Review Article
Meta-analysis of the association between Apo-A1 rs670, rs5069 polymorphisms and coronary artery diseases

Li-Ping Dong[1,2], Da Huang[1], Wei-Jun Cai[1]

[1]Department of Histology and Embryology, School of Basic Medicine, Central South University, Changsha 410013, China; [2]Department of Anatomy, Histology and Embryology, Institute of Neuroscience, Changsha Medical University, Changsha 410219, China

Abstract: Coronary artery disease (CAD) is a major cause of mortality and morbidity around the whole world. The polymorphisms of Apolipoprotein A-I (Apo-A1), including rs670 (-75 G/A) and rs5069 (+83 C/T), have been found to be probably associated with the risk of CAD. However, the results were inconsistent. To determine the association between Apo-A1 rs670 and rs5069 polymorphisms with CAD, we conducted the meta-analysis of all available studies cited in Pubmed, Embase, CBM and CNKI before 11 Mar 2017. A total of 6 studies, including 1358 cases and 863 controls, were identified for the meta-analysis. The results showed that rs670 and rs5069 had no significant associations with risk of CAD in the overall analysis. But in subgroup analysis by ethnicity, the GG of rs670 was associated with a significantly lower risk of CAD in allelic model (OR = 0.61, 95% CI = 0.61 [0.38, 0.96], p = 0.03) and homozygous model (OR = 0.25, 95% CI = 0.25 [0.15, 0.44], p<0.00001) in Caucasians, the GG of rs670 was associated with a significantly higher risk of CAD in homozygous model (OR = 2.12, 95% CI = 2.12 [1.27, 3.53], p = 0.004) in Asian, and a lower risk of CAD for the CC genotype and C allele of rs5069 in allelic model (OR = 0.21, 95% CI = 0.21 [0.06, 0.72], p = 0.01) and homozygous model (OR = 0.11, 95% CI = 0.11 [0.04, 0.32], p<0.00001) in Caucasians. In conclusion, this study suggested that Apo-A1 rs670 and rs5069 had no significant associations with risk of CAD in the overall analysis. However, the results of this meta-analysis are hypothesis-generating results which should be interpreted with caution because of the heterogeneity and publication bias among study designs.

Keywords: Apo-A1, rs670, rs5069, polymorphism, coronary artery disease

Introduction

Cardiovascular Diseases (CVDs) is the major cause of death around the world. According to the World Health Organization (WHO) report in 2014, more than 17.5 million individuals died from cardiovascular disease in 2012, accounting for 46.2% of noncommunicable diseases death [1]. Coronary artery disease (CAD), one of the CVDs, has a complex pathogenesis generated by interactions between genetic and environment risk factors. Besides the environmental risk factors, many studies discussed an association of gene polymorphisms with the risk of CAD.

Apo-A1 is the main protein component of high density lipoprotein (HDL) which provides protection against atherosclerosis. The human

Apo-A1 gene is located in chromosome 11q23 [2]. The polymorphisms in Apo-A1 have been found to be probably associated with the risk of CAD. However, the results were controversial results. Some studies have showed that the Apo-A1 polymorphisms, including rs760 and rs5069, were related to the risk of CAD [3-7], while others considered they were not [8]. Thus, in this study, we included 6 studies (1358 cases and 863 controls) to obtain a more accurate and comprehensive estimation of the association between these polymorphisms and CAD.

Experimental section

Publication search strategy

We used the following electronic databases to search studies: Pubmed, Embase, Chinese

Figure 1. PRISMA flowchart of study inclusion and exclusion.
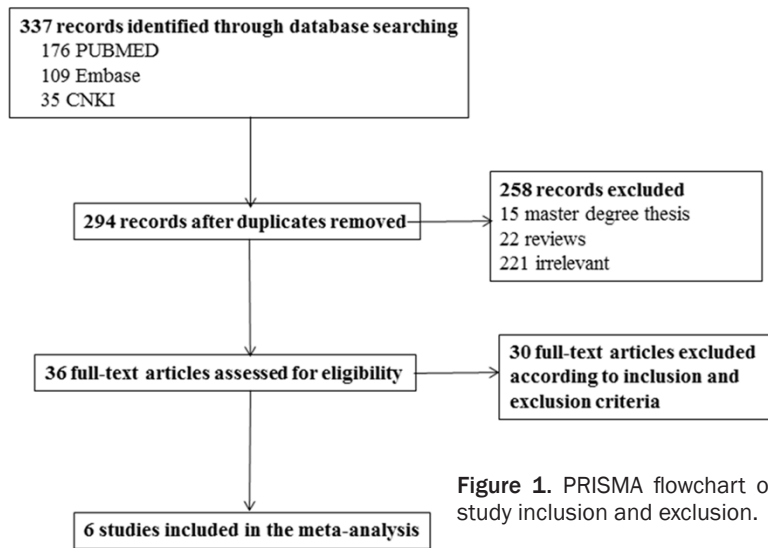
Quality assessment

