

Research Article

# Significant association between the endothelial lipase gene 584C/T polymorphism and coronary artery disease risk

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Several studies have investigated a potential association between the endothelial lipase gene (*LIPG*) 584C/T polymorphism and susceptibility to coronary artery disease (CAD), but a uniform conclusion is yet to be reached. To better evaluate the true relationship between the *LIPG* 584C/T polymorphism and the risk of CAD, a meta-analysis of 14 case-control studies with 9731 subjects was performed. Relevant articles published through August 2020 were searched in the CNKI, PubMed, Embase and Web of Science databases. Thirteen articles, including 14 eligible case-control studies with 4025 cases and 5706 controls, were enrolled in the present meta-analysis. The Newcastle-Ottawa Scale (NOS) scores of the case-control studies ranged from 6 to 8. The pooled results indicated that there is a significant association between the *LIPG* 584C/T polymorphism and CAD in the homozygote comparison model and the allelic comparison model. Subgroup analyses revealed that the *LIPG* 584C/T mutation significantly decreased the risk of CAD in the subgroups of African, CAD, hospital-based (HB), and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) populations in some genetic models. No publication bias was found in our meta-analysis, which certifies the robustness of the current meta-analysis. Trial sequential analysis (TSA) also confirmed the stability of our results. The results of our meta-analysis indicate that the *LIPG* 584C/T polymorphism plays a protective role in the incidence of CAD. More high-quality case-control studies on various ethnicities are needed to confirm our results.

## Introduction

Coronary artery disease (CAD), also called coronary heart disease (CHD), characterized by myocardial hypoxia and ischemia is triggered by coronary atherosclerosis [1]. It is a medical problem of human society and one of the leading causes of disability and deaths in every country [2,3]. The precise mechanism of the onset and development of CAD is still obscure. The pathogenesis of CAD involves many risk factors, including hereditary and environmental factors. Recently, increasing evidence has suggested that genetic factors may play an important role in its pathogenesis. Many genetic variants have been identified to be related to the risk of CAD by previous genetic association studies [4]. The single-nucleotide polymorphism (SNP) is one of the most common genetic variants. Some SNPs may be related to the occurrence and development of CAD, while others are not [5,6].

Endothelial lipase (EL), a new member of the triglyceride (TG) lipase family, was first discovered in 1999. EL consists of 483 amino acids, with a molecular weight of approximately 55 kDa and is mainly secreted from endothelial cells and other cells such as hepatocytes and macrophages [7]. Compared with lipoprotein lipase (LPL) and hepatic lipase (HL), which are also members of the TG lipase family, EL has

Received: 12 January 2020  
Revised: 26 August 2020  
Accepted: 02 September 2020

Accepted Manuscript online:  
07 September 2020  
Version of Record published:  
16 September 2020

higher phospholipase activity and lower TG lipase. A large number of studies have demonstrated that EL plays a key role in high-density lipoprotein (HDL) metabolism. As a regulator of plasma HDL-C levels, EL can modulate the levels of plasma HDL-C inversely [8]. Elevated plasma HDL levels are associated with a protective effect on CAD and low plasma HDL levels are associated with an elevated risk of CAD [9]. Recently, increasing evidence has indicated that EL plays a pivotal role in the pathogenesis of CAD in part by reducing plasma HDL levels.

The EL gene (*LIPG*), which encodes the EL protein and is located on chromosome 18q21.1, spans approximately 30 kb with ten exons and nine introns [10]. Several genetic polymorphisms have been confirmed in *LIPG*. Among these, the 584C/T gene variant (rs2000813) has been the most frequently investigated variant that can lead the amino acid threonine substitution for isoleucine at codons [11]. Several published studies have assessed the association between *LIPG* 584C/T polymorphism and the risk of CAD; however, the results are still inconclusive and contradictory [12–14]. To testify these results, Cai et al. [15] carried out a meta-analysis to explore the association between the *LIPG* 584C/T variation and CAD risk in 2014. Unfortunately, the result of their meta-analysis was still inconclusive. Thereafter, several new studies have investigated the correlation between the *LIPG* 584C/T polymorphism and CAD risk, but the results of these studies remain inconsistent. Therefore, to elucidate the precise correlation of the *LIPG* 584C/T polymorphism with CAD susceptibility, we performed this updated meta-analysis.

## Materials and methods

### Search strategy

A systematic literature network search without language limitations was performed in the CNKI, PubMed, Embase and Web of Science databases to acquire all eligible case–control studies published before 15 August 2020. The relevant search terms included the following: (endothelial lipase gene OR EL OR *LIPG*) AND (polymorphism OR mutation OR variation OR genotype) AND (cardiovascular disease OR coronary heart disease OR coronary artery disease OR angina pectoris OR acute coronary syndrome OR myocardial infarction). Furthermore, to acquire other relevant published articles, the reference lists of the studies and reviews, which were included from the search parameters illuminated above, were searched.

### Inclusion and exclusion criteria

CAD was defined as acute myocardial infarction (AMI), CHD, CAD, myocardial infarction (MI), acute coronary syndrome (ACS), cardiovascular disease. The included articles fulfilled the following criteria: (1) studies assessed the correlation between the *LIPG* 584C/T polymorphism and CAD risk; (2) studies were case–control or cohort; (3) articles reported in Chinese or English; and (4) studies provided precise data for genotype distribution estimation in both groups. Studies were excluded according to the following criteria: (1) not case–control and cohort studies, letters, case reports, reviews or meta-analyses; (2) deficient data; (3) deviating from Hardy–Weinberg equilibrium (HWE) in the control group; and (4) overlapping data or duplicated publications.

### Data extraction

Two researchers (Yue-e Wu and Lan Ma) independently extracted data from the qualified articles based on the inclusion criteria. The following information was extracted from the eligible studies: first author, year of publication, ethnicity and country of participants, type of diseases, genotyping method, sources of controls, number of cases and controls for the 584C/T genotypes of *LIPG* and the *P*-value of the HWE test of controls. When we encountered inconsistent evaluations, all researchers were consulted to acquire an agreement regarding the exclusion or inclusion of the study in the present article.

### Methodological quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of each included study [16]. For the selection and exposure categories, each study can be awarded a maximum of one star for each numbered item. A maximum of two stars can be given for the comparability categories. The NOS has a score range of 0–9, and a study with a score higher than 5 could be included in the present meta-analysis.

### Statistical analysis

The present meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. Chi-square test was applied to assess the HWE in the control groups with significance set at *P* less than 0.05. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate

