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Association of rs2230806 in *ABCA1* with coronary artery disease

An updated meta-analysis based on 43 research studies

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Abstract

Background: As a key gene in the reverse transport pathway of cholesterol, *ABCA1* (ATP-binding cassette transporter A1) plays an important role in the pathogenesis of coronary artery disease (CAD). In the *ABCA1,* rs2230806 is the most widely studied polymorphism and its role has been controversial.

Methods: We performed an updated meta-analysis by searching online electronic databases using the PubMed, Web of Science, Embase, Cochrane Library, EMBASE, Google Scholar, China National Knowledge Infrastructure, and Wan Fang databases before June 28, 2019. STATA12.0 software was used to perform a series of analyses on the data, including genetic effect model, heterogeneity, sensitivity, and publication bias analysis.

Results: Based on our inclusion and exclusion criteria, finally 43 articles including a total of 34,348 subjects (14,085 CAD cases and 20,263 healthy controls) were investigated. Results showed that carrying the K allele in rs223086 in the overall population significantly reduced the risk of CAD (OR = 0.745, 95% CI = 0.687–0.809, $P < .001$). After the ethnicity stratification analysis, the above phenomenon was found to be significant in Asian populations (OR = 0.686, 95% CI = 0.633–0.744, $P < .001$), marginally significant in Caucasians (OR = 0.887, 95% CI = 0.786–1.001, $P = .051$), and not significant in other populations (OR = 0.851, 95% CI = 0.558–1.297, $P = .452$). Further stratified according to the sample size in the Asian and Caucasian populations, in the Asian the K allele is more protective in small samples than large samples; however, in the Caucasian small samples carrying the K allele play a protective role while large samples are negative. In addition, according to the source of the control population and the geographical location in China, the results showed that rs2230806 was significantly associated with CAD in any group. Five genetic models (allelic, recessive, dominant, homozygote, and heterozygote) were analyzed in the above analysis.

Conclusion: The K allele of rs2230806 was significantly associated with decreased risk of CAD, especially in Asian populations and small sample Caucasians.

Abbreviations: 95% CI = 95% confidence interval, ABCA1 = ATP binding cassette transporter A1, AS = atherosclerosis, CAD = coronary artery disease, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RCT = reverse cholesterol transport, SNP = single nucleotide polymorphism.

Keywords: *ABCA1*, CAD, gene polymorphism, rs2230806, systematic review

1. Introduction

Coronary artery disease (CAD) is currently being the main cause of death and disability in developed and developing countries.[1–3] Epidemiological studies have shown that CAD is a multifactor and multigene regulated disease, mainly affected by genetic variation, environmental factors, blood lipid level imbalance, and the interaction between them. Atherosclerosis (AS) is generally regarded as the pathological basis of CAD. Studies have shown that cholesterol accumulation in the arterial wall may be the starting cause of AS, which leads to an imbalance between the

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For this type of study formal consent is not required.

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lipoprotein influx and the cholesterol efflux. At present, the cholesterol efflux pathways are mainly found in the following: ABCA1 pathway, scavenger receptor type B1 pathway, ATP-binding cassette transporter G1 pathway, and less efficient pathways such as passive efflux. Macrophages and ABCA1-mediated reverse cholesterol transport (RCT) account for approximately 90% of cholesterol excretions.[4–7]

ABCA1, a conserved transmembrane-spanning protein, plays crucial roles in the efflux of cellular cholesterol to HDL. Moreover, ABCA1 affects cellular inflammatory cytokine secretion by modulating cholesterol content in the plasma membrane and within intracellular compartments. In humans, *ABCA1* mutations can cause a severe HDL-deficiency syndrome characterized by cholesterol deposition in tissue macrophages and prevalent AS. Disrupting Abca1 in mice promotes accumulation of excessive cholesterol in macrophages, and physiological manipulation of ABCA1 expression affects AS. Transplantation of bone marrow from $Abca1^{-/-}$ mice into $Ldlr^{-/-}$ or $apoE^{-/-}$ recipients caused an increase in AS.[8–10] Based on the above clinical and experimental studies, it is confirmed that *ABCA1* indeed play an important role during the pathogenesis of CAD.