We evaluated the quality of the included studies according to the predefined scale for quality assessment [9]. The score scale includes total sample size, source of cases, source of controls, specimens used for determining genotypes, and evidence of Hardy-Weinberg equilibrium (HWE). The quality scores range from 0-15, higher scores indicating better quality. Generally considered publications scoring ≥10 were "high quality", and those <10 were "low quality".

National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBM). The search terms and key words were ("Coronary artery disease", or "CAD"), ("Apo-A1"), and ("polymorphism" or "mutation" or "SNP" or "single nucleotide polymorphism"), without restrictions to language. The deadline for publication was 11 Mar 2017. All the results from the databases were read. First, we read the title. If the titles met our criteria, we then read the abstract. We read the full text if the abstract also met our criteria to determine eligible studies.

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) case-control design; (2) the association of Apo-A1 rs670 or rs5069 polymorphisms with CAD risks should be evaluated; (3) sufficient data should be provided for this estimation.

Exclusion criteria: (1) abstracts, letters, reviews and master degree thesis; (2) repeat publications; (3) studies not satisfying all of the inclusion criteria.

Data extraction

We extracted information from each included study by two investigators independently. Any discrepancy between the reviewers was resolved by consensus or a third investigator. For each study, we gathered the first authors' name, publishing year, country, ethnicity, genotyping method, age and sex match, genotype numbers and source of cases and controls.

Statistical methods

We evaluate the HWE of the control group polymorphism by χ^2-test. If $p<0.05$, it was considered to be deviated from HWE.

We used the odds ratio (OR) with 95% confidence interval (CI) to assessed the association between Apo-A1 polymorphisms and CAD risk. The pooled ORs were calculated in homozygous, heterozygous, dominant, and allelic genetic model. The statistical significance was evaluated by the Z-test, $p<0.05$ was considered to be statistically significant.

Heterogeneity between studies was evaluated by an I^2 statistical test, which was not dependent on the number of studies in the present study [10]. $I^2>50\%$ was considered an obvious heterogeneity among the studies, the random-effects model was used for the meta-analysis [11]. Otherwise, the fixed-effect model was used [12]. Subgroup analysis was conducted to identify the heterogeneity.

Sensitivity analysis was conducted to detect the effect of each study on pooled results and the stability of results.

To detect publication bias, we used Begg's funnel plot and Egger's linear regression method, and $p<0.05$ was regarded as statistically significant [13].

All statistical analysis was performed using the STATA 12.0 software and Revman 5.3.

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

Author	Year	Country	Ethnicity	Genotype method	Sex/age match	Quality score	Sample size (case/control)	Case			Control			HWE of control
								GG	GA	AA	GG	GA	AA	
					Apo-A1 rs670 and CAD									
S. Chhabra [3]	2005	India	Caucasians	PCR	match	10	164/36	102	51	11	29	7	0	0.518
Himanshu Rai [8]	2016	India	Caucasians	PCR-RFLP	match	10	200/200	117	71	12	118	75	7	0.236
BiHong Liao [4]	2015	China	Asian	PCR-RFLP	match	8	300/300	175	104	21	161	100	39	<0.01
Zou Yangchun [5]	2003	China	Asian	PCR	match	9	92/45	78	8	6	26	12	7	0.019
X.L. Wang [6]	1996	Australia	Caucasians	PCR	match	11	462/182	306	133	23	125	55	2	0.129
Taranjit Singh Rai [7]	2008	India	Caucasians	PCR	match	9	140/100	45	44	51	51	39	10	0.533

