controls	TG, HDL-C
Song YY [28]	rs2854117	2015	Asian	M/F	Healthy children	TG, TC, LDL-C, HDL-C

Table S2. Characteristics of the studies included in the meta-analysis for the rs2854116-rs2854117 interaction

First author, reference	Year	Ethnicity	Gender	Study population	Outcomes
Petersen KF [29]	2010	Asian	M	Subjects with NAFLD and controls	APOC3, TG, TC, LDL-C, HDL-C
Valenti L1 [30]	2011	Caucasian	M/F	Healthy subjects	TG, LDL-C, HDL-C
Valenti L2 [30]	2011	Caucasian	M/F	NAFLD patients	TG, LDL-C, HDL-C
Hyysalo J [31]	2012	Caucasian	M/F	Subjects with diabetes and controls	TG, TC, LDL-C, HDL-C
Zampino R [32]	2013	Caucasian	M/F	HCV patients	TG, TC
Niu TH1 [33]	2014	Asian	M/F	NAFLD patients	TG, TC, LDL-C, HDL-C
Niu TH2 [33]	2014	Asian	M/F	Healthy subjects	TG, TC, LDL-C, HDL-C

Table S3. The plasma APOC3 and lipid levels according to the *APOC3* rs2854116 genotypes

First author, reference	Genotype		ApoC3, mg/dL		TG, mmol/L		TC, mmol/L		LDL-C, mmol/L		HDL-C, mmol/L	
	TT	TC + CC	TT	TC + CC	TT	TC + CC	TT	TC + CC	TT	TC + CC	TT	TC + CC
Shoulders CC [11]	173	330	5.59 ± 1.41	5.76 ± 1.41	0.63 ± 0.02	0.68 ± 0.03	-	-	-	-	-	-
Hegele RA1 [12]	64	156	-	-	1.53 ± 0.77	1.65 ± 0.7	-	-	-	-	-	-
Hegele RA2 [12]	83	206	-	-	1.34 ± 0.84	1.6 ± 0.77	-	-	-	-	-	-
Dallongeville J1 [13]	187	312	4.70 ± 4.20	4.98 ± 5.51	1.68 ± 1.54	1.79 ± 2.77	5.82 ± 1.08	5.88 ± 1.01	3.79 ± 1.04	3.88 ± 1.01	1.34 ± 0.37	1.34 ± 0.44
Dallongeville J2 [13]	188	320	4.00 ± 2.10	4.36 ± 2.66	1.08 ± 0.77	1.08 ± 0.77	5.71 ± 0.99	5.95 ± 1.08	3.52 ± 0.93	3.73 ± 1.00	1.72 ± 0.50	1.64 ± 0.46
Miller M [16]	24	75	-	-	-	-	-	-	-	-	1.14 ± 0.38	1.02 ± 0.26
Olivieri O [17]	206	328	11.47 ± 3.90	11.61 ± 4.10	1.79 ± 0.94	1.82 ± 1.02	-	-	-	-	-	-