The *ABCA1* gene spanning 149 kb genomic DNA is located on human chromosome 9q22-q31 consisting of 50 exons and 49 introns and belongs to the superfamily of ATP-binding cassette.[11] It is abundantly expressed on the plasma membrane and Golgi complex.[12] To date approximately 100 gene mutation sites have been reported in *ABCA1* including coding regions and noncoding regions such as rs2230806, rs2422493, rs146292819, rs4149339, −191G/C, and so on. Among them, rs2230806 (R219K, 107620867C>T) is the most widely studied common missense polymorphism. However, the relationship between rs2230806 and CAD was not consistent in the reported researches. Based on these findings, we carried out an update meta-analysis combining the latest data in different countries on 14,085 CAD patients and 20,263 controls to investigate rs2230806 and its effect on CAD risk and further classified the combined populations according to ethnicity, geographical location in China, and the source of control population. To further investigate the sample size impact on the results, large and small samples were divided in the Asian and Caucasian.

2. Methods

2.1. Study selection

A systematic search was conducted on online electronic databases using the PubMed, Web of Science, Embase, Cochrane Library, EMBASE, Google Scholar, China National Knowledge Infrastructure, and Wan Fang databases (the last search update was June 28, 2019). The following search terms were used: "genetic polymorphism or single nucleotide polymorphism or SNP (single nucleotide polymorphism) or mutation or variants," "coronary artery disease or coronary heart diseases or acute coronary syndrome or myocardial infarction or ischemic heart disease," "ATP binding cassette transporter A1 or *ABCA1*" and "rs2230806 or R219K or G596A, or 107620867C>T." As this article is a meta-analysis of the previous published studies, hence patients' consent and approval of the ethics committee were not required.

Eligible studies in this meta-analysis had to meet the following inclusion criteria: evaluation of the association between rs2230806 and CAD; case-control design; studies focusing on humans; sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); the genotype in the control group should be agreed with the Hardy-Weinberg equilibrium (HWE); published in Chinese or English. Exclusion criteria were as follows: comment, review, and editorial articles; duplication of previous publications; family-based studies of pedigrees.

2.2. Data extraction

Two investigators (QF and YFZ) independently extracted data of the eligible studies and the result was reviewed by a third author (FZ). For each of the publication, the extracted information included: first author's name, published year, country of study population, ethnicity, geographical location in China, the source of control, total number of cases and controls, genotype numbers of cases and controls, genotyping methods.

2.3. Quality assessment

The study quality was assessed using the Newcastle–Ottawa scale (NOS) for case-control studies. The study quality based on 8 items ranged from 0 to 9 points. If the score was higher than 6, then the study was considered high quality.

2.4. Statistical methods

All statistical analyses were performed with the STATA 12.0 (StataCorp, College Station, TX). The relationship between rs2230806 and CAD risk by calculating pooled OR and 95% CI. The following 5 genetic models were employed to calculate the OR and 95% CI of rs2230806 under the allele, dominant, recessive, homogenetic, and heterogenetic model. Genotype distribution of controls with HWE was assessed using a χ^2test. Q-statistical test and I^2 test were used to evaluate the heterogeneity. All outcome measures were determined using random-effects models based on DerSimonian and Laird method to obtain the frank heterogeneity.[13] Subgroup analyses were performed to detect the source of heterogeneity based on ethnicity, geographical location in China, source of control population, and the sample size in different races. In addition, stratification analyses were also performed under 5 genetic models. Sensitivity analysis was calculated by removing each individual study to evaluate effect of the result. The significance of publication bias was checked separately in all and different groups by Egger and Begg tests, and P value less than.05 was considered as statistically significant.

