Genetics and Molecular Research

Review

APOA5 -1131T/C polymorphism and coronary artery disease susceptibility in Chinese population: an updated meta-analysis and review

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ABSTRACT. Although many studies have investigated the association of the APOA5 -1131T/C polymorphism with coronary artery disease (CAD), definite conclusions have not been drawn. To understand the effects of the APOA5 -1131T/C polymorphism on the risk of developing CAD, we performed an updated meta-analysis in the Chinese population. Relevant studies published till April 2015 were identified from databases such as PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine. A total of 19 studies including 3983 patients and 4358 controls were involved in this meta-analysis. The crude OR with 95%CI was calculated to assess the strength of the association. With the pooled data from the studies included in this meta-analysis, we found a significant association between the APOA5 -1131T/C polymorphism and CAD risk in the Chinese population (C *vs* T: OR = 1.34, 95%CI = 1.16-1.54; CC *vs* TT: OR = 1.73, 95%CI = 1.30-2.30; CC *vs* TT and TC: OR = 1.51, 95%CI = 1.17-1.95; CC *vs* TC: OR = 1.30, 95%CI = 1.03-1.65). Stratified analyses

according to the geographical location and source of controls revealed significantly increased risk in South China and in population-based studies. In conclusion, our meta-analysis provides substantial evidence that the APOA5 -1131T/C polymorphism might contribute to CAD development in the Chinese population.

Key words: Meta-analysis; APOA5 -1131T/C; Coronary artery disease; Polymorphism

INTRODUCTION

Cardiovascular disease is responsible for 30% of all deaths worldwide, with most of its current burden being in developing countries (Gaziano, 2005). After a peak around 1968, death from coronary artery disease (CAD) has declined significantly in the United States (Rosamond et al., 2007). However, in China, CAD has become a public health problem in the past few decades. The overall CAD mortality rate (per 100,000 individuals per year) in China rose from 95.3 in 1999 to 103.4 in 2008 (Jiang et al., 2012). In 2008, the crude morbidity rate of ischemic heart disease was 12.7% among Chinese urban residents (Li et al., 2013a). Epidemiological studies have identified several risk factors for CAD including age, gender, hypertension, diabetes mellitus, hypercholesterolemia, smoking, and family history (Dalen et al., 2014). However, only a subset of individuals exposed to these risk factors eventually develop CAD indicating a pivotal role of genetic factors in susceptibility to CAD. Most recently, genomic studies have revealed a series of new candidate markers that may contribute to the pathogenesis of CAD (Sayols-Baixeras et al., 2014). Among these, apolipoprotein A5 (APOA5), a relatively new member of the apolipoprotein family discovered in 2001 is of significance (Pennacchio et al., 2001; van der Vliet et al., 2001). Evidence suggests that APOA5 plays a crucial role in triglycerides metabolism (van Dijk et al., 2004) and increased level of plasma triglycerides is known to predict the prevalence of CAD (Hokason et al., 1996).

Since the discovery of the APOA5 gene and its association with triglycerides, 16 single nucleotide polymorphisms (SNPs) have been discovered in this gene (Li et al., 2013b). Among these SNPs, -1131T/C gene polymorphism was considered to be closely associated with CAD morbidity (Zhang et al., 2011). The first report on the association between APOA5 -1131T/C polymorphism and CAD was by Szalai and co-workers among the Hungarian population (Szalai et al., 2004). Although many subsequent studies analyzed the influence of APOA5 -1131T/C polymorphism on CAD risk, no clear consensus has been reached. Two meta-analyses (Zhai et al., 2011; Li et al., 2013b) have been conducted to investigate the relationship between APOA5 -1131T/C and CAD in Chinese population. However, there is scope for improvement in these studies. Therefore, we have performed this updated meta-analysis to understand the relationship of APOA5 -1131T/C polymorphism with risk of CAD in Chinese population. In addition, we have implemented subgroup analyses stratified by geographic location and the source of control population to explore the possible effects of gene-environment interactions with respect to CAD risk.