**Table 1** Characteristics of eligible case–control studies included in this meta-analysis

| First author              | Year | Country | Ethnicity | Type of disease | Source of controls | Genotyping method | Number of cases | Number of controls | HWE (Control) | NOS score |
|---------------------------|------|---------|-----------|-----------------|--------------------|-------------------|-----------------|--------------------|---------------|-----------|
| Zhu et al. [12]           | 2007 | China   | Asian     | CHD             | HB                 | PCR-RFLP          | 242             | 196                | 0.063         | 7         |
| Ji et al. [23]            | 2015 | China   | Asian     | ACS             | HB                 | PCR-RFLP          | 195             | 159                | 0.077         | 6         |
| Jensen et al. [24]        | 2009 | Denmark | Caucasian | ACS             | PB                 | TaqMan            | 998             | 1643               | 0.888         | 8         |
| Rimm et al. [25]          | 1992 | America | Caucasian | CAD             | PB                 | PCR               | 262             | 519                | 0.063         | 8         |
| Colditz et al. [26]       | 1997 | America | Caucasian | CAD             | PB                 | PCR               | 241             | 477                | 0.220         | 8         |
| Tjonneland et al.(1) [27] | 2007 | Denmark | Caucasian | CHD             | PB                 | TaqMan            | 235             | 763                | 0.838         | 8         |
| Tjonneland et al.(2) [27] | 2007 | Denmark | Caucasian | CHD             | PB                 | TaqMan            | 763             | 880                | 0.997         | 8         |
| Tang et al. [9]           | 2008 | China   | Asian     | CAD             | HB                 | PCR-RFLP          | 265             | 265                | 0.103         | 7         |
| Xie et al. [13]           | 2015 | China   | Asian     | CAD             | HB                 | PCR               | 287             | 367                | 0.065         | 7         |
| Solim et al. [28]         | 2018 | Turkey  | Caucasian | CAD             | HB                 | TaqMan            | 74              | 73                 | 0.545         | 7         |
| Elnaggar et al. [29]      | 2019 | Egypt   | African   | CAD             | HB                 | PCR-RFLP          | 84              | 42                 | 0.492         | 8         |
| Dalan et al. [30]         | 2013 | Turkey  | Caucasian | CAD             | HB                 | PCR-RFLP          | 104             | 76                 | 0.286         | 7         |
| Cai et al. [14]           | 2014 | China   | Asian     | CAD             | HB                 | PCR-RFLP          | 135             | 166                | 0.146         | 7         |
| Toosi et al. [31]         | 2015 | Iran    | Asian     | CAD             | HB                 | PCR-RFLP          | 140             | 80                 | 0.092         | 8         |

the strength of the relationship between the *LIPG* 584C/T polymorphism and the risk of CAD in five genetic models: heterozygote comparisons (*CT* vs. *CC*), homozygote comparisons (*TT* vs. *CC*), recessive model (*TT* vs. *CT* + *CC*), dominant model (*TT* + *CT* vs. *CC*), and allelic comparisons (*T* vs. *C*). Stratified analyses were also performed according to ethnicity (Asian, Caucasian, and African populations), types of diseases (CHD, ACS, and CAD), genotyping method (polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP), Taqman, and PCR), and sources of controls (hospital-based (HB) and population-based (PB)). Differences in terms of a Z-test were considered statistically significant if the *P*-value was less than 0.05. The Cochran’s Q statistical test and the *I*<sup>2</sup> test were used to measure the heterogeneity within the studies, and the significance was set at *P* less than 0.05 [18]. A fixed-effects model or random-effects model was used to calculate the pooled OR according to the heterogeneity [19]. Influence analysis was carried out to examine the effect of an individual study on the pooled OR by omitting a single study each time to assess the stability of the pooled results. Publication bias was examined by Begg’s funnel plot test and Egger’s test [20,21]. Trial sequential analysis (TSA) was carried out as described in our previous study [22]. STATA 12.0 software (version 12.0; STATA Corp. College Station, TX, U.S.A.) was used to conduct all statistical analyses.

## Results

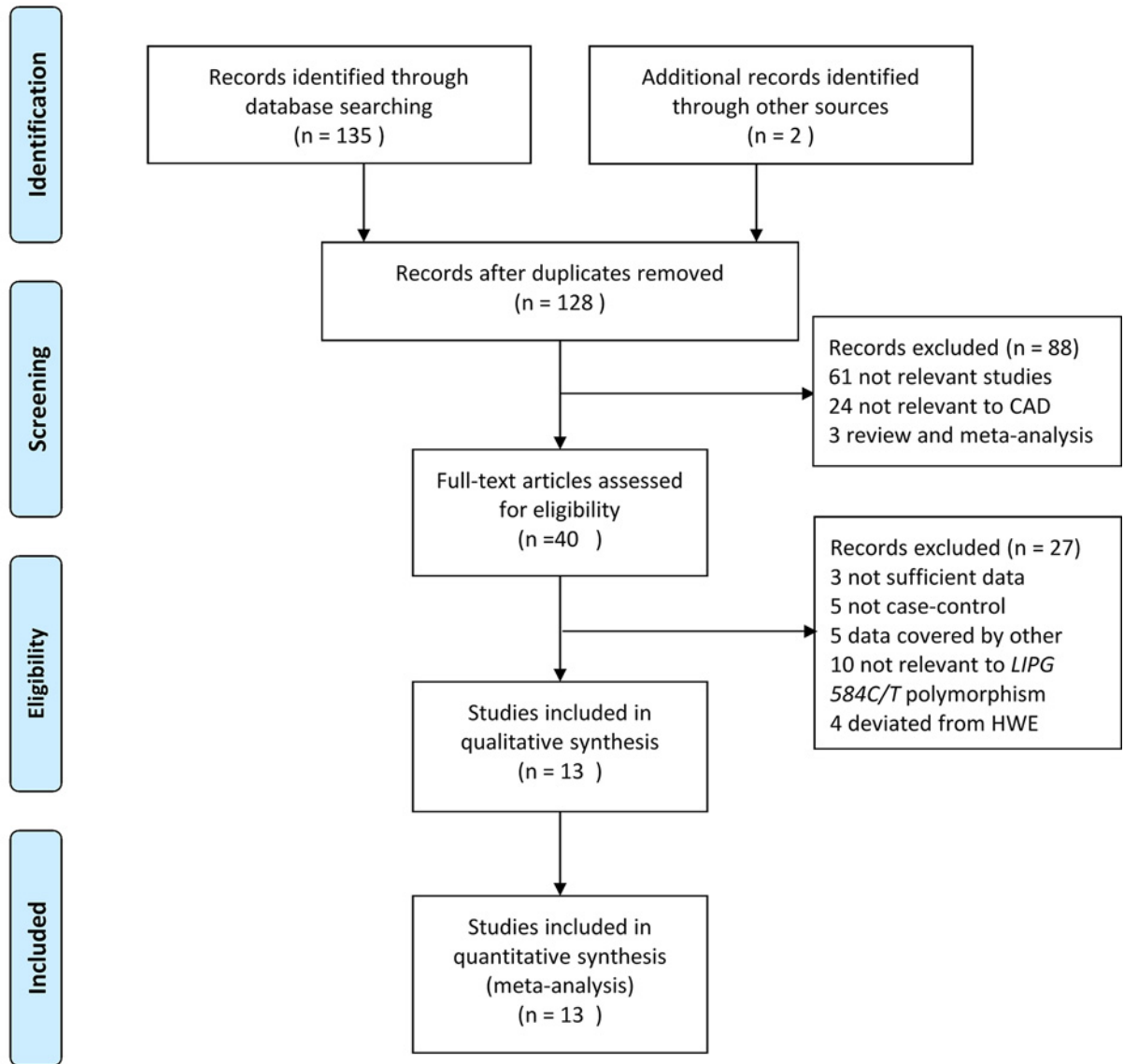
### Characteristics of eligible studies

The process of screening eligible articles is shown in Figure 1. One hundred and thirty-seven potential articles were acquired after a systematic literature search. One hundred and twenty-four articles were removed after the comprehensive examining procedures according to the article titles, abstracts, and full-texts. Finally, the remaining 13 articles, including 14 eligible independent case–control studies with 4025 patients and 5706 controls, were identified and included in the meta-analysis based on the inclusion and exclusion criteria [9,12–14,23–31].