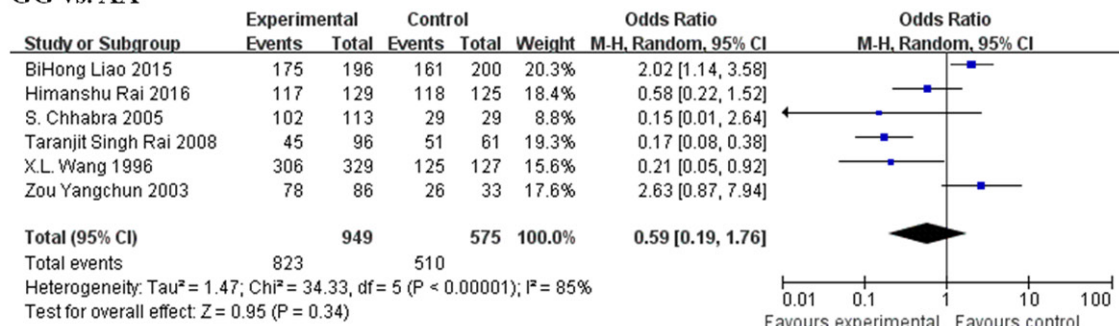| Author	Year	Country	Ethnicity	Genotype method	Sex/age match	Quality score	Sample size (case/control)	Case			Control			HWE of control
								CC	CT	TT	CC	CT	TT	
					Apo-A1 rs5069 and CAD									
BiHong Liao [4]	2015	China	Asian	PCR-RFLP	match	8	300/300	221	54	25	230	39	31	<0.01
Zou Yangchun [5]	2003	China	Asian	PCR	match	6	92/45	77	10	5	30	8	7	<0.01
X.L. Wang [6]	1996	Australia	Caucasians	PCR	match	11	462/182	420	42	0	175	7	0	0.791
Taranjit Singh Rai [7]	2008	India	Caucasians	PCR	match	6	140/100	44	74	22	89	6	5	<0.01

Table 2. Pooled ORs and 95% CIs of the association between Apo-A1 rs670, rs5069, and CAD risks

Genetic model		N	OR (95% CI)	P	I^2 (%)	Model	Genetic model		N	OR (95% CI)	P	I^2 (%)	Model
				Apo-A1 rs670 and CAD									
GG vs. AA	Overall	6	0.59 [0.19, 1.76]	0.34	85	R	GG vs. GA	Overall	6	1.04 [0.75, 1.44]	0.83	58	R
	Asian	2	2.12 [1.27, 3.53]	0.004	0	F		Asian	2	2.01 [0.48, 8.32]	0.34	86	R
	Caucasians	4	0.25 [0.15, 0.44]	<0.00001	23	F		Caucasians	4	0.92 [0.72, 1.17]	0.51	0	F
GG vs. AA/GA	Overall	6	0.95 [0.61, 1.48]	0.82	80	R	G vs. A	Overall	6	0.89 [0.54, 1.45]	0.63	89	R
	Asian	2	2.09 [0.64, 6.82]	0.22	86	R		Asian	2	1.99 [0.80, 4.93]	0.14	85	R
	Caucasians	4	0.69 [0.46, 1.04]	0.08	63	R		Caucasians	4	0.61 [0.38, 0.96]	0.03	80	R
				Apo-A1 rs5069 and CAD									
CC vs. TT	Overall	4	0.78 [0.14, 4.44]	0.78	91	R	CC vs. CT	Overall	4	0.39 [0.10, 1.58]	0.19	93	R
	Asian	2	1.80 [0.63, 5.13]	0.27	61	R		Asian	2	1.08 [0.38, 3.07]	0.89	72	R
	Caucasians	2	0.11 [0.04, 0.32]	<0.00001	-	F		Caucasians	2	0.13 [0.01, 1.22]	0.07	93	R
CC vs. TT/CT	Overall	4	0.47 [0.11, 1.98]	0.30	95	R	C vs. T	Overall	4	0.60 [0.18, 2.03]	0.41	95	R
	Asian	2	1.38 [0.47, 4.05]	0.55	82	R		Asian	2	1.53 [0.57, 4.10]	0.40	86	R
	Caucasians	2	0.15 [0.02, 1.01]	0.05	92	R		Caucasians	2	0.21 [0.06, 0.72]	0.01	83	R

R: Random model; F: Fixed model.