MATERIAL AND METHODS

Literature search

A comprehensive literature search was performed using PubMed, Springer Link,

Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure, and Chinese Biology Medicine for relevant published articles with the following MeSH terms: ("APOA5" OR "apolipoprotein A5") AND ("genetic polymorphism" OR "gene" OR "polymorphism") AND ("coronary artery disease" OR "CAD") AND ("China" OR "Chinese" OR "Taiwan"). An upper date limit of April 6, 2015, was applied but no lower date limit was used. The search was not limited by language restrictions and focused on studies conducted in humans. Concurrently, the reference lists of reviews and retrieved articles were searched manually.

Inclusion/exclusion criteria

Studies were included if they met the following criteria: 1) case-control study or cohort study on the association between APOA5 -1131T/C polymorphism and CAD risk; 2) patient diagnoses based on angiographic features, clinical or laboratory findings; 3) sufficient published data on sample size, OR, and their 95%CI; 4) only Chinese participants; and 5) detailed published information on genotype frequency. Studies were excluded if they were: 1) not case-control or cohort studies, 2) duplicates of a previous publication; 3) based on incomplete data; 4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Two independent investigators carefully extracted information from all eligible studies according to the inclusion criteria listed above. The title and abstract of all potential articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following data was collected from each study: first author's surname, year of publication, geographical location, source of controls, sample size, and the number of subjects with APOA5 -1131T/C genotypes. Disagreements were resolved through discussions between the two authors and if consensus was not achieved, the decision was made by all the authors.

Statistical analysis

STATA statistical package (version 10, STATA, College Station, TX, USA) was used for statistical analyses. Chi-square (χ^2) test was used for Hardy-Weinberg equilibrium of genotypes in the control group of each reviewed study and the heterogeneity of rare allele frequencies in the control groups among all studies. Crude ORs with 95%CIs were used to assess the strength of the association between APOA5 -1131T/C polymorphism and CAD risk. Depending on the results of the heterogeneity test of individual studies, the fixed-effect model (Mantel-Haenszel) or the random-effect model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95%CIs. Sensitivity analysis was conducted using both the models to verify the stability of the meta-analysis. Begg's funnel plot and the Egger linear regression test were used to assess the publication bias. In addition to comparison among all subjects, stratification analyses by geographical location and source of controls was performed. All the P values were two-sided; $P < 0.05$ was considered to be statistically significant.

RESULTS

Eligible studies

A total of 98 articles regarding APOA5 gene polymorphism with respect to CAD were identified. After screening the titles and abstracts, 72 articles were excluded because they were on non-Chinese population, review articles, duplicates, or irrelevant to the current study. Of the 26 potentially relevant articles, 25 were identified for full study retrieval (Wang, 2004; Bi et al., 2004, 2005; Liu et al., 2005; Tang et al., 2005; Yan et al., 2005; Hsu et al., 2006; Tang, 2006; Yin, 2006; Cheng et al., 2007; Li et al., 2007; Qiu, 2007; Qiu et al., 2007; Yang et al., 2007; Yu et al., 2007; Zhang, 2007; Zhu et al., 2007; Xu and He, 2008; Zhao, 2008; Zhang, 2009; Han et al., 2010; Chen et al., 2011; Han, 2011; Yuan et al., 2011; Dai et al., 2013), one was excluded because it had no controls (Qiu et al., 2007), and five (Wang, 2004; Bi et al., 2005; Tang, 2006; Cheng et al., 2007; Han, 2011) were excluded because they concerned subjects included in an expanded series. Finally, 19 studies (Bi et al., 2004; Liu et al., 2005; Tang et al., 2005; Yan et al., 2005; Yin, 2006; Hsu et al., 2006; Qiu, 2007; Yang et al., 2007; Yu et al., 2007; Zhang, 2007; Zhu et al., 2007; Li et al., 2007; Xu and He, 2008; Zhao, 2008; Zhang, 2009; Han et al., 2010; Chen et al., 2011; Yuan et al., 2011; Dai et al., 2013) including 3983 CAD patients and 4358 controls were involved in this meta-analysis according to the inclusion criteria. The publication year of studies ranged from 2004 to 2013. Fourteen of these studies were written in Chinese and five in English. Figure 1 illustrates the trial flow chart and the characteristics of the included studies are summarized in Table 1.