Table 1 displays the characteristics of all case–control studies included in our meta-analysis. All studies were reported in English except for two studies that were published in Chinese. Among the 14 studies, 7 studies were conducted in Caucasian populations, 6 in Asian populations, and only 1 in African populations. There were nine HB studies and five PB studies. Seven studies used PCR-RFLP as the genotyping method, four studies used TaqMan, and three studies used PCR. The genotype distributions of controls in all included studies were accordance with HWE. Table 2 shows the distribution of genotypes and allele frequencies of the *LIPG* 584C/T polymorphism in the cases



## PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

Figure 1. The flow diagram of the included and excluded studies

**Table 2** *LIPG* 584C/T polymorphism genotype distribution and allele frequency in cases and controls

| First author              | Year | Genotype (n) |     |     |    |         |     |     |     | Allele frequency (n) |     |         |     | HWE (Control) |
|---------------------------|------|--------------|-----|-----|----|---------|-----|-----|-----|----------------------|-----|---------|-----|---------------|
|                           |      | Case         |     |     |    | Control |     |     |     | Case                 |     | Control |     |               |
|                           |      | Total        | CC  | CT  | TT | Total   | CC  | CT  | TT  | C                    | T   | C       | T   |               |
| Zhu et al. [12]           | 2007 | 242          | 186 | 56  | 0  | 196     | 150 | 46  | 0   | 428                  | 56  | 346     | 46  | 0.063         |
| Ji et al. [23]            | 2015 | 195          | 112 | 76  | 7  | 159     | 81  | 71  | 7   | 300                  | 90  | 233     | 85  | 0.077         |
| Jensen et al. [24]        | 2009 | 998          | 509 | 406 | 83 | 1643    | 837 | 673 | 133 | 1424                 | 572 | 2347    | 939 | 0.888         |
| Rimm et al. [25]          | 1992 | 262          | 129 | 117 | 16 | 519     | 240 | 239 | 40  | 375                  | 149 | 719     | 319 | 0.063         |
| Colditz et al. [26]       | 1997 | 241          | 115 | 110 | 16 | 477     | 224 | 214 | 39  | 340                  | 142 | 662     | 292 | 0.220         |
| Tjønneland et al.(1) [27] | 2007 | 235          | 116 | 102 | 17 | 763     | 391 | 312 | 60  | 334                  | 136 | 1094    | 432 | 0.838         |
| Tjønneland et al.(2) [27] | 2007 | 763          | 393 | 304 | 66 | 880     | 446 | 361 | 73  | 1090                 | 436 | 1253    | 507 | 0.997         |
| Tang et al. [9]           | 2008 | 265          | 174 | 85  | 6  | 265     | 125 | 122 | 18  | 433                  | 97  | 372     | 158 | 0.103         |
| Xie et al. [13]           | 2015 | 287          | 160 | 116 | 11 | 367     | 216 | 139 | 12  | 436                  | 138 | 571     | 163 | 0.065         |
| Solim et al. [28]         | 2018 | 74           | 40  | 27  | 6  | 73      | 26  | 33  | 14  | 107                  | 39  | 85      | 61  | 0.545         |
| Elnaggar et al. [29]      | 2019 | 84           | 58  | 23  | 2  | 42      | 17  | 21  | 4   | 139                  | 27  | 55      | 29  | 0.492         |
| Dalan et al. [30]         | 2013 | 104          | 44  | 59  | 1  | 76      | 45  | 29  | 2   | 147                  | 61  | 119     | 33  | 0.286         |
| Cai et al. [14]           | 2014 | 135          | 84  | 45  | 6  | 166     | 97  | 64  | 5   | 213                  | 57  | 258     | 74  | 0.146         |
| Toosi et al. [31]         | 2015 | 140          | 67  | 70  | 3  | 80      | 28  | 46  | 6   | 204                  | 76  | 102     | 58  | 0.092         |

and controls. Supplementary Table S1 indicated that the studies included in our study were reliable according to the NOS.

### Test of heterogeneity

To assess the heterogeneity among the included studies, Q-test and  $I^2$  statistics were applied. High heterogeneity was found across studies in all genetic models except for the recessive comparisons. Thus, random-effects analysis was applied to synthesize the data. Moreover, we explored the heterogeneity of all genetic models based on different ethnicities, type of diseases, genotyping method, and sources of controls. However, the significant heterogeneity could not be entirely explained by diverse ethnicities (Table 3).

### Meta-analysis results

The association between the *LIPG* 584C/T polymorphism and the risk of CAD was assessed. The integrated results indicated that the *LIPG* 584C/T variation was significantly associated with CAD risk in the homozygote comparison model ( $TT$  vs.  $CC$ : OR = 0.74, 95% CI = 0.56–0.99,  $P=0.041$ ,  $P_{\text{heterogeneity}}=0.029$ , Table 3 and Figure 2) and allelic comparison model ( $T$  vs.  $C$ : OR = 0.87, 95% CI = 0.76–0.99,  $P=0.037$ ,  $P_{\text{heterogeneity}}=0.000$ , Table 3 and Figure 3). There was no significant association with CAD risk in the other three models, including  $CT$  vs.  $CC$ : OR = 0.89, 95% CI = 0.77–1.03,  $P=0.115$ ,  $P_{\text{heterogeneity}}=0.001$ ;  $TT + CT$  vs.  $CC$ : OR = 0.86, 95% CI = 0.73–1.01,  $P=0.066$ ,  $P_{\text{heterogeneity}}=0.000$ ; and  $TT$  vs.  $CT + CC$ : OR = 0.88, 95% CI = 0.75–1.04,  $P=0.136$ ,  $P_{\text{heterogeneity}}=0.182$  (Table 3).

In the subgroup analysis according to ethnicity, the results showed a decreased CAD risk in African populations under four genetic models ( $TT$  vs.  $CC$ : OR = 0.15, 95% CI = 0.03–0.87,  $P=0.035$ ;  $CT$  vs.  $CC$ : OR = 0.32, 95% CI = 0.14–0.72,  $P=0.005$ ;  $TT + CT$  vs.  $CC$ : OR = 0.29, 95% CI = 0.14–0.64,  $P=0.002$ ; and  $T$  vs.  $C$ : OR = 0.37, 95% CI = 0.20–0.68,  $P=0.001$ ). However, there was no significant association between the *LIPG* 584C/T polymorphism and the risk of CAD that was identified in Asian and Caucasian populations in all genetic models. In the subgroup analysis stratified by type of diseases, the results indicated that the *LIPG* 584C/T polymorphism was significantly associated with decreased CAD risk in the subgroup of CAD in three genetic models ( $TT$  vs.  $CC$ : OR = 0.55, 95% CI = 0.34–0.88,  $P=0.014$ ;  $TT$  vs.  $CT + CC$ : OR = 0.66, 95% CI = 0.49–0.89,  $P=0.006$ ; and  $T$  vs.  $C$ : OR = 0.79, 95% CI = 0.62–0.99,  $P=0.043$ ), and the same results were shown in the HB group ( $TT$  vs.  $CC$ : OR = 0.48, 95% CI = 0.26–0.88,  $P=0.018$ ) and PCR-RFLP ( $TT$  vs.  $CC$ : OR = 0.42, 95% CI = 0.25–0.70,  $P=0.001$ ). Detailed results are shown in Table 3.