GG vs. AA

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
BiHong Liao 2015	175	196	161	200	20.3%	2.02 [1.14, 3.58]	
Himanshu Rai 2016	117	129	118	125	18.4%	0.58 [0.22, 1.52]	
S. Chhabra 2005	102	113	29	29	8.8%	0.15 [0.01, 2.64]	
Taranjit Singh Rai 2008	45	96	51	61	19.3%	0.17 [0.08, 0.38]	
X.L. Wang 1996	306	329	125	127	15.6%	0.21 [0.05, 0.92]	
Zou Yangchun 2003	78	86	26	33	17.6%	2.63 [0.87, 7.94]	
Total (95% CI)		**949**		**575**	**100.0%**	**0.59 [0.19, 1.76]**	
Total events	823		510				

Heterogeneity: Tau² = 1.47; Chi² = 34.33, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 0.95 (P = 0.34)

0.01 0.1 1 10 100
Favours experimental Favours control

GG vs. GA

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
BiHong Liao 2015	175	279	161	261	23.3%	1.05 [0.74, 1.48]	
Himanshu Rai 2016	117	188	118	193	21.0%	1.05 [0.69, 1.58]	
S. Chhabra 2005	102	153	29	36	9.6%	0.48 [0.20, 1.18]	
Taranjit Singh Rai 2008	45	89	51	90	15.7%	0.78 [0.43, 1.41]	
X.L. Wang 1996	306	439	125	180	22.3%	1.01 [0.69, 1.48]	
Zou Yangchun 2003	78	86	26	38	8.1%	4.50 [1.66, 12.22]	
Total (95% CI)		**1234**		**798**	**100.0%**	**1.04 [0.75, 1.44]**	
Total events	823		510				

Heterogeneity: Tau² = 0.09; Chi² = 12.01, df = 5 (P = 0.03); I² = 58%
Test for overall effect: Z = 0.22 (P = 0.83)

0.01 0.1 1 10 100
Favours experimental Favours control

GG vs. AA/GA

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
BiHong Liao 2015	175	300	161	300	20.0%	1.21 [0.88, 1.67]	
Himanshu Rai 2016	117	200	118	200	19.0%	0.98 [0.66, 1.46]	
S. Chhabra 2005	102	164	29	36	11.9%	0.40 [0.16, 0.96]	
Taranjit Singh Rai 2008	45	140	51	100	17.0%	0.46 [0.27, 0.77]	
X.L. Wang 1996	306	462	125	182	19.4%	0.89 [0.62, 1.29]	
Zou Yangchun 2003	78	92	26	45	12.7%	4.07 [1.79, 9.25]	
Total (95% CI)		**1358**		**863**	**100.0%**	**0.95 [0.61, 1.48]**	
Total events	823		510				

Heterogeneity: Tau² = 0.23; Chi² = 25.51, df = 5 (P = 0.0001); I² = 80%
Test for overall effect: Z = 0.23 (P = 0.82)

0.01 0.1 1 10 100
Favours experimental Favours control

G vs. A

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
BiHong Liao 2015	454	600	422	600	18.7%	1.31 [1.02, 1.69]	
Himanshu Rai 2016	305	400	311	400	18.1%	0.92 [0.66, 1.28]	
S. Chhabra 2005	255	328	65	72	12.7%	0.38 [0.17, 0.86]	
Taranjit Singh Rai 2008	134	280	141	200	17.6%	0.38 [0.26, 0.56]	
X.L. Wang 1996	745	924	305	364	18.2%	0.81 [0.58, 1.11]	
Zou Yangchun 2003	164	184	64	90	14.7%	3.33 [1.74, 6.38]	
Total (95% CI)		**2716**		**1726**	**100.0%**	**0.89 [0.54, 1.45]**	
Total events	2057		1308				

Heterogeneity: Tau² = 0.32; Chi² = 47.55, df = 5 (P < 0.00001); I² = 89%
Test for overall effect: Z = 0.48 (P = 0.63)

0.01 0.1 1 10 100
Favours experimental Favours control
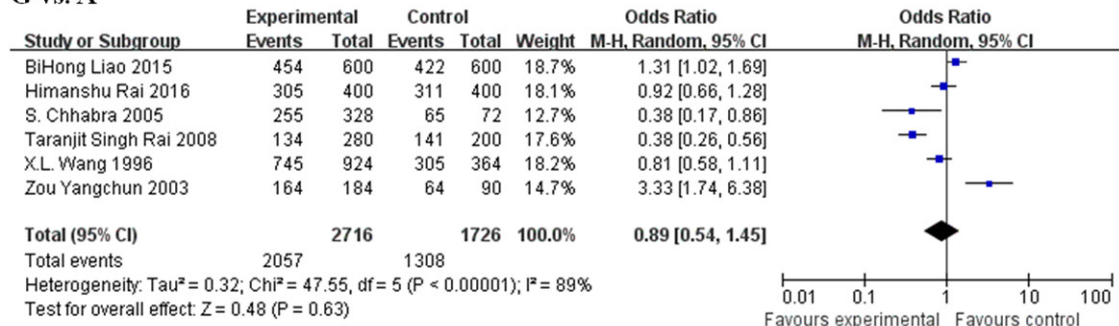
Figure 2. Forest plots of odds ratios for the association of Apo-A1 rs670 with risk of CAD.