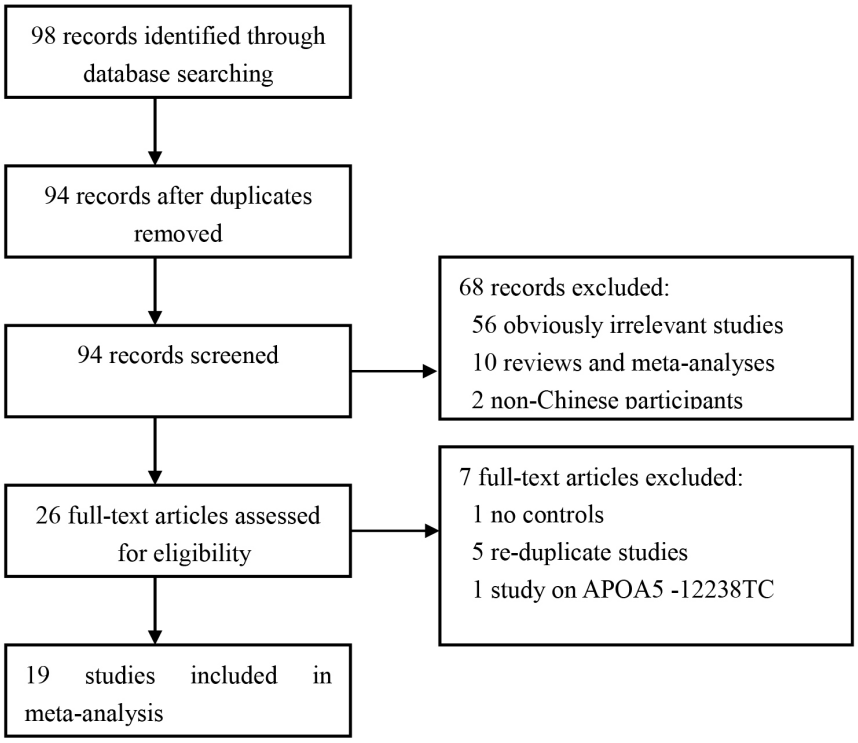

Figure 1. Flow diagram of literature search and selection of eligible studies.

Table 1. Characteristics of studies included in the meta-analysis.

References	Source of controls	Geographic location	No. of cases	No. of controls	Patient			Control			HWE	
					TT	CT	CC	TT	CT	CC	χ^2	P
Bi 2004	PB	Beijing	312	317	108	159	45	136	151	30	1.67	0.196
Tang 2005	PB	Jiangsu	235	262	80	120	35	107	130	25	2.63	0.105
Liu 2005	PB	Sichuan	483	502	181	226	76	246	212	44	0.03	0.861
Yan 2005	PB	Beijing	113	155	41	60	12	83	58	14	0.69	0.407
Yin 2006	PB	Shandong	195	181	71	103	21	78	85	18	0.55	0.458
Hsu 2006	PB	Taiwan	211	317	104	83	24	145	156	16	10.22	0.001
Qiu 2007	PB	Jiangsu	260	316	126	106	28	177	123	16	0.84	0.361
Yang 2007	HB	Jiangsu	168	160	58	80	30	77	67	16	0.06	0.800
Yu 2007	PB	Beijing	140	156	46	67	27	67	75	14	1.18	0.277
Zhang 2007	HB	Zhejiang	141	129	54	59	28	61	52	16	0.87	0.351
Zhu 2007	PB	Hubei	119	210	42	57	20	106	72	32	9.89	0.002
Li 2007	PB	Hunan	186	268	83	49	54	149	66	53	50.70	0.000
Xu 2008	PB	Shandong	195	181	71	103	21	78	85	18	0.55	0.458
Zhao 2008	HB	Xinjiang	155	145	46	86	23	59	75	11	3.80	0.051
Zhang 2009	PB	Xinjiang	112	136	54	49	9	95	36	5	0.46	0.498
Han 2010	PB	Shandong	195	181	71	103	21	78	85	18	0.55	0.458
Chen 2011	PB	Shanxi	249	176	97	119	33	63	78	35	1.45	0.229
Yuan 2011	HB	Xinjiang	344	408	172	149	23	163	184	61	0.59	0.444
Dai 2013	PB	Hunan	170	158	74	44	52	101	42	15	9.45	0.002

PB: Population-based, HB: hospital-based; HWE: Hardy-Weinberg equilibrium.