Couillard C [18]	41	62	15.00 ± 3.50	14.61 ± 3.28	2.39 ± 0.91	2.55 ± 1.17	5.43 ± 0.79	5.47 ± 0.74	3.74 ± 0.68	3.66 ± 0.76	0.85 ± 0.17	0.87 ± 0.14
de França E1 [19]	64	157	-	-	0.90 ± 0.40	0.91 ± 0.37	3.91 ± 0.60	4.02 ± 0.66	2.36 ± 0.51	0.91 ± 0.57	1.14 ± 0.23	1.13 ± 0.23
de França E2 [19]	63	130	-	-	0.97 ± 0.45	1.00 ± 0.42	4.03 ± 0.69	4.18 ± 0.73	2.47 ± 0.56	2.54 ± 0.67	1.11 ± 0.23	1.19 ± 0.25
Fiegenbaum M1 [20]	62	115	-	-	1.54 ± 0.93	1.56 ± 0.80	-	-	-	-	1.14 ± 0.29	1.03 ± 0.24
Fiegenbaum M2 [20]	97	155	-	-	1.38 ± 0.79	1.39 ± 0.76	-	-	-	-	1.22 ± 0.31	1.22 ± 0.25
Lahiry P [21]	468	840	-	-	1.06 ± 0.21	1.21 ± 0.22	-	-	-	-	1.48 ± 0.14	1.38 ± 0.14
Pollex RL1 [22]	35	71	-	-	1.91 ± 1.19	1.72 ± 0.99	5.26 ± 1.05	5.13 ± 0.91	3.30 ± 0.90	3.33 ± 0.77	1.07 ± 0.36	1.04 ± 0.28
Pollex RL2 [22]	47	79	-	-	1.37 ± 0.74	1.42 ± 0.89	5.01 ± 0.83	4.96 ± 0.91	3.04 ± 0.71	2.96 ± 0.81	1.36 ± 0.39	1.35 ± 0.35
Pollex RL3 [22]	91	237	-	-	1.90 ± 1.67	2.16 ± 1.36	5.17 ± 0.98	5.31 ± 0.99	3.29 ± 0.88	3.44 ± 0.82	1.05 ± 0.32	0.95 ± 0.26
Pollex RL4 [22]	80	218	-	-	1.37 ± 1.00	1.75 ± 1.23	4.97 ± 0.89	5.01 ± 0.90	3.12 ± 0.81	3.01 ± 0.74	1.25 ± 0.28	1.22 ± 0.38
Pollex RL5 [22]	253	533	3.60 ± 2.26	3.63 ± 1.76	1.22 ± 0.78	1.28 ± 0.72	5.58 ± 1.36	5.52 ± 1.20	3.56 ± 1.22	3.51 ± 1.05	1.46 ± 0.48	1.43 ± 0.45
Pollex RL6 [22]	345	686	3.96 ± 2.07	4.15 ± 2.15	1.07 ± 0.49	1.30 ± 1.13	6.08 ± 1.77	5.47 ± 1.23	3.46 ± 1.08	3.42 ± 1.12	1.62 ± 0.46	1.46 ± 0.39
Yu J [25]	47	98	8.15 ± 2.69	9.44 ± 3.70	1.52 ± 0.79	2.03 ± 1.47	4.58 ± 0.80	4.68 ± 0.85	2.65 ± 0.62	2.59 ± 0.68	1.32 ± 0.30	1.35 ± 0.33
Yu J [26]	202	389	8.10 ± 4.10	8.28 ± 4.22	1.29 ± 1.05	1.39 ± 1.18	3.92 ± 1.16	3.96 ± 1.21	2.34 ± 0.94	2.45 ± 0.81	1.12 ± 0.35	1.13 ± 0.36
Ding Y [27]	113	370	-	-	1.43 ± 0.34	2.06 ± 0.45	-	-	-	-	1.22 ± 0.36	1.04 ± 0.30