3. Results

3.1. Characteristics of eligible studies

A total of 476 potentially eligible papers were initially identified based on keyword-related and manual search. After screening titles and abstract review, 20 studies were discarded for duplicates and 413 studies were further excluded for comment, review, editorial and so on. Finally, 43 articles including a total of 34,348 subjects (14,085 CAD cases and 20,263 healthy controls) were involved in our meta-analysis.[14–56] All the eligible studies were ranged from 2001 to 2019. The detailed flow diagram was shown in Figure 1. The characteristics and genotype frequencies of eligible studies were summarized in Tables 1 and 2. Twenty-eight studies were on East Asian populations and 12 on

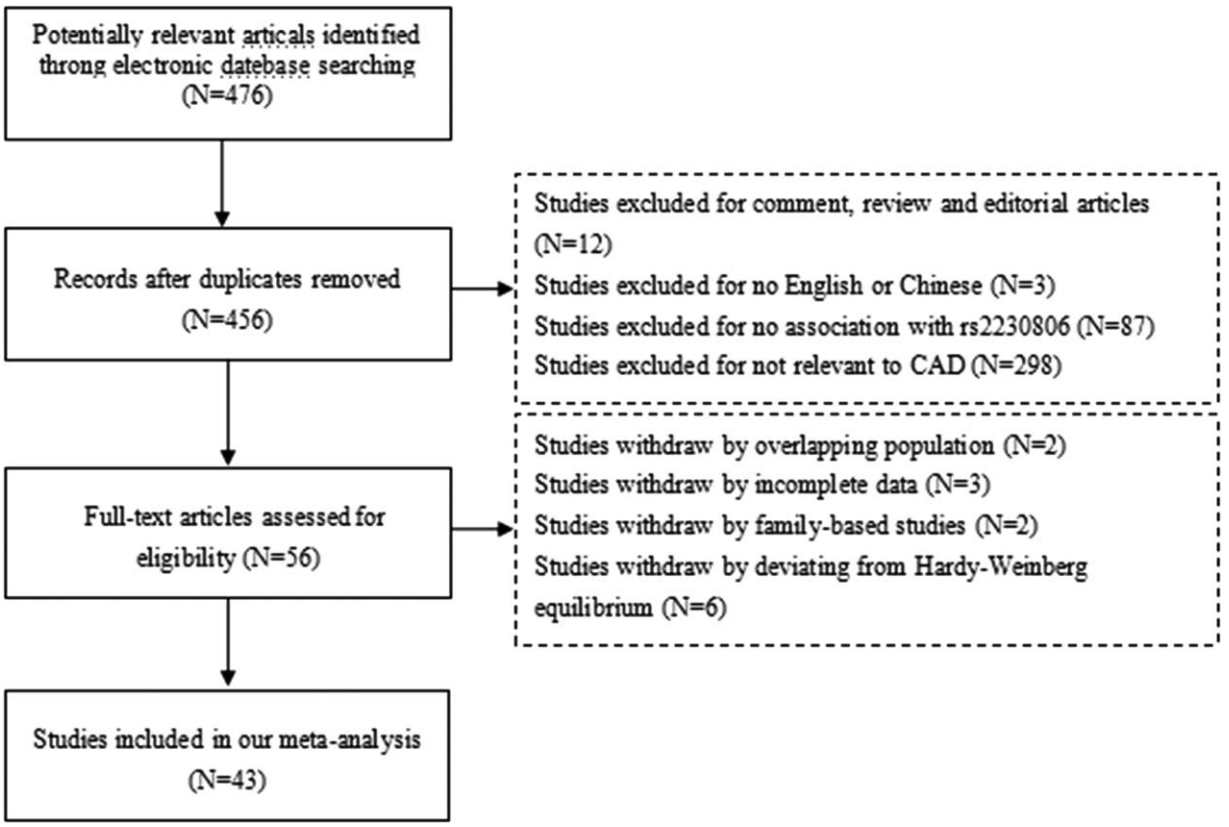

Figure 1. Flow diagram of the study selection process.

Caucasians. Eleven studies were from the South and 13 were North according to geographical location in China. Thirty-one studies were hospital-based and 12 were population-based in the controls. In addition, according to the sample size, the Asian populations divided into large sample (≥500) and small sample (<500), similarly, large sample (≥1000) and small sample (<1000) were grouped in the Caucasians. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used in 33 studies, 4 studies used probe method, and 2 studies utilized DNA sequencing to detect the genotypes. HWE of genotype distribution among the controls was tested in all the included studies.