Results

Characteristics of eligible studies

A total of 294 studies were found from the literature search after duplicates were removed.
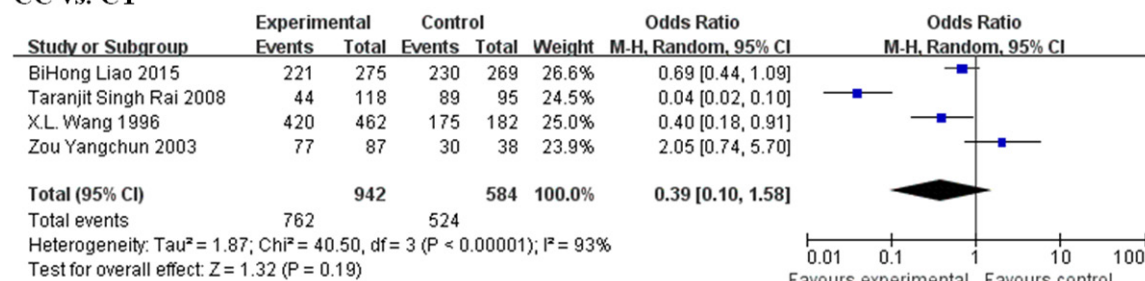
Among them, 243 studies were excluded for irrelevance and reviews, 15 were master's degree theses, and 30 full text articles excluded according to inclusion and exclusion criteria. Finally, 6 studies met the criteria, including 1358 cases and 863 controls [4-10]. Among
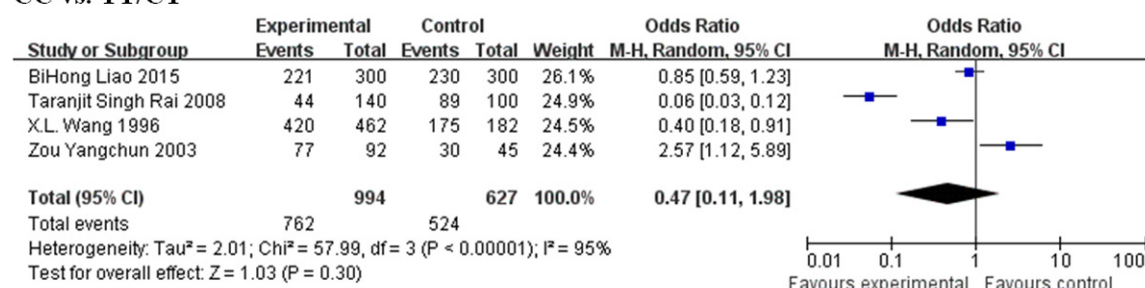
CC vs. TT
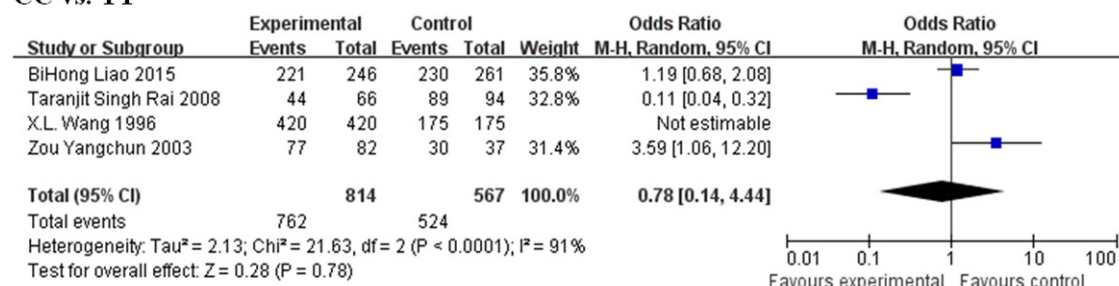
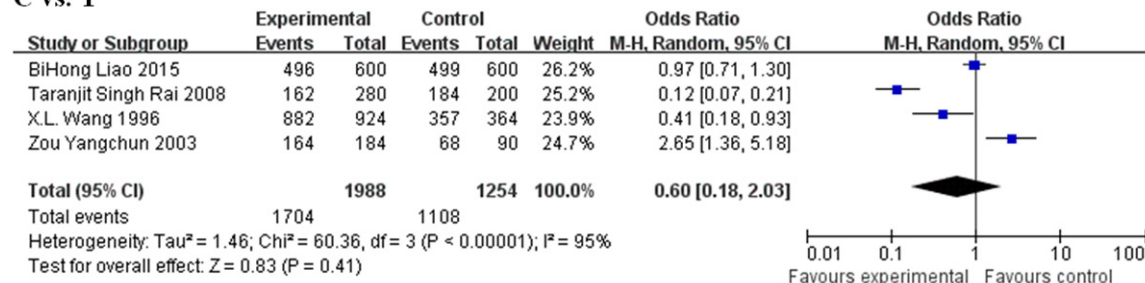**CC vs. CT**