### Sensitivity analysis

Sensitivity analysis was carried out to examine the influence of each eligible study on the pooled ORs by the sequential removal of each individual study from the analysis. The individual removal procedure affected the pooled ORs in the

**Table 3 Meta-analysis results**

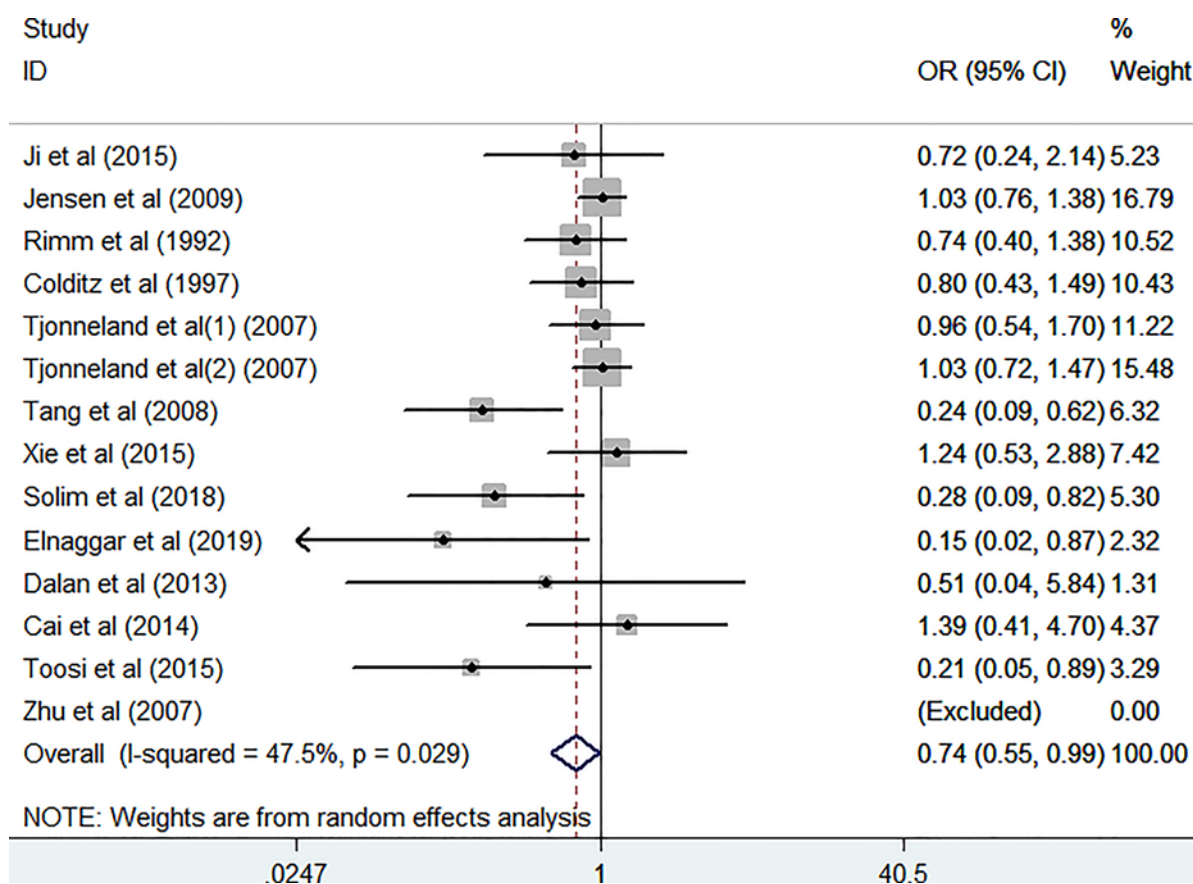
| Genetic model             | Category                   | n       | Model | OR (95% CI)          | P                    | Heterogeneity  |       | Begg's test  | Egger's test |       |
|---------------------------|----------------------------|---------|-------|----------------------|----------------------|----------------|-------|--------------|--------------|-------|
|                           |                            |         |       |                      |                      | I <sup>2</sup> | P     | P            | P            |       |
| Homozygote (TT vs. CC)    | Overall                    | 14      | R     | 0.740 [0.555; 0.987] | <b>0.041</b>         | 47.5%          | 0.029 | 0.059        | 0.121        |       |
|                           | Asian                      | 6       | R     | 0.599 [0.275; 1.303] | 0.196                | 61.2%          | 0.035 | 0.806        | 0.747        |       |
|                           | Caucasian                  | 7       | F     | 0.920 [0.764; 1.110] | 0.384                | 7.7%           | 0.370 | 0.072        | 0.115        |       |
|                           | African                    | 1       | F     | 0.147 [0.025; 0.870] | <b>0.035</b>         | -              | -     | -            | -            |       |
|                           | CHD                        | 3       | F     | 1.006 [0.741; 1.364] | 0.972                | 0.0%           | 0.836 | 1.000        | -            |       |
|                           | ACS                        | 2       | F     | 1.002 [0.753; 1.333] | 0.990                | 0.0%           | 0.542 | 1.000        | -            |       |
|                           | CAD                        | 9       | R     | 0.545 [0.336; 0.884] | <b>0.014</b>         | 49.6%          | 0.044 | 0.602        | 0.651        |       |
|                           | HB                         | 9       | R     | 0.474 [0.255; 0.880] | <b>0.018</b>         | 50.6%          | 0.048 | 0.711        | 0.814        |       |
|                           | PB                         | 5       | F     | 0.963 [0.796; 1.165] | 0.696                | 0.0%           | 0.860 | 0.086        | 0.080        |       |
|                           | PCR-RFLP                   | 7       | F     | 0.420 [0.253; 0.698] | <b>0.001</b>         | 39.1%          | 0.145 | 1.000        | 0.709        |       |
|                           | Taqman                     | 4       | F     | 0.963 [0.783; 1.186] | 0.725                | 44.4%          | 0.145 | 0.089        | 0.151        |       |
|                           | PCR                        | 3       | F     | 0.850 [0.577; 1.252] | 0.411                | 0.0%           | 0.613 | 0.296        | 0.077        |       |
|                           | Heterozygote (CT vs. CC)   | Overall | 14    | R                    | 0.883 [0.765; 1.031] | 0.115          | 61.1% | 0.001        | 0.063        | 0.441 |
|                           |                            | Asian   | 6     | R                    | 0.786 [0.599; 1.031] | 0.082          | 59.5% | 0.030        | 0.707        | 0.856 |
| Caucasian                 |                            | 7       | F     | 0.994 [0.898; 1.101] | 0.910                | 37.2%          | 0.145 | 1.000        | 0.790        |       |
| African                   |                            | 1       | F     | 0.321 [0.144; 0.715] | <b>0.005</b>         | -              | -     | -            | -            |       |
| CHD                       |                            | 3       | F     | 0.997 [0.850; 1.168] | 0.966                | 0.0%           | 0.747 | 1.000        | 0.707        |       |
| ACS                       |                            | 2       | F     | 0.961 [0.824; 0.715] | 0.614                | 9.5%           | 0.293 | 1.000        | -            |       |
| CAD                       |                            | 9       | R     | 0.804 [0.605; 1.121] | 0.131                | 72.6%          | 0.000 | 0.251        | 0.675        |       |
| HB                        |                            | 9       | R     | 0.779 [0.574; 1.056] | 0.108                | 71.5%          | 0.000 | 0.466        | 0.848        |       |
| PB                        |                            | 5       | F     | 0.986 [0.888; 1.094] | 0.788                | 0.0%           | 0.929 | 1.000        | 0.725        |       |
| PCR-RFLP                  |                            | 7       | R     | 0.760 [0.529; 1.092] | 0.138                | 72.5%          | 0.001 | 0.764        | 0.541        |       |
| Taqman                    |                            | 4       | F     | 0.978 [0.871; 1.099] | 0.712                | 14.4%          | 0.320 | 0.734        | 0.444        |       |
| PCR                       |                            | 3       | F     | 1.006 [0.838; 1.208] | 0.947                | 0.0%           | 0.643 | 1.000        | 0.421        |       |
| Dominant (TT + CT vs. CC) |                            | Overall | 14    | R                    | 0.856 [0.725; 1.010] | 0.066          | 68.3% | 0.000        | 0.051        | 0.361 |
|                           |                            | Asian   | 6     | R                    | 0.772 [0.570; 1.044] | 0.093          | 68.6% | 0.007        | 0.707        | 0.898 |
|                           | Caucasian                  | 7       | F     | 0.984 [0.893; 1.085] | 0.752                | 46.7%          | 0.081 | 0.764        | 0.996        |       |
|                           | African                    | 1       | F     | 0.293 [0.135; 0.636] | <b>0.002</b>         | -              | -     | -            | -            |       |
|                           | CHD                        | 3       | F     | 0.998 [0.857; 1.162] | 0.979                | 0.0%           | 0.830 | 1.000        | 0.739        |       |
|                           | ACS                        | 2       | F     | 0.966 [0.834; 1.120] | 0.649                | 22.0%          | 0.258 | 1.000        | -            |       |
|                           | CAD                        | 9       | R     | 0.764 [0.566; 1.032] | 0.079                | 77.1%          | 0.000 | 0.348        | 0.649        |       |
|                           | HB                         | 9       | R     | 0.745 [0.538; 1.031] | 0.076                | 76.4%          | 0.000 | 0.466        | 0.802        |       |
|                           | PB                         | 5       | F     | 0.983 [0.889; 1.086] | 0.730                | 0.0%           | 0.923 | 0.806        | 0.922        |       |
|                           | PCR-RFLP                   | 7       | R     | 0.734 [0.503; 1.072] | 0.109                | 75.9%          | 0.000 | 0.764        | 0.529        |       |
|                           | Taqman                     | 4       | F     | 0.977 [0.874; 1.091] | 0.677                | 46.0%          | 0.136 | 0.734        | 0.326        |       |
|                           | PCR                        | 3       | F     | 0.988 [0.828; 1.180] | 0.898                | 0.0%           | 0.527 | 0.296        | 0.346        |       |
|                           | Recessive (TT vs. CT + CC) | Overall | 14    | F                    | 0.881 [0.745; 1.041] | 0.136          | 26.0% | 0.182        | 0.100        | 0.103 |
|                           |                            | Asian   | 6     | F                    | 0.682 [0.435; 1.068] | 0.094          | 47.1% | 0.109        | 0.806        | 0.781 |
| Caucasian                 |                            | 7       | F     | 0.932 [0.778; 1.117] | 0.448                | 0.0%           | 0.529 | <b>0.016</b> | <b>0.031</b> |       |
| African                   |                            | 1       | F     | 0.235 [0.041; 1.337] | 0.103                | -              | -     | -            | -            |       |
| CHD                       |                            | 3       | F     | 1.007 [0.750; 1.352] | 0.962                | 0.0%           | 0.686 | 1.000        | -            |       |
| ACS                       |                            | 2       | F     | 1.013 [0.768; 1.336] | 0.925                | 0.0%           | 0.668 | 1.000        | -            |       |
| CAD                       |                            | 9       | F     | 0.658 [0.487; 0.889] | <b>0.006</b>         | 26.7%          | 0.207 | 0.602        | 0.659        |       |
| HB                        |                            | 9       | F     | 0.578 [0.390; 0.856] | 0.006                | 30.6%          | 0.184 | 0.902        | 0.726        |       |
| PB                        |                            | 5       | F     | 0.969 [0.806; 1.165] | 0.136                | 0.0%           | 0.860 | 0.086        | <b>0.035</b> |       |
| PCR-RFLP                  |                            | 7       | F     | 0.499 [0.302; 0.825] | <b>0.007</b>         | 21.3%          | 0.273 | 0.707        | 0.881        |       |
| Taqman                    |                            | 4       | F     | 0.976 [0.798; 1.193] | 0.814                | 18.7%          | 0.297 | 0.089        | 0.104        |       |
| PCR                       |                            | 3       | F     | 0.855 [0.586; 1.246] | 0.414                | 0.0%           | 0.700 | 0.296        | <b>0.028</b> |       |
| Allelic (T vs. C)         |                            | Overall | 14    | R                    | 0.869 [0.761; 0.992] | <b>0.037</b>   | 68.5% | 0.000        | 0.080        | 0.288 |
|                           |                            | Asian   | 6     | R                    | 0.813 [0.630; 1.048] | 0.110          | 69.7% | 0.006        | 1.000        | 0.912 |
|                           | Caucasian                  | 7       | F     | 0.978 [0.907; 1.055] | 0.571                | 44.2%          | 0.096 | 0.174        | 0.484        |       |
|                           | African                    | 1       | F     | 0.368 [0.200; 0.678] | <b>0.001</b>         | -              | -     | -            | -            |       |