Meta-analysis results

Table 2 lists the primary results. Overall, a significantly elevated risk of CAD was associated with APOA5 -1131T/C variants (CC *vs* TT: OR = 1.73, 95%CI = 1.30-2.30; CC *vs* TT and TC: OR = 1.51, 95%CI = 1.17-1.95; CC *vs* TC: OR = 1.30, 95%CI = 1.03-1.65). For allele C versus allele T, the pooled OR was 1.34 (95%CI = 1.16-1.54; P = 0.000 for heterogeneity) (Figure 2). However, there was significant heterogeneity between studies. Hence, subgroup analyses by geographical location and source of controls was performed. In the stratified analysis by geographical location, significantly increased risk was found in the population from South China (C *vs* T: OR = 1.48, 95%CI = 1.29-1.70; CC *vs* TT: OR = 2.25, 95%CI = 1.85-2.73; CC *vs* TC: OR = 1.65, 95%CI = 1.36-2.01; CC *vs* TT + TC: OR = 1.95, 95%CI = 1.63-2.34), but not in the North. In the subgroup analysis by source of controls, significantly increased risk was found in population-based studies (C *vs* T: OR = 1.37, 95%CI = 1.21-1.56; CC *vs* TT: OR = 1.83, 95%CI = 1.44-2.33; CC *vs* TC: OR = 1.35, 95%CI = 1.07-1.72; CC *vs* TT + TC: OR = 1.58, 95%CI = 1.25-2.01), but not in hospital-based studies.

Sensitivity analysis and bias diagnosis

To validate the credibility of the outcomes of this meta-analysis, a sensitivity analysis was performed by comparing results of random-effect and fixed-effect models. None of the results were substantially different with respect to the model type (Table 2). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. Begg's funnel plot and the Egger test were employed to assess the publication bias of literatures. The shape of the funnel plots did not reveal obvious asymmetry (Figure 3). Then, the Egger test was used to provide statistical evidence of funnel plot symmetry. The Egger test indicated that there was no obvious publication bias under the allele model in the overall analyses (t = 0.84, P = 0.412).

Table 2. Primary results from the total and subgroup analyses.

Analysis model	Study groups	N	Random-effect model	Fixed-effect model	Heterogeneity	
			OR (95%CI)	OR (95%CI)	χ^2	P
C *vs* T	Total analysis	19	1.34 (1.16-1.54)	1.29 (1.21-1.37)	81.17	0.000
	PB	15	1.37 (1.21-1.56)	1.36 (1.26-1.46)	40.21	0.000
	HB	4	1.21 (0.75-1.95)	1.04 (0.91-1.20)	30.93	0.000
	South China	9	1.48 (1.29-1.70)	1.47 (1.34 -1.61)	18.08	0.021
	North China	10	1.22 (0.98-1.51)	1.13 (0.96-1.24)	47.54	0.000
CC *vs* TT	Total analysis	19	1.73 (1.30-2.30)	1.65 (1439-1.90)	67.19	0.000
	PB	15	1.83 (1.44-2.33)	1.85 (1.58-2.16)	29.94	0.008
	HB	4	1.44 (0.49-4.21)	1.08 (0.79-1.46)	30.10	0.000
	South China	9	2.23 (1.83-2.70)	2.25 (1.85-2.73)	7.65	0.468
	North China	10	1.36 (0.85-2.17)	1.16 (0.94-1.42)	40.90	0.000
CC *vs* TC	Total analysis	19	1.30 (1.03-1.65)	1.28 (1.11-1.47)	44.78	0.000
	PB	15	1.35 (1.07-1.72)	1.36 (1.16-1.60)	28.68	0.012
	HB	4	1.16 (0.57-2.36)	0.99 (0.72-1.35)	13.44	0.004
	South China	9	1.67 (1.30-2.13)	1.65 (1.36-2.01)	11.80	0.160
	North China	10	1.01 (0.73-1.39)	0.96 (0.78-1.18)	19.75	0.020
CC *vs* TT + TC	Total analysis	19	1.51 (1.17-1.95)	1.46 (1.28-1.67)	60.88	0.000
	PB	15	1.58 (1.25-2.01)	1.60 (1.38-1.85)	33.08	0.003
	HB	4	1.28 (0.53-3.07)	1.03 (0.77-1.38)	22.71	0.000
	South China	9	1.94 (1.57-2.41)	1.95 (1.63-2.34)	10.52	0.230
	North China	10	1.16 (0.79-1.71)	1.05 (0.86-1.27)	31.50	0.000

PB = population-based, HB = hospital-based, South China includes Taiwan, Jiangsu, Sichuan, Zhejiang, Hubei, and Hunan; North China includes Beijing, Xinjiang, Shandong, and Shanxi.