CC vs. TT/CT

C vs. T

Figure 3. Forest plots of odds ratios for the association of Apo-A1 rs5609 with risk of CAD.

them, 6 studies described the associations between Apo-A1 rs670 and CAD, and 4 studies described the associations between Apo-A1 rs5069 and CAD. The PRISMA flowchart is shown in **Figure 1** and the information for included studies is presented in **Table 1**.

Results of meta-analysis

The results of the meta-analysis for the associations between Apo-A1 rs670, rs5069 and CAD risks were shown in **Table 2** and **Figures 2**, **3**.

Apo-A1 rs670 and CAD

Six studies, with 1358 cases and 863 controls, were included in this study. No significant associations were found between Apo-A1 rs670 and CAD susceptibility in overall analysis for all genetic models. But in subgroup analysis by ethnicity, the rs670 was associated with a significantly lower risk of CAD in allelic model (G vs. A, OR = 0.61, 95% CI = 0.61 [0.38, 0.96], *p* = 0.03) and homozygous model (GG vs. AA, OR
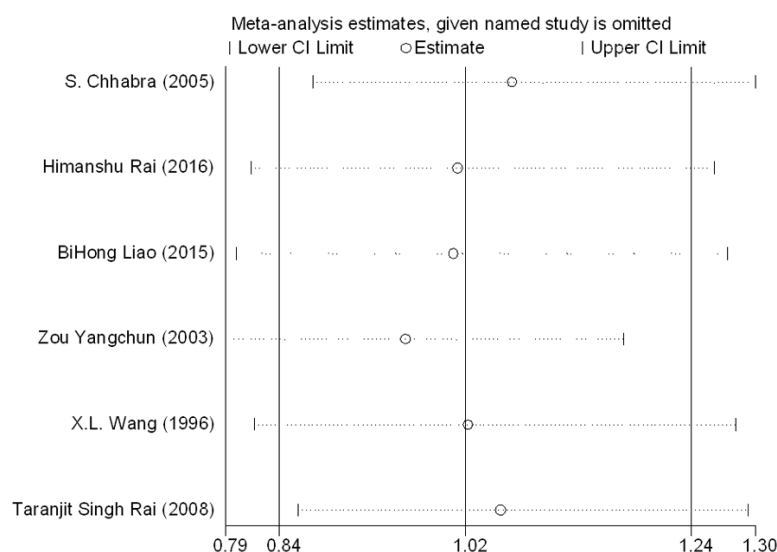
Figure 4. The influence of each study by removal of individual studies for GG vs. GA model of Apo-A1 rs670.

Table 3. Egger's and Begg's test for the publication bias of rs670

Genetic model	Egger's test *p* Value	Begg's Test *p* Value
GG vs. AA	0.477	0.707
GG vs. GA	0.733	0.707
GG vs. AA/GA	0.896	0.707
G vs. A	0.957	0.707

Table 4. Egger's and Begg's test for the publication bias of rs5069

Genetic model	Egger's test *p* Value	Begg's Test *p* Value
CC vs. TT	0.828	1.000
CC vs. CT	0.690	1.000
CC vs. TT/CT	0.726	0.734
C vs. T	0.769	1.000

= 0.25, 95% CI = 0.25 [0.15, 0.44], *p*<0.00001) in Caucasians, and associated with a significantly higher risk of CAD in homozygous model (GG vs. AA, OR = 2.12, 95% CI = 2.12 [1.27, 3.53], *p* = 0.004) in Asian.