Continued over

**Table 3** Meta-analysis results (Continued)

| Genetic model | Category | n | Model | OR (95% CI)          | P            | Heterogeneity  |       | Begg's test | Egger's test |
|---------------|----------|---|-------|----------------------|--------------|----------------|-------|-------------|--------------|
|               |          |   |       |                      |              | I <sup>2</sup> | P     | P           | P            |
|               | CHD      | 3 | F     | 1.000 [0.886; 1.128] | 0.999        | 0.0%           | 0.953 | 1.000       | 0.871        |
|               | ACS      | 2 | F     | 0.981 [0.874; 1.102] | 0.750        | 13.5%          | 0.282 | 1.000       | -            |
|               | CAD      | 9 | R     | 0.785 [0.622; 0.992] | <b>0.043</b> | 76.3%          | 0.000 | 0.348       | 0.620        |
|               | HB       | 9 | R     | 0.772 [0.595; 1.001] | 0.051        | 75.3%          | 0.000 | 0.466       | 0.830        |
|               | PB       | 5 | F     | 0.984 [0.910; 1.064] | 0.682        | 0.0%           | 0.909 | 0.462       | 0.471        |
|               | PCR-RFLP | 7 | R     | 0.765 [0.571; 1.026] | 0.074        | 73.0%          | 0.001 | 0.548       | 0.434        |
|               | Taqman   | 4 | F     | 0.981 [0.900; 1.070] | 0.669        | 58.0%          | 0.066 | 0.308       | 0.231        |
|               | PCR      | 3 | F     | 0.971 [0.845; 1.117] | 0.682        | 0.0%           | 0.467 | 0.296       | <b>0.028</b> |

Abbreviations: F, fixed-effects model; n, number of studies; R, random-effects model.