3.2. Meta-analysis results

3.2.1. Overall analyses. As shown in Table 3, the pooled results indicate a statistically significant association between rs2230806 polymorphism and the risk of CAD under different genetic models: an allelic genetic model (OR=0.745, 95% CI=0.687–0.809, $P<.001$), a recessive genetic model (OR=0.683, 95% CI=0.603–0.774, $P<.001$), a dominant genetic model (OR=0.703, 95% CI=0.633–0.781, $P<.001$), a homozygote genetic model (OR=0.573, 95% CI=0.488–0.672, $P<.001$), and a heterozygote genetic model (OR=0.761, 95% CI=0.693–0.837, $P<.001$). Forest plot under allelic model is demonstrated in Figure 2.

3.2.2. Subgroup analyses. In the subgroup analysis by ethnicity, for the Asian ethnicity, a significant association between rs2230806 and CAD risk was found in all 5 genetic model: an allelic genetic model (OR=0.686, 95% CI=0.633–0.744, $P<.001$), a recessive genetic model (OR=0.621, 95% CI=0.561–0.688, $P<.001$), a dominant genetic model (OR=0.645, 95% CI=0.595–0.700, $P<.001$), a homozygote genetic model (OR=0.505, 95% CI=0.450–0.566, $P<.001$), and a heterozygote genetic model (OR=0.707, 95% CI=0.649–0.770, $P<.001$). Stratified according to the sample size, we found that the association in the large and small sample size was also significant (Table 3). For Caucasian populations, the association did not return significant in all 5 genetic model: an allelic genetic model (OR=0.887, 95% CI=0.786–1.001, $P=.051$), a recessive genetic model (OR=0.915, 95% CI=0.804–1.041, $P=.177$), a dominant genetic model (OR=0.857, 95% CI=0.730–1.007, $P=.060$), a homozygote genetic model (OR=0.903, 95% CI=0.791–1.031, $P=.132$), and a heterozygote genetic model (OR=0.870, 95% CI=0.741–1.021, $P=.088$). Similarly, stratified by the sample size, a statistically significant association was observed in the small sample under 4 genetic models except the recessive model, but not in the subjects from the large sample under 5 genetic models (Table 3).

We also performed stratified analyses by geographical location in China and source of the control population. The results suggested the polymorphism was associated with decreased CAD risk in any group under 5 genetic models (Table 3).

3.2.3. Heterogeneity analysis. Strong evidence of heterogeneity among the whole population was demonstrated in all 5 models (R vs K: $I^2=76.3\%$, $P_{heterogeneity}<.001$; KK vs RK+RR: $I^2=55.8\%$, $P_{heterogeneity}<.001$; KK+RK vs RR: $I^2=71.9\%$, $P_{heterogeneity}<.001$; KK vs RR: $I^2=68.2\%$, $P_{heterogeneity}<.001$; RK vs RR:

Table 1

Characteristics of all eligible studies included in this meta-analysis.