Apo-A1 rs5069 and CAD

Four studies, with 994 cases and 622 controls, were included in this study. No significant associations were found between Apo-A1 rs5069 and CAD susceptibility in overall analysis for all genetic models. But subgroup analysis by eth-

nicity discovered CC genotype of rs5069 was associated with a significantly lower risk of CAD in allelic model (C vs. T, OR = 0.21, 95% CI = 0.21 [0.06, 0.72], *p* = 0.01) and homozygous model (CC vs. TT, OR = 0.11, 95% CI = 0.11 [0.04, 0.32], *p*< 0.00001) in Caucasians.

Test of heterogeneity

For Apo-A1 rs670 polymorphism, there was significant heterogeneity between studies in all comparison models. However, in the subgroup analysis of ethnicity, heterogeneity decreased or even disappeared in homozygous and heterozygous model. But the heterogeneity still existed in allelic and dominant model. In addition, for rs5069, significant heterogeneity existed in all genetic models. Although we also performed subgroup analysis, we failed to explain the source of the heterogeneity.

Sensitivity analysis

The influence of each study on the pooled OR and 95% CI was evaluated by excluding one single study at a time using STATA 12.0 software. The analysis showed that no single individual study significantly affected the pool OR in all genetic models for rs670 and rs5069 (only the heterozygous model of rs670 results are shown in **Figure 4**).

Publication bias

To assess the publication bias, the Begg's and Egger's test were performed. The *p* values for Begg's and Egger's tests are shown in **Tables 3**, **4**. These results showed that there was no evidence of publication bias in all comparison models. These results were also demonstrated by the shape of the funnel plot (the homozygous model of rs670 and the allelic model of rs5069 results are shown in **Figures 5**, **6**).

Discussion

Previous studies have reported the importance of inflammation in the risk of atherosclerosis

Begg's funnel plot with pseudo 95% confidence limits
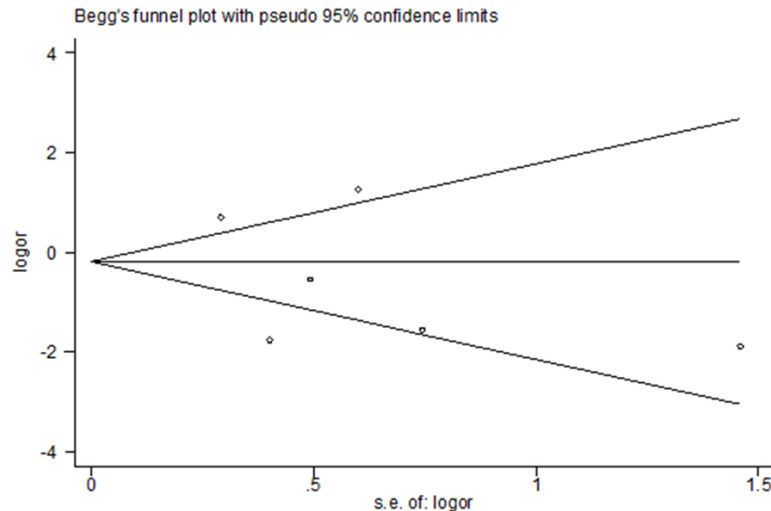
Figure 5. Begg's funnel plot with pseudo 95% confidence limits for homozygous model (GG vs. AA) of rs670.

Begg's funnel plot with pseudo 95% confidence limits
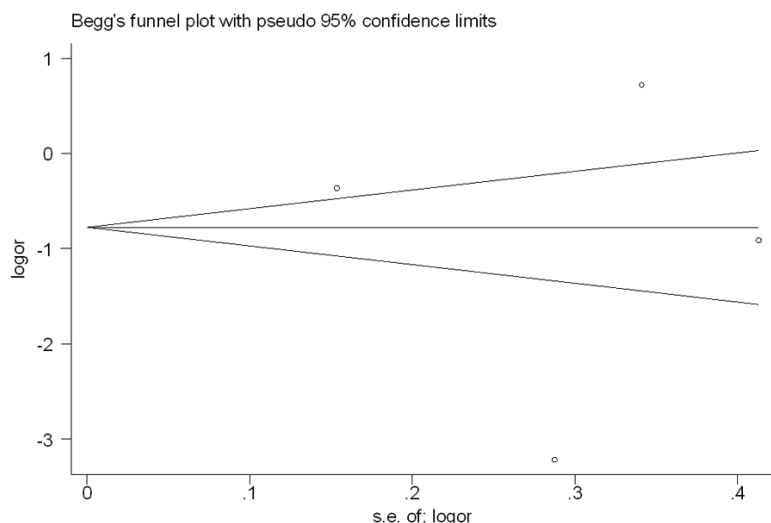
Figure 6. Begg's funnel plot with pseudo 95% confidence limits for allelic model (C vs. T) of rs5069.