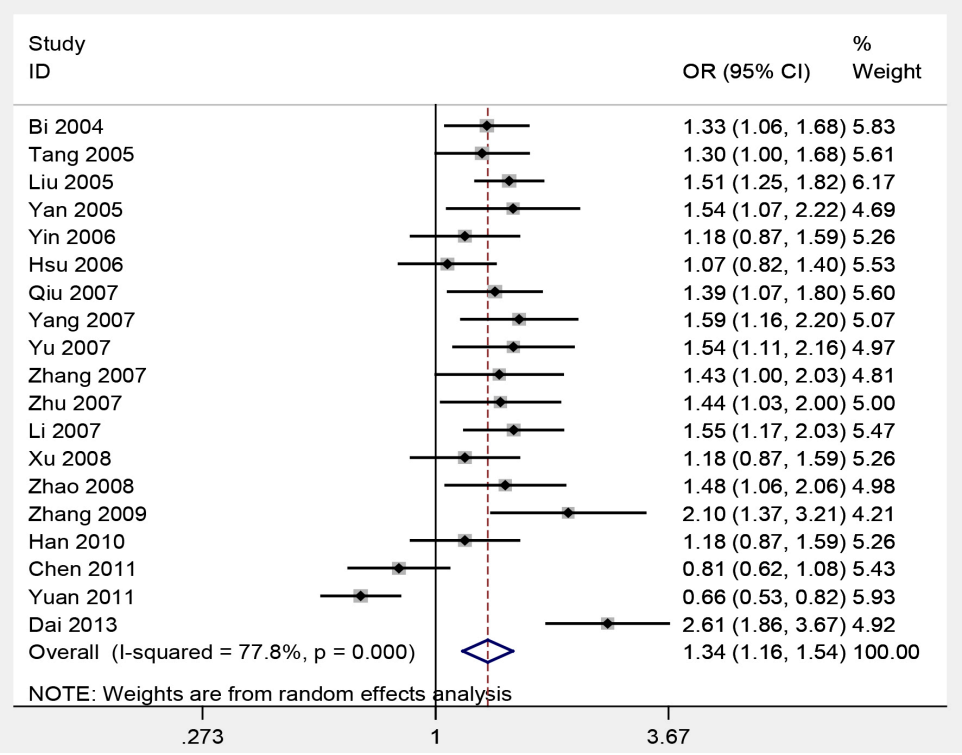

Figure 2. Forest plot of CAD risk associated with APOA5 -1131T/C polymorphism (C *vs* T model).