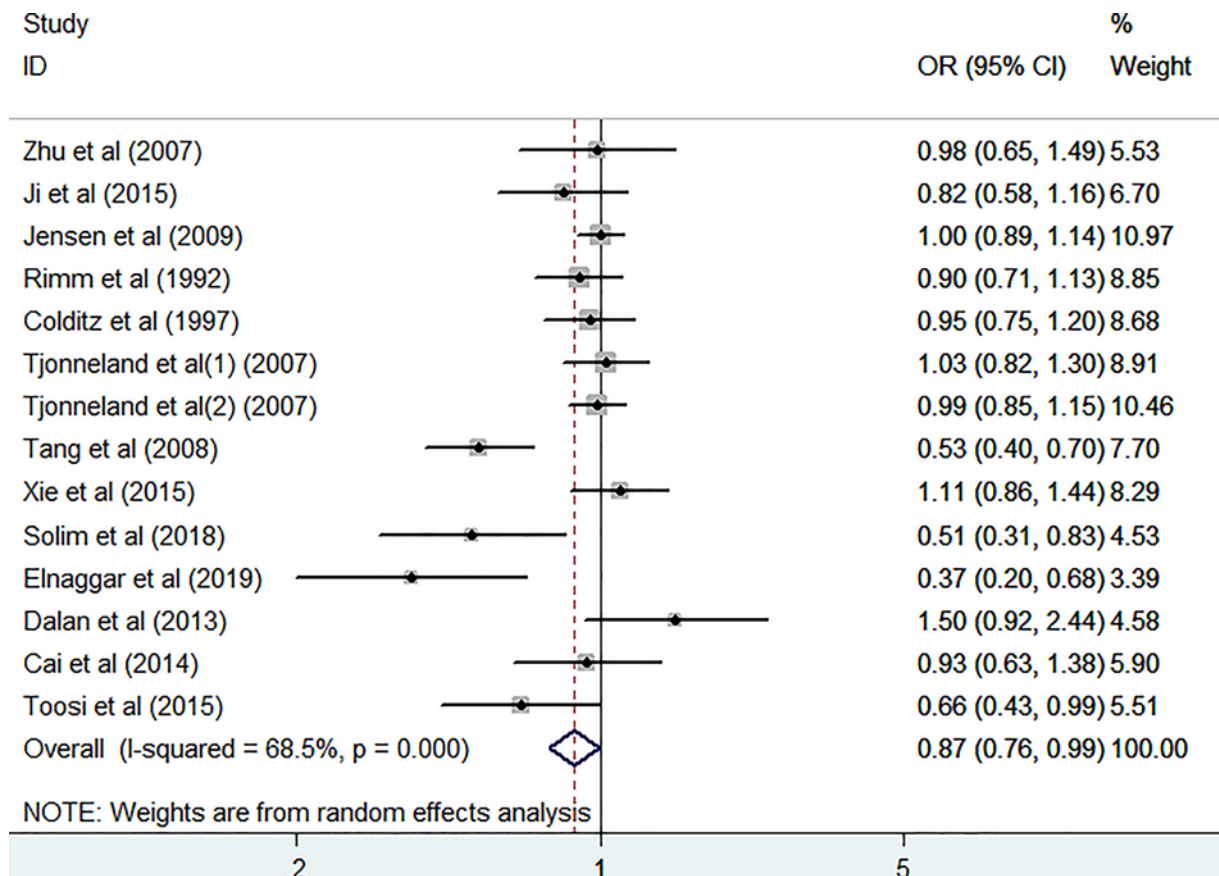


**Figure 2.** Forest plots of the *LIPG* 584C/T polymorphism and CAD risk (homozygote comparisons: TT vs. CC)

homozygote and allelic comparisons model, indicating the instability and unreliability of our findings. Sensitivity analyses of the other three genetic models showed similar results (Figure 4).

### Publication bias

To assess the potential for publication bias among the studies on the the *LIPG* 584C/T polymorphism included in the present meta-analysis, Begg's and Egger's tests were performed for the five genetic models. No evidence of asymmetry was observed by the appearance of the shape in the Begg's funnel plots, and neither Egger's regression nor Begg's rank correlation indicated publication bias among the studies in the five genetic models. The publication bias tests of



**Figure 3.** Forest plots of the *LIPG* 584C/T polymorphism and CAD risk (allelic comparisons: T vs. C)

subgroups were also performed, and no significant publication bias were found, except in few subgroups (Table 3 and Figure 5).

### TSA

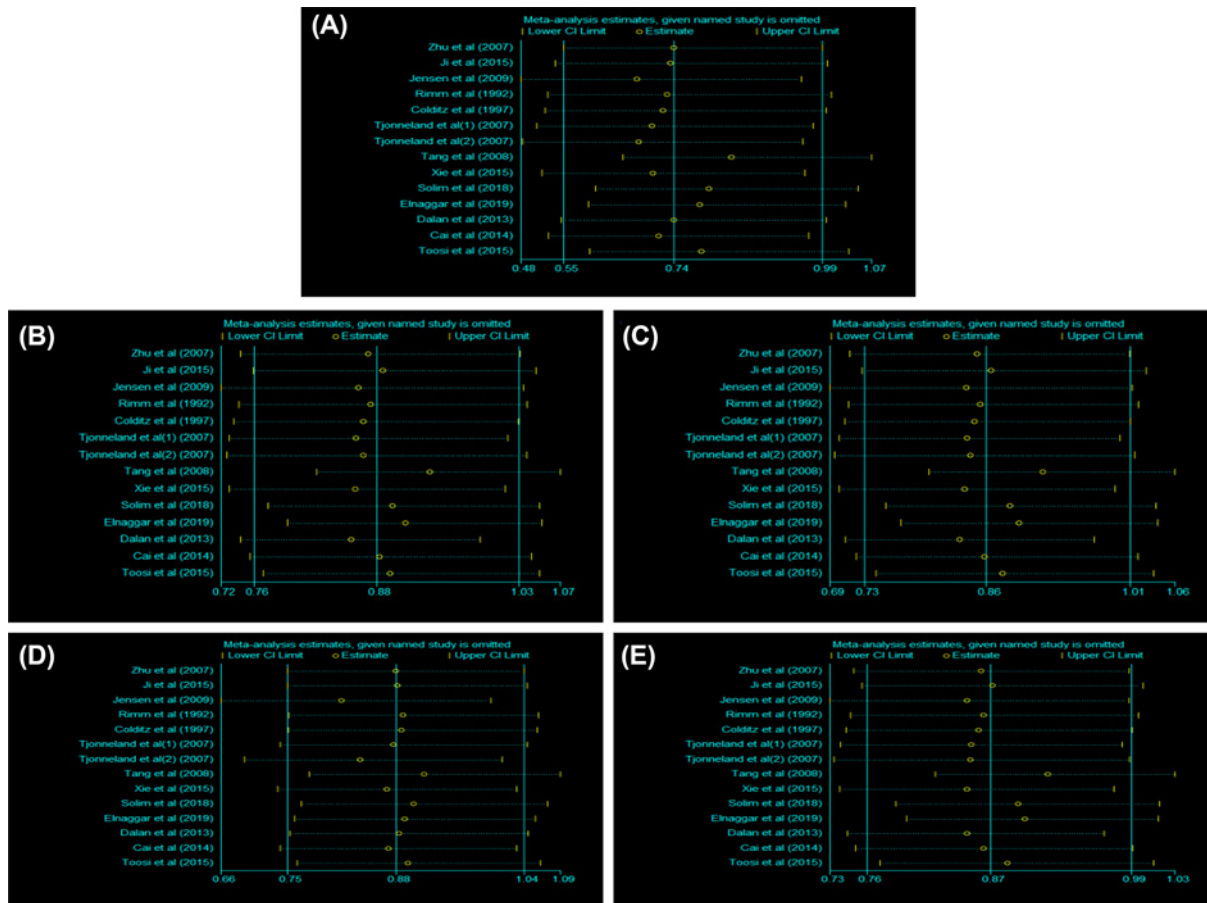
The results of the TSA using the homozygote and allelic comparisons model are shown in Figures 6 and 7. The cumulative z-curve obviously crossed the traditional boundary, and it further confirmed the results of our meta-analysis that the *LIPG* 584C/T polymorphism was significantly associated with decreased CAD risk. Nevertheless, the cumulative z-curve had crossed the TSA monitoring boundary without success before reaching the required information size and demonstrated that the cumulative sample size is insufficient and the more eligible case-control studies are necessary.

### Discussion

The present meta-analysis indicated that the *LIPG* 584C/T variation was significantly associated with CAD risk in the homozygote comparison model (TT vs. CC: OR = 0.74, 95% CI = 0.56–0.99, P=0.041) and allelic comparison model (T vs. C: OR = 0.87, 95% CI = 0.76–0.99, P=0.037). According to the integrated analyses of 14 eligible case-control studies, our study revealed that the *LIPG* 584C/T polymorphism was significantly associated with a decreased risk of CAD, which suggested that the *LIPG* 584C/T polymorphism plays a protective role in the incidence of CAD in individuals and that the T allele may be a protective factor against CAD.