Table S4. The plasma APOC3 and lipid levels according to the *APOC3* rs2854117 genotypes

First author, reference	Genotype		APOC3, mg/dL		TG, mmol/L		TC, mmol/L		LDL-C, mmol/L		HDL-C, mmol/L	
	CC	TC + TT	CC	TC + TT	CC	TC + TT	CC	TC + TT	CC	TC + TT	CC	TC + TT
Shoulders CC [11]	245	258	5.67 ± 1.41	5.74 ± 1.41	0.63 ± 0.02	0.69 ± 0.03	-	-	-	-	-	-
Waterworth DM [14]	117	155	-	-	1.60 ± 11.36	1.68 ± 10.80	5.51 ± 1.08	5.55 ± 1.10	-	-	-	-
Waterworth DM1 [15]	434	322	-	-	1.58 ± 0.76	1.50 ± 0.71	-	-	-	-	-	-
Waterworth DM2 [15]	549	386	-	-	1.63 ± 0.86	1.70 ± 0.82	-	-	-	-	-	-
Waterworth DM3 [15]	385	299	-	-	1.70 ± 0.79	1.84 ± 0.96	-	-	-	-	-	-
Miller M [16]	31	68	-	-	-	-	-	-	-	-	0.78 ± 0.35	0.68 ± 0.26
Couillard C [18]	60	51	15.2 ± 3.5	14.67 ± 3.17	2.43 ± 0.91	2.64 ± 1.28	5.46 ± 0.72	5.42 ± 0.77	3.74 ± 0.66	3.57 ± 0.79	0.87 ± 0.17	0.86 ± 0.15
de França E1 [19]	77	144	-	-	0.91 ± 0.37	0.91 ± 0.38	3.94 ± 0.63	4.01 ± 0.65	2.40 ± 0.55	2.46 ± 0.55	1.13 ± 0.23	1.14 ± 0.24
de França E2 [19]	68	125	-	-	0.96 ± 0.43	1.01 ± 0.43	4.04 ± 0.70	4.18 ± 0.73	2.47 ± 0.58	2.54 ± 0.66	1.12 ± 0.24	1.19 ± 0.25
Fiegenbaum M1 [20]	85	93	-	-	1.51 ± 0.87	1.59 ± 0.81	-	-	-	-	1.12 ± 0.27	1.03 ± 0.25
Fiegenbaum M2 [20]	122	131	-	-	1.33 ± 0.73	1.44 ± 0.81	-	-	-	-	1.22 ± 0.29	1.22 ± 0.26
Dallongeville J [23]	1148	1058	-	-	1.27 ± 1.0	1.34 ± 1.0	-	-	-	-	1.47 ± 0.4	1.49 ± 0.4
Muendlein A1 [24]	191	196	-	-	2.03 ± 1.42	2.01 ± 1.30	5.56 ± 1.11	5.53 ± 1.01	3.36 ± 0.88	3.36 ± 0.85	3.59 ± 1.01	1.16 ± 0.26
Muendlein A2 [24]	88	82	-	-	1.50 ± 0.73	1.54 ± 0.79	5.74 ± 1.03	5.95 ± 1.24	3.39 ± 0.85	3.59 ± 1.01	1.45 ± 0.36	1.53 ± 0.41
Yu J [25]	46	99	8.12 ± 2.69	9.45 ± 3.69	1.45 ± 0.78	2.06 ± 1.45	4.62 ± 0.76	4.66 ± 0.87	2.67 ± 0.61	2.58 ± 0.68	1.36 ± 0.29	1.33 ± 0.34
Yu J [26]	100	390	8.4 ± 4.3	8.15 ± 4.18	1.25 ± 0.98	1.40 ± 1.22	3.91 ± 1.18	3.96 ± 1.20	2.34 ± 0.90	2.45 ± 0.84	1.13 ± 0.37	1.12 ± 0.36
Song YY [28]	231	492	-	-	1.07 ± 0.38	1.14 ± 0.46	3.59 ± 0.55	3.60 ± 0.58	1.69 ± 0.46	1.66 ± 0.49	1.40 ± 0.29	1.41 ± 0.28

Table S5. The plasma APOC3 and lipid levels of the wild-type homozygotes (rs2854117 CC and rs2854116 TT) and the carriers of one or more variant alleles (rs2854117 T and rs2854116 C)

First author, reference	Genotype		TG, mmol/L		TC, mmol/L		LDL-C, mmol/L		HDL-C, mmol/L	
	Noncarriers	Carriers	Noncarriers	Carriers	Noncarriers	Carriers	Noncarriers	Carriers	Noncarriers	Carriers
Petersen KF [29]	19	75	0.84 ± 0.35	1.33 ± 0.98	3.78 ± 0.80	4.14 ± 0.91	2.15 ± 0.67	2.15 ± 0.67	1.27 ± 0.23	1.22 ± 0.44
Valenti L1 [30]	114	202	0.99 ± 0.50	1.06 ± 0.56	-	-	2.97 ± 0.78	3.18 ± 0.59	1.50 ± 0.36	1.42 ± 0.31
Valenti L2 [30]	272	486	2.23 ± 1.89	1.95 ± 1.34	-	-	3.39 ± 1.17	3.31 ± 1.09	1.22 ± 0.36	1.23 ± 0.34
Hyysalo J [31]	53	364	1.6 ± 0.8	1.7 ± 1.3	5.3 ± 1.1	4.9 ± 1.0	3.2 ± 1.0	2.8 ± 0.9	1.4 ± 0.4	1.4 ± 0.4
Zampino R [32]	45	121	1.17 ± 0.53	1.16 ± 0.62	4.93 ± 1.19	4.63 ± 1.03	-	-	-	-
Niu TH1 [33]	96	294	2.88 ± 1.29	2.92 ± 1.48	5.18 ± 0.96	5.17 ± 1.01	4.43 ± 3.71	4.24 ± 3.35	1.51 ± 0.46	1.78 ± 1.10
Niu TH2 [33]	101	308	2.46 ± 1.97	2.20 ± 1.39	4.77 ± 0.96	4.76 ± 0.81	3.28 ± 2.24	3.14 ± 1.61	2.96 ± 2.89	2.19 ± 2.14