in these involved studies, some of which found a significant association between rs670 and CAD, while others denied it.

In the present meta-analysis of 6 studies including 1358 cases and 863 controls, we found that Apo-A1 rs670 and rs5069 had no significant associations with risk of CAD in the overall analysis. But in subgroup analysis by ethnicity, the GG of rs670 was associated with a significantly lower risk of CAD in allelic model (OR = 0.61) and homozygous model (OR = 0.25) in Caucasians, the GG of rs670 was associated with a significantly higher risk of CAD in homozygous model (OR = 2.12) in Asian, and a lower risk of CAD for the CC genotype and C allele of rs5069 in allelic model (OR = 0.21) and homozygous model (OR = 0.11) in Caucasians. In the subgroup analysis of ethnicity, we found that the opposite directions of the observed association among Caucasians and Asians, which may be related to the difference in race.

We found that significant deviation from HWE (p<0.05) in one of the rs670 studies and three of the rs5069 studies, which may be due to the small sample size. Therefore, further studies need larger sample size to confirm the results.

Significant heterogeneity was found in this study for rs670 and rs5069. Thus, we conducted subgroup analysis by ethnicity and found that it was in part sources of the heterogeneity for rs670 and rs5069. Thus, further studies are needed to confirm these results. In the sensitivity analysis, no significant changes were found when omitting each study one at a time, showing the relative stability and credibility of the results of this study.

[14]. HDL is involved in reverse cholesterol transport and has important anti-inflammatory and anti-oxidant properties [15]. Apo-A1, which is the major protein of HDL, is a major participant in the regulation of reverse cholesterol transport [16]. The variation in the Apo-A1 gene was associated with Apo-A1 serum concentrations [17-19], and serum levels of Apo-A1 may influence the risk of CAD [18, 20, 21], diabetic retinopathy [22].

Recently, several SNPs in Apo-A1 have been studied to investigate their relations with CAD risk. Rs670 has gained the greatest attention

Since no significant *p*-values for rs670 and rs5069 through Begg's and Egger's test were found in this study, we think that several limitations should be considered. Firstly, only 6 studies were included and all studies were small sample sizes in this study. There are not large-scale studies available. Secondly, heterogeneity may have distorted the meta-analysis. Furthermore, studies only in English or Chinese have been searched. There might be studies in other languages which are not included. Thus, the conclusion in the present meta-analysis might be only of generalizability for Asians. The last limitation is that CAD is a multifactorial disease influenced by both genetic and environmental factors, but most studies lack the information on multiple SNPs in haplotypes and environmental exposure.

Conclusions

In conclusion, this study suggested that Apo-A1 rs670 and rs5069 had no significant associations with risk of CAD in the overall analysis. But the GG of rs670 was associated with a significantly lower risk of CAD in allelic model (OR = 0.61) and homozygous model (OR = 0.25) in Caucasians and the GG of rs670 was associated with a significantly higher risk of CAD in homozygous model (OR = 2.12) in Asian. In addition, the CC genotype and C allele of rs-5069 was associated with a significantly lower risk of CAD for in allelic model (OR = 0.21) and homozygous model (OR = 0.11) in Caucasians. However, the results of this meta-analysis are hypothesis-generating results which should be interpreted with caution because of the heterogeneity and publication bias among study designs. Further studies are required to evaluate the association between Apo-A1 polymorphisms and CAD in various ethnic groups.

Acknowledgements

Disclosure of conflict of interest

None.

Address correspondence to: Wei-Jun Cai, Department of Histology and Embryology, School of Basic Medicine, Central South University, Changsha 410013, China. Tel: +86-731-8578-9635; Fax: +86-731-8578-9635; E-mail: caiweijun@csu.edu.cn

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