It has been proven that elevated plasma HDL levels are associated with a protective effect on CAD, and low plasma HDL levels are associated with an elevated risk of CAD [9]. The role of EL in the pathogenesis of CAD is regulated by its effect on the metabolism of HDL by its increasing clearance. Therefore, it is speculated that *LIPG* is closely related to the incidence of CAD by affecting the expression of EL. In recent years, more and more attention has been paid to genetic research on CAD, which is not surprising considering the impact of CAD on the health of people around the world [13]. To date, many molecular epidemiological studies have been performed to investigate the





**Figure 4.** The results of sensitivity analysis between the *LIPG* 584C/T polymorphism and susceptibility to CAD (A) homozygous model; (B) heterozygous model; (C) dominant model; (D) recessive model; (E) allele model.

association between the *LIPG* 584C/T variant and CAD risk. However, the results of these studies are inconsistent or even contradictory. The results found by Ji et al. [23], Zhu et al. [12], and Jensen et al. [24] revealed that there was no significant association between the *LIPG* 584C/T polymorphism and risk of CAD; in contrast, Tang et al. [9], Solim et al. [28], and Elnaggar et al. [29] found similar results as ours that the *LIPG* 584C/T polymorphism was significantly associated with a decreased risk of CAD. Cai et al. conducted a meta-analysis to investigate the true association between the *LIPG* 584C/T variant and CAD risk in 2014. However, their analysis included only 9 case–control studies, including 3036 cases and 4777 controls, and concluded that there was no significant association between the *LIPG* 584C/T polymorphism and the susceptibility to CAD. Their results were inconsistent with our study, but three case–control studies of their meta-analysis did not conform to HWE [32–34]. A latest meta-analysis of 13 published case–control studies was performed by Zhao et al. (2020) [35], and also significant results were found. However, in addition to also including three case–control studies that did not conform to HWE, some qualified studies were not included in their meta-analysis. Compared with their meta-analyses, the results of our meta-analysis, which included 14 case–control studies that all were in line with HWE, had more statistical power and reliability.

We noticed significant heterogeneities among the studies and carried out subgroup analyses according to ethnicity. According to previous studies, the *LIPG* 584C/T variant had different effects on CAD in different ethnicities. Even results from studies on the same ethnicity were inconsistent. For example, Tang et al. conducted a study including 530 Chinese subjects to assess the relationship between the common variant and CAD risk [9]. They demonstrated that the T allele could significantly reduce the CAD risk. The same results were found in studies conducted by Solim et al. [28] on the Turkish population, by Shimizu et al. [32] on the Japanese population, and by Toosi et al. [31] on the Iranian population. However, Jensen et al. [24] and Zhu et al. [12] showed no relationship between the *LIPG* 584C/T variant and CAD susceptibility in Caucasian and Asian populations. Our present study showed that the *LIPG* 584C/T

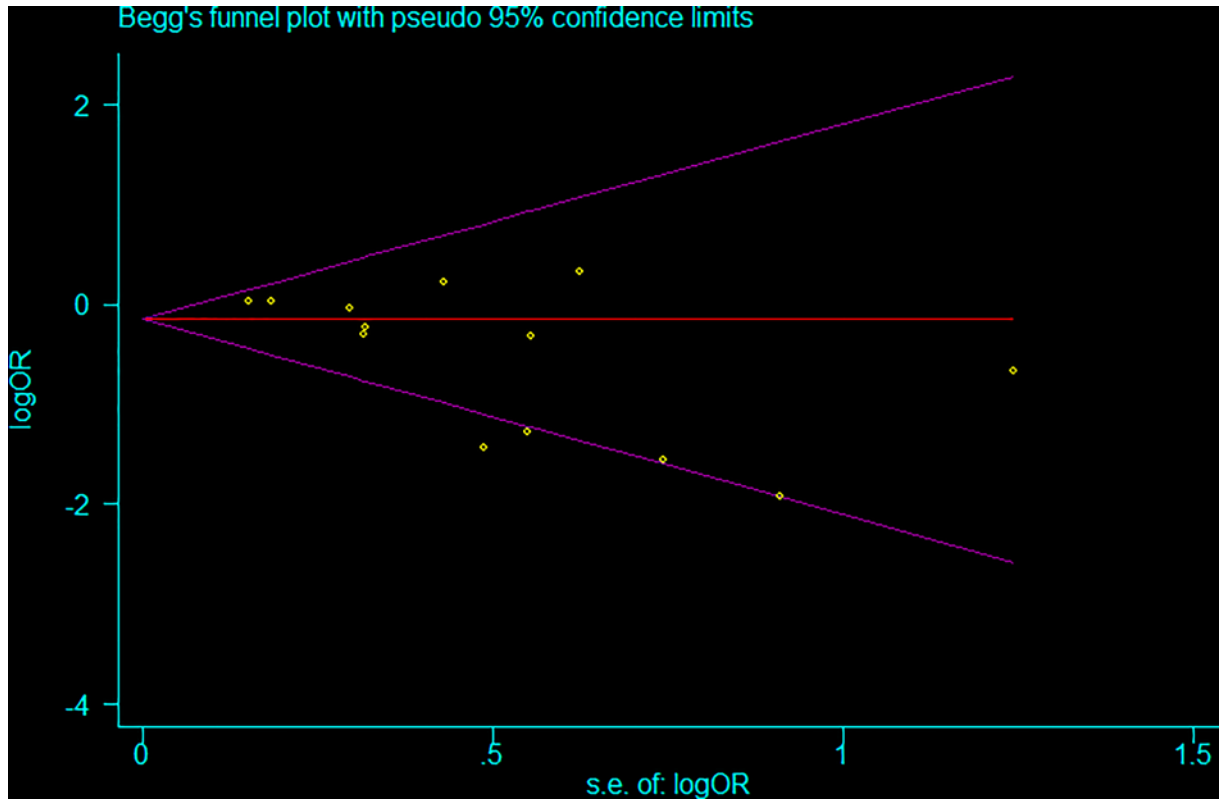


Figure 5. Funnel plot assessing evidence of publication bias (homozygote comparisons: *TT* vs. *CC*)