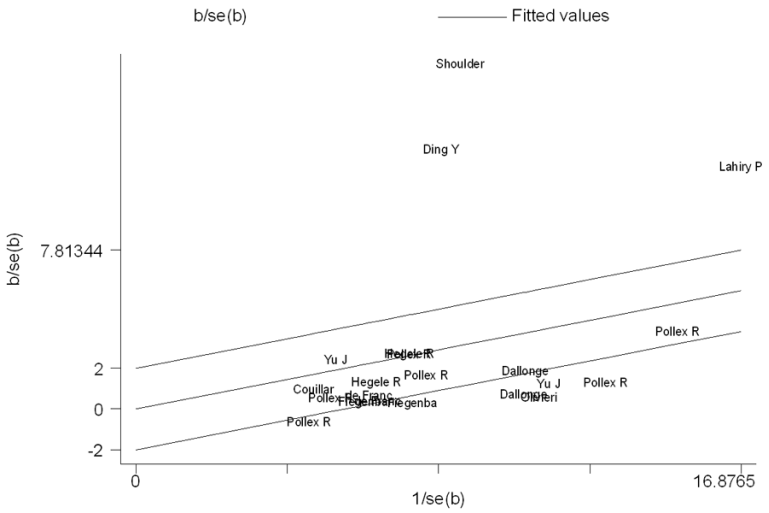

Figure S1. Galbraith plot of the association analysis between the *APOC3* rs2854116 polymorphism and TG.

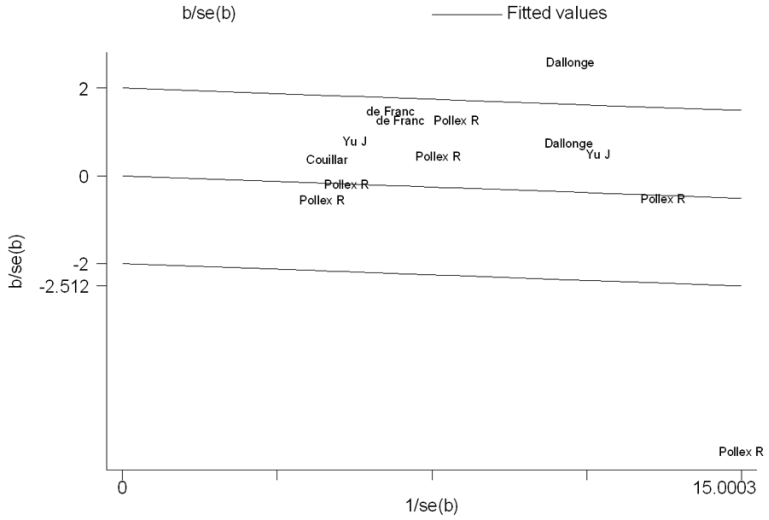

Figure S2. Galbraith plot of the association analysis between the *APOC3* rs2854116 polymorphism and TC.

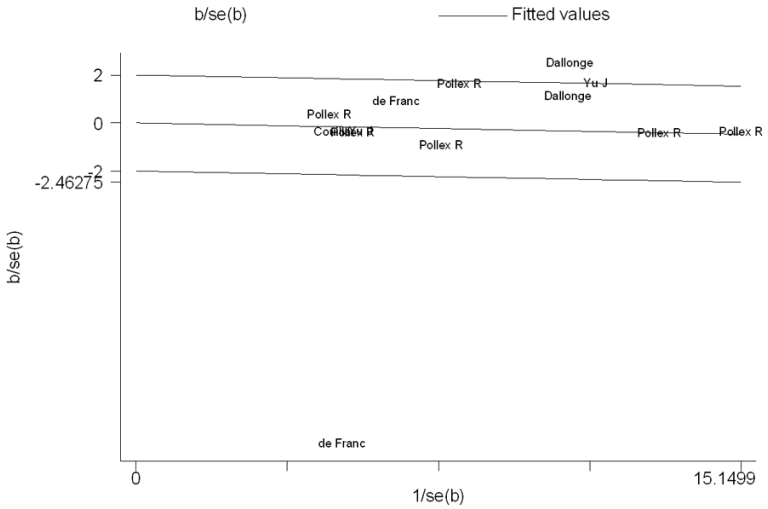

Figure S3. Galbraith plot of the association analysis between the *APOC3* rs2854116 polymorphism and LDL-C.