Author	Year	Country	Ethnicity	Geographical location	Control source	Subjects Cases/controls	Genotyping method	HWE	NOS score
Clee et al [14]	2001	Canada	Caucasian	NA	HB	432/358	PCR-RFLP	0.067	6
Brousseau et a1 [15]	2001	American	Caucasian	NA	HB	1014/1013	Probe	0.580	7
Cenarro et al [16]	2003	Spain	Caucasian	NA	HB	216/158	PCR-RFLP	0.676	6
Evans and Bei[17]	2003	Germany	Caucasian	NA	HB	114/629	Probe	0.789	7
Harada et al [18]	2003	Japan	Asian	NA	HB	273/137	Probe	0.440	6
Bertolini et al [19]	2004	Italy	Caucasian	NA	HB	97/97	PCR-RFLP	0.076	7
Zhao et al [20]	2004	China	Asian	South	PB	236/251	PCR-RFLP	0.952	8
Wang et al [21]	2004	China	Asian	North	HB	222/278	PCR-RFLP	0.093	7
Li et al[22]	2005	China	Asian	South	PB	396/417	PCR-RFLP	0.350	7
Sun et al [23]	2005	China	Asian	South	HB	224/248	PCR-RFLP	0.521	8
Woll et al [24]	2005	American	Caucasian	NA	HB	838/257	PCR-RFLP	0.732	7
Whiting et al [25]	2005	American	Caucasian	NA	HB	2468/834	PCR-RFLP	0.313	6
Li[26]	2005	China	Asian	South	PB	264/278	PCR-RFLP	0.449	7
Andrikovics et al [27]	2006	Germany	Caucasian	NA	PB	150/193	Probe	0.116	7
Martin et al [28]	2006	Spain	Caucasian	NA	HB	100/100	NA	0.516	6
Wang et al [29]	2006	China	Asian	North	HB	234/198	PCR-RFLP	0.422	8
Zha et al [30]	2006	China	Asian	South	HB	112/108	PCR-RFLP	0.795	7
Frikke-Schmidt et al [31]	2008	Denmark	Caucasian	NA	PB	1107/7858	DNA Sequencing	0.405	6
Balcerzyk et al [32]	2008	Poland	Caucasian	NA	PB	178/180	PCR-RFLP	0.283	6
Zhang et al [33]	2008	China	Asian	South	HB	162/186	PCR-RFLP	0.992	8
Yu and Deng[34]	2008	China	Asian	South	HB	49/72	PCR-RFLP	0.969	7
Liu et al [35]	2008	China	Asian	North	HB	113/155	PCR-RFLP	0.426	7
Wang et al [36]	2008	China	Asian	South	HB	321/294	PCR-RFLP	0.350	7
Porchay-Balderelli et al [37]	2009	France	Caucasian	NA	PB	482/2647	Allele-specific PCR	0.347	6
Li et al [38]	2009	China	Asian	North	PB	365/246	PCR-RFLP	0.886	8
Shi et al [39]	2009	China	Asian	South	HB	132/157	PCR-RFLP	0.540	7
Rejeb et a1 [40]	2010	Tunisia	Asian	NA	HB	212/104	PCR-RFLP	0.465	8
Guo et al [41]	2010	China	Asian	North	PB	71/83	PCR-RFLP	0.577	7
Xia et al [42]	2011	China	Asian	South	HB	227/162	PCR-RFLP	0.750	7
Xu et al [43]	2011	China	Asian	North	HB	141/109	PCR-RFLP	0.798	8
Yuan et al [44]	2011	China	Asian	North	HB	60/55	PCR-RFLP	0.081	7
Li et al [45]	2012	China	Asian	North	HB	150/100	PCR-RFLP	0.735	7
Wang et al [46]	2012	China	Asian	North	HB	141/109	PCR-RFLP	0.798	7
Zargar et a1 [47]	2013	Saudi Arabia	Other	NA	PB	120/100	PCR-RFLP	0.971	7
Wang[48]	2013	China	Asian	North	HB	103/114	PCR-RFLP	0.609	8
Mao et al [49]	2013	China	Asian	North	HB	377/178	PCR-RFLP	0.266	7
Abd El-Aziz et a1 [50]	2014	Egypt	Other	NA	HB	116/119	PCR-RFLP	0.121	7
An[51]	2014	China	Asian	North	PB	126/119	DNA Sequencing	0.822	6
Cyril et a1 [52]	2016	Saudi Arabia	Other	NA	HB	990/618	Allele-Specific PCR	0.237	7
Ghaznavi et a1 [53]	2018	Iran	Asian	NA	HB	100/100	PCR-RFLP	0.949	8
Jia[54]	2018	China	Asian	North	HB	96/98	PCR-RFLP	0.255	7
Fouladseresht et a1 [55]	2019	Iran	Asian	NA	PB	272/258	PCR-RFLP	0.626	7
Wang et a1 [56]	2019	China	Asian	South	HB	484/488	SNaPshot method	0.179	7

HB = hospital-based, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, PB = population-base, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

$I^2 = 60.2\%$, $P_{heterogeneity} < .001$). Next, we detected the cause of heterogeneity in any of genetic models by ethnicity, geographical location, source of control population, and the sample size in Asian and Caucasian. Statistical analysis showed the main contributors of heterogeneity resulted from Caucasians, after further subgroup analysis, the heterogeneity was significantly decreased in the small population (R vs K: $I^2 = 29.5\%$, $P_{heterogeneity} = .203$) whereas significant heterogeneity was observed in the large population (R vs K: $I^2 = 83.4\%$, $P_{heterogeneity} < .001$).