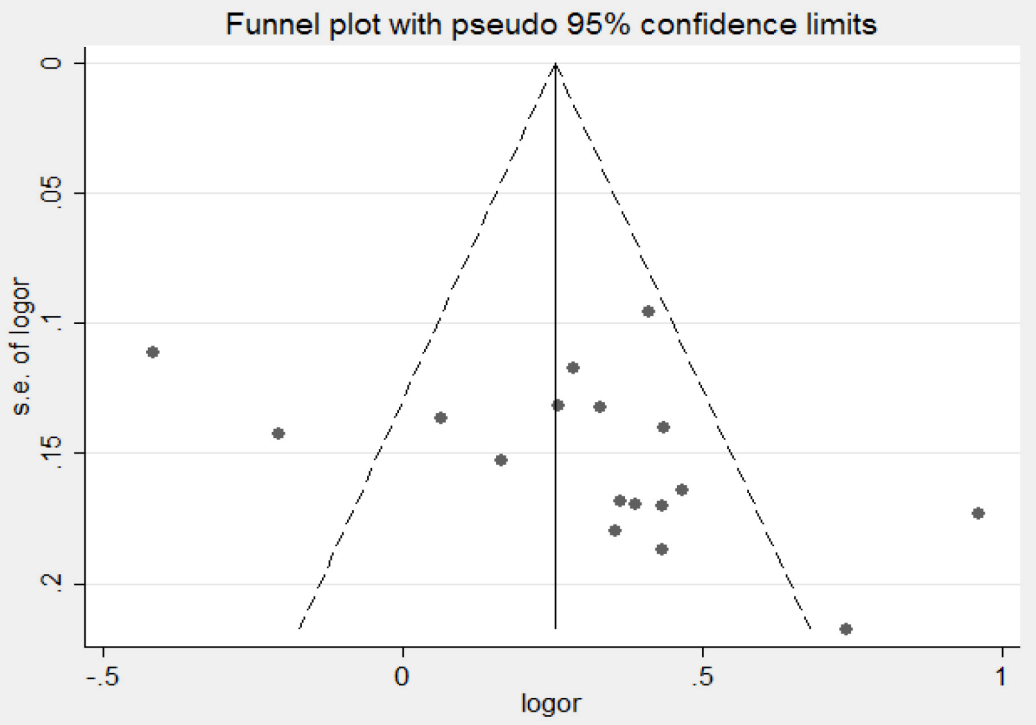

Figure 3. Begg's funnel plot of APOA5 -1131T/C polymorphism and CAD risk (C *vs* T model).

DISCUSSION

Despite several studies investigating APOA5 -1131T/C polymorphism and its association with CAD, researchers have not been able to derive definite conclusions. Until now, three meta-analyses have been published (Zhai et al., 2011; Zhang et al., 2011; Li et al., 2013b), of which, two were in Chinese population. Nevertheless, there are some drawbacks in these analyses, which could be improved on (Zhai et al., 2011; Li et al., 2013b). Therefore, we conducted an updated meta-analysis to derive a more precise estimation of APOA5 -1131T/C and susceptibility to CAD in Chinese population. Our meta-analysis involved 19 case-control studies with a total of 3983 CAD cases and 4358 controls. The overall results showed that a significantly elevated risk of CAD was associated with all APOA5 -1131T/C variants. Our results were consistent with the previously published meta-analysis in Chinese population (Zhai et al., 2011; Li et al., 2013b). However, these analyses did not investigate the modification of polymorphic genotypes by environmental risk factors and included a smaller number of studies on the Chinese than ours.

Further, we performed subgroup analyses stratified by geographical locations and source of controls to explore whether environmental factors can modulate this risk. We found that the APOA5 -1131T/C variants significantly increase the risk of CAD in South China and population-based studies, but not in North China or hospital-based studies. One possible explanation is that the impact of this gene on CAD susceptibility might be ethnicity-based. However, we did not perform subgroup analysis based on nationality or other ethnicity due to lack of sufficient data. In addition, genetic backgrounds and the different living habits in South and North China could play

an important role in susceptibility to CAD. In such cases, gene-gene and/or gene-environmental interactions need to be accounted as additional contributing factors. Moreover, hospital-based studies usually have some biases because such controls may just represent a sample of ill-defined reference population and may not be representative of the general population.

CAD is a multi-factorial and polygenic disorder, which is thought to be the result of interaction between an individual's genetic background and various environmental factors (Nora et al., 1980; Marenberg et al., 1994). The effect of any single gene might have a limited impact on CAD risk than has so far been anticipated. Therefore, some limitations of this study should be acknowledged. Firstly, our study evaluates only the influence of geographical location and source of control, whereas few investigators have reported the effects of this polymorphism under other environment factors such as smoking, alcohol intake, physical activities, and diets. Another potential limitation could be that our results are based on unadjusted estimates. Analyses that are more precise could be conducted if individual data were available, which would allow for the adjustment of covariates including age, gender, race, and other factors. Finally, heterogeneity can interfere with the interpretation of the results of a meta-analysis. Although we minimized this likelihood by performing a careful search of published studies and subgroup analyses, significant inter-study heterogeneity nevertheless existed in most of the comparison.

In conclusion, this meta-analysis suggests that the minor allele of the APOA5 -1131T/C polymorphism is a risk factor for CAD in Chinese, especially in the population from South China. Considering that CAD has multifactorial etiology, larger studies in selected populations with different environmental background or other risk factors are required to further evaluate the influence of gene-gene and gene-environment interactions on APOA5 -1131T/C polymorphism concerning CAD risk. Such studies may eventually lead to a better and comprehensive understanding of this association.

Conflicts of interest

The authors declare no conflict of interest.

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