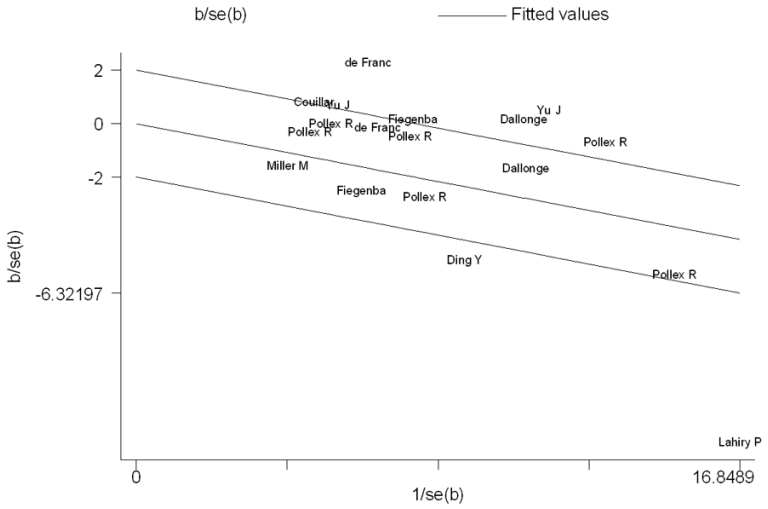

Figure S4. Galbraith plot of the association analysis between the *APOC3* rs2854116 polymorphism and HDL-C.

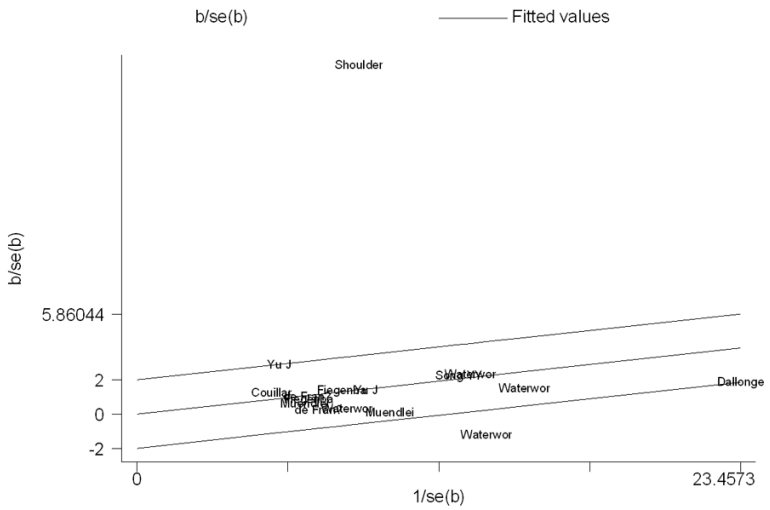

Figure S5. Galbraith plot of the association analysis between the *APOC3* rs2854117 polymorphism and TG.

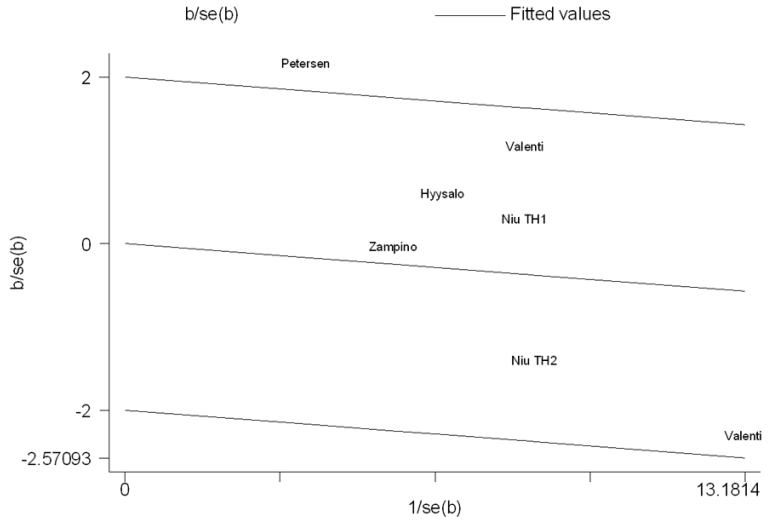

Figure S6. Galbraith plot of the association analysis between the *APOC3* rs2854116-rs2854117 interaction and TG.