3.2.4. Sensitivity analysis. To better examine the influence on the pooled OR, we performed a sensitivity analysis omitting any individual study using STATA 12.0 software. The result suggested no significant difference was found, suggesting our results were relatively stable and credible (Table 4).

3.2.5. Publication bias. As outlined in Figure 3, the shape of funnel plots in overall population between rs2230806 and CAD under the allelic model indicated publication bias in the current meta-analysis. Considering ethnicity heterogeneity, we make a statistics analysis for different races. The result showed publication bias was not found in the Asian group, with similar in Caucasian populations. The Egger test ($t = 0.590$, $P = .563$ in Asian; $t = -0.070$, $P = .944$ in Caucasian) and Begg test ($t = 0.560$, $P = .574$ in Asian; $z = 1.58$, $P = .115$ in Caucasian) were also performed to investigate the symmetry of the funnel plot.

Table 2

Genotype frequencies in the studies included in the meta-analysis.

		Cases (n)					Controls (n)				
Author	Year	RR	RK	KK	R	K	RR	RK	KK	R	K
Clee et al	2001	248	170	14	666	198	176	160	22	512	204
Brousseau et a1	2001	454	484	76	1392	636	543	402	68	1488	538
Cenarro et al	2003	123	78	15	324	108	72	71	15	215	101
Evans and Bei	2003	72	35	7	179	49	337	245	47	919	339
Harada et al	2003	73	139	61	285	261	31	73	33	135	139
Bertolini et al	2004	65	29	3	159	35	47	46	4	140	54
Zhao et al	2004	96	111	29	303	169	80	123	48	283	219
Wang et al	2004	79	94	49	252	192	76	125	77	277	279
Li et al	2005	158	174	64	490	302	124	198	95	446	388
Sun et al	2005	105	85	34	295	153	62	129	57	253	243
Woll et al	2005	450	327	61	1227	449	115	112	30	342	172
Whiting et al	2005	1298	975	195	3571	1365	449	318	67	1216	452
Li	2005	104	116	44	324	204	83	132	63	298	258
Andrikovics et al	2006	84	55	11	223	77	97	73	23	267	119
Martin et al	2006	48	42	10	138	62	49	40	11	138	62
Wang et al	2006	108	105	21	321	147	67	101	30	235	161
Zha et al	2006	47	53	12	147	77	34	52	22	120	96
Frikke-Schmidt et al	2008	603	429	75	1635	579	4260	3032	566	11552	4164
Balcerzyk et al	2008	90	68	20	248	108	91	78	11	260	100
Zhang et al	2008	71	65	26	207	117	49	93	44	191	181
Yu and Deng	2008	29	18	2	76	22	24	35	13	83	61
Liu et al	2008	71	39	3	181	45	57	70	28	184	126
Wang et al	2008	85	161	75	331	311	67	155	72	289	299
Porchay-Balderelli et al	2009	270	175	37	715	249	1326	1109	212	3761	1533
Li et al	2009	140	170	55	450	280	92	116	38	300	192
Shi et al	2009	49	60	23	158	106	53	66	38	172	142
Rejeb et a1	2010	85	101	26	271	153	37	53	14	127	81
Guo et al	2010	30	37	4	97	45	29	38	16	96	70
Xia et al	2011	96	107	24	299	155	51	78	33	180	144
Xu et al	2011	63	63	15	189	93	31	53	25	115	103
Yuan et al	2011	22	28	10	72	48	16	21	18	53	57
Li et al	2012	52	74	24	178	122	30	48	22	108	92
Wang et al	2012	63	63	15	189	93	31	53	25	115	103
Zargar et a1	2013	84	33	3	201	39	60	35	5	155	45
Wang	2013	45	47	11	137	69	34	54	26	122	106
Mao et al	2013	154	149	74	457	297	56	81	41	193	163
Abd El-Aziz et a1	2014	28	52	36	108	124	21	48	50	90	148
An	2014	55	58	13	168	84	36	60	23	132	106
Cyril et a1	2016	291	473	226	1055	925	195	317	106	707	529
Ghaznavi et a1	2018	50	40	10	140	60	29	50	21	108	92
Jia	2018	32	51	13	115	77	14	53	31	81	115
Fouladseresht et a1	2019	100	136	36	336	208	79	124	55	282	234
Wang et a1	2019	182	251	51	615	353	161	251	76	573	403