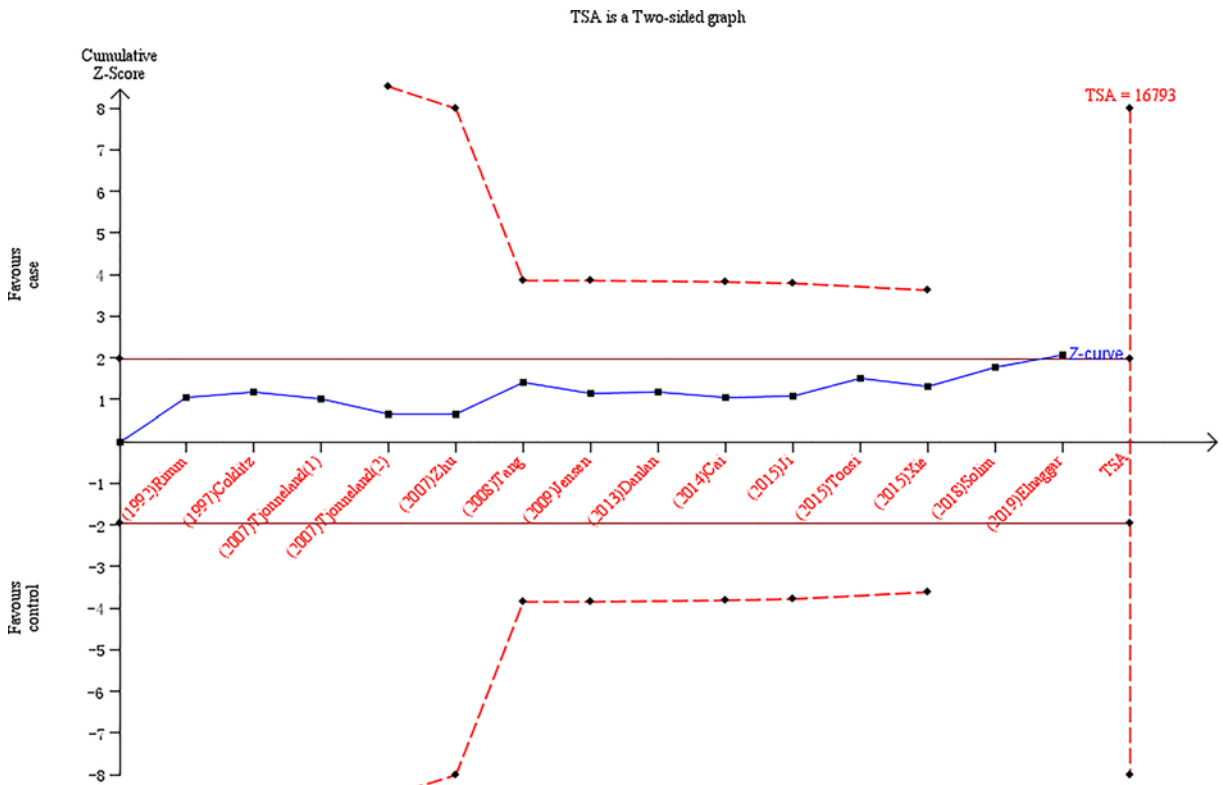


Figure 6. TSA for the *LIPG* 584C/T polymorphism and CAD risk in the homozygote comparisons

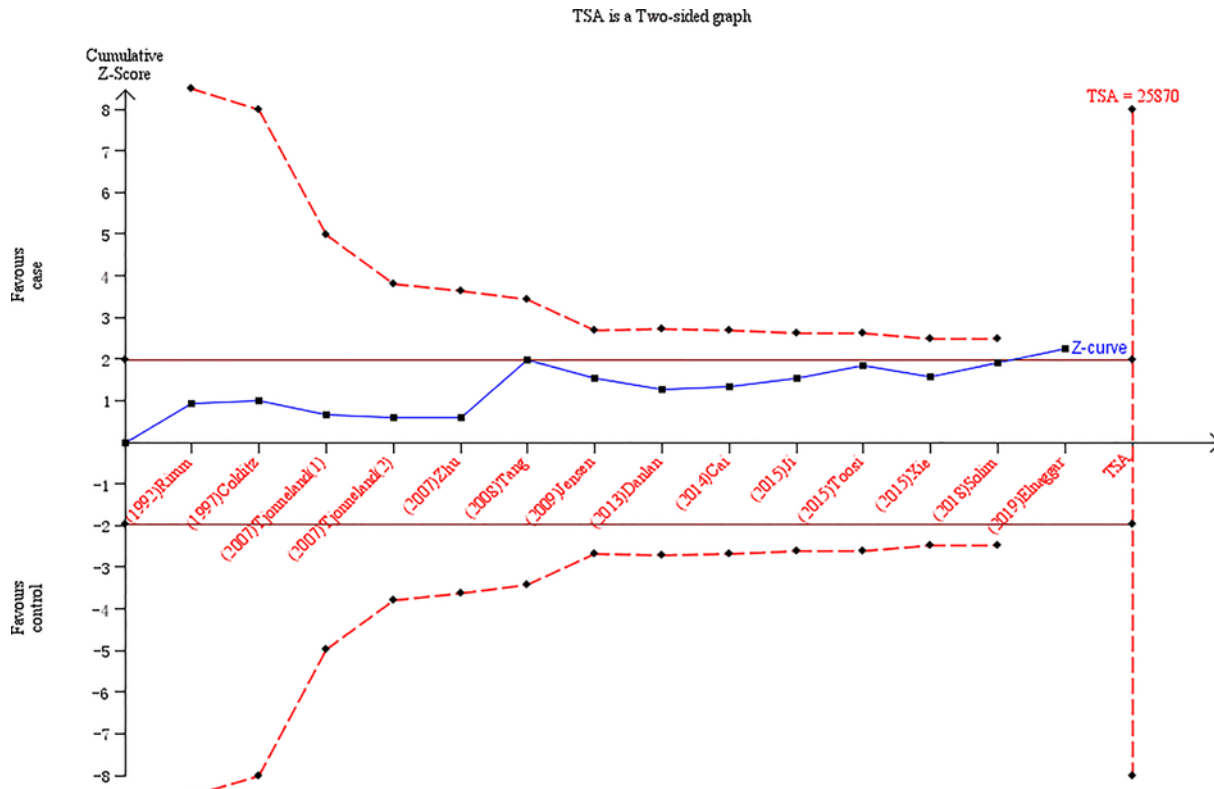


Figure 7. TSA for the *LIPG* 584C/T polymorphism and CAD risk in the allelic comparisons

variant be connected with a decreased CAD risk only in African populations. However, there was no significant association between the *LIPG* 584C/T polymorphism and the risk of CAD that was identified in Asian and Caucasian populations. This result was not convincing enough, because only one case-control study was included in the African subgroup; therefore, this result needs to be confirmed by more high-quality case-control studies in various ethnicities. When carrying out subgroup analysis by type of diseases, we found that the *LIPG* 584C/T polymorphism was significantly associated with a reduced risk in the CAD group, but we failed to find a significant risk association in other types. This result may be explained by the inherent heterogeneity of development in diverse diseases types.

Some inherent drawbacks of our meta-analysis should be illustrated when interpreting our results. First, only unadjusted estimates were applied to evaluate the strength of the relationship between the *LIPG* 584C/T variant and CAD risk. Due to a lack of raw data, such as exposing factors, life habits, gene-environment interactions, interactions between gene-gene and even diverse mutation loci in the same gene factors, a further exact adjustment analysis adjusting for confounding factors could not be carried out. Second, there is still high heterogeneity in our meta-analysis, although we used strict inclusion criteria, accurate data extraction, and rigorous data analysis to perform the present meta-analysis. The persuasiveness of the significant association between the *LIPG* 584C/T polymorphism and CAD susceptibility was affected. Third, the sample sizes of our study were still small, especially in subgroup analysis. Only one eligible study was included in the analysis of African populations. TSA identified that the cumulative sample size was insufficient. There were not enough eligible case-control studies, weakening the statistical power to detect the real correlation between the *LIPG* 584C/T polymorphism and susceptibility to CAD. Fourth, the result of our meta-analysis should be interpreted with caution and needs to be confirmed by more case-control studies, because the sensitivity analyses indicated that deletion of certain individual study had an impact on the reliability of our results. Fifth, although Begg's and Egger's tests proved that there was no publication bias, it may inevitably exist in our meta-analysis. Only published articles reported in English or Chinese were included in the present study. Some candidate studies may not be included because they were not published, discovered, or because they were not published in English or Chinese.

In conclusion, our meta-analysis suggested that the *LIPG* 584C/T polymorphism plays a protective role in the incidence of CAD in individuals. The T allele may be a protective factor against CAD. Because of the limitations mentioned above, more high-quality case-control studies in various ethnicities are needed to confirm our results.

### Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

### Funding

This work was supported by the Anhui Provincial Postdoctoral Science Foundation [grant number 2016B097]; and the Major Project of Natural Science Research of Colleges and Universities in Anhui Province [grant number KJ2019ZD65].

### Author Contribution

Y.W. and Z.H. conceived the study. Y.W., L.M. and H.Z. searched the databases and extracted the data. X.C. and X.X. analyzed the data. Y.W. wrote the draft of the paper. Z.H. and L.M. reviewed the manuscript.

### Acknowledgements

We thank those who helped us in the present study.

### Abbreviations

ACS, acute coronary syndrome; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CNKI, China National Knowledge Infrastructure; EL, endothelial lipase; HB, hospital-based; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HWE, Hardy-Weinberg equilibrium; *LIPG*, endothelial lipase gene; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PB, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SNP, single-nucleotide polymorphism; TG, triglyceride; TSA, trial sequential analysis.

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