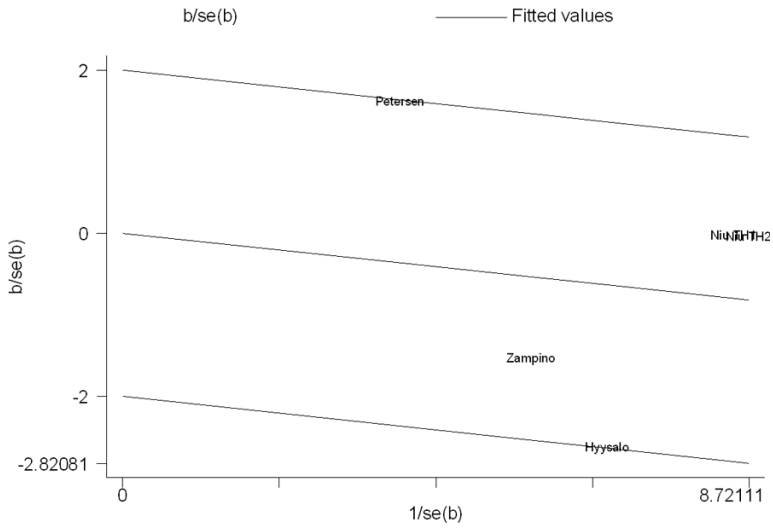

Figure S7. Galbraith plot of the association analysis between the *APOC3* rs2854116-rs2854117 interaction and TC.

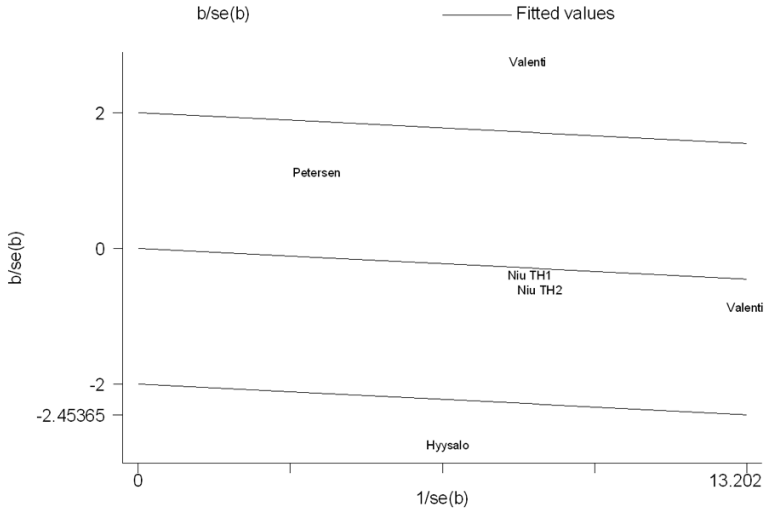

Figure S8. Galbraith plot of the association analysis between the *APOC3* rs2854116-rs2854117 interaction and LDL-C.

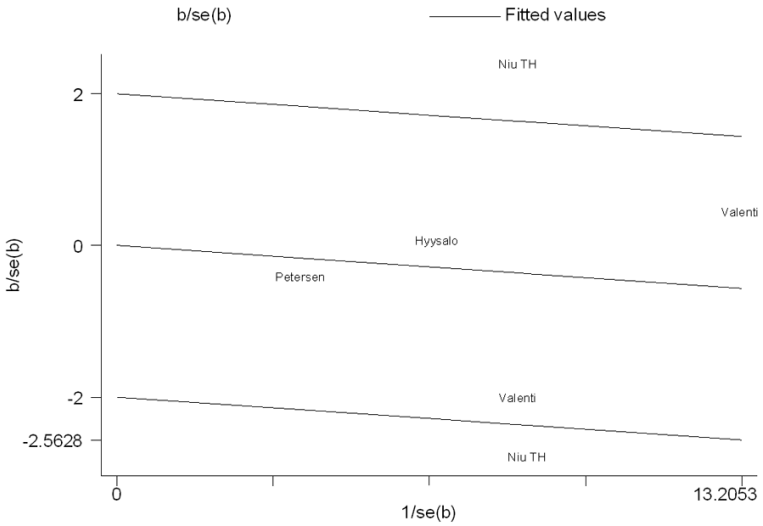

Figure S9. Galbraith plot of the association analysis between the *APOC3* rs2854116-rs2854117 interaction and HDL-C.