4. Discussion

CAD is a serious threat to human health with the acceleration of social development and the prevalence of unhealthy lifestyles. A large number of epidemiological investigations and clinical trials have shown lipid accumulation and vascular wall inflammation may be 2 key factors in the pathogenesis. Although decreasing LDL-C levels is an important therapeutic intervention for reducing cardiovascular events, however, it has been observed in the clinic that the level of LDL-C in some patients is in a suitable range or reduced to less than 70 mg/dL by lipid-lowering drugs, atherosclerotic lesions remain in progress. Thus, there are other lipid indicators involved in AS such as HDL-C. The antiatherosclerosis effect of HDL-C can inhibit the development of AS and serum HDL-C level is significantly negatively correlated with the incidence of CAD because of the important role of HDL-C in cholesterol metabolism, especially RCT. More and more genes have been discovered in the HDL lipid metabolism, such as *HMGA*, *TNNT1*, and so on. Some of them may have similar regulatory mechanisms. For example, *ABCA1* and *HMGA* are both targeted by miR-33.[57–59]

Animals and human studies document that functional effects in the ABCA1 pathway are important determinants of CAD.[60] ABCA1 expression and ABCA1-dependent efflux of cell cholesterol are closely associated with increased surface binding of apoA-1.[61] Abca1-deficient mice increased circulating levels of chemokines, cytokines, and growth factors, which are most evident after the injection of LPS.[62] Genetic mutations in the *ABCA1* cause Tangier disease and familial hypoalphalipoproteinemia.[63]

Plenty of evidence demonstrated that candidate gene case-control association studies were frequently used method for identifying the susceptibility genes for CAD.[64] The polymorphism

Table 3

Overall and stratified meta-analysis under different genetic models.

Genetic model	Group analysis	Pooled OR (95% CI)	*P* value	Literature number	CAD size	Control size	$P_{heterogeneity}$	I^2, %
Allelic genetic model	Whole population	0.745 (0.687–0.809)	<.001	43	14, 085	20,263	<.001	76.3%
	Ethnicity							
	Asian subgroup	0.686 (0.633–0.744)	<.001	28	5663	5102	.002	49.2%
	Caucasian subgroup	0.887 (0.786–1.001)	.051	12	7196	14,324	<.001	74.5%
	Other	0.851 (0.558–1.297)	.452	3	1226	837	.005	80.8%
	Geographical location							
	South China	0.717 (0.663–0.775)	<.001	11	2607	2661	.065	42.7%
	North China	0.644 (0.558–0.744)	<.001	13	2199	1842	.006	56.8%
	Control source							
	HB	0.718 (0.643–0.802)	<.001	31	10,318	7633	<.001	80.2%
	PB	0.809 (0.728–0.899)	<.001	12	3767	12,630	.009	76.3%
	Sample size							
	≥500 in Asian subgroup	0.796 (0.736–0.862)	<.001	8	2701	2437	.476	0.00%
	<500 in Asian subgroup	0.633 (0.586–0.683)	<.001	20	2962	2665	.048	37.2%
	≥1000 in Caucasian subgroup	0.887 (0.786–1.001)	.932	5	5909	12,609	<.001	83.4%
	<1000 in Caucasian subgroup	0.796 (0.704–0.900)	<.001	7	1287	1715	.203	29.5%
Recessive genetic model	Whole population	0.683 (0.603–0.774)	<.001	43	14,085	20,263	<.001	55.8%
	Ethnicity							
	Asian subgroup	0.621 (0.561–0.688)	<.001	28	5663	5102	.092	27.4%
	Caucasian subgroup	0.915 (0.804–1.041)	.177	12	7196	14324	.259	18.8%
	Other	0.851 (0.558–1.297)	.711	3	1226	837	.011	77.9%
	Geographical location							
	South China	0.645 (0.559–0.745)	<.001	11	2607	2661	.568	0.00%
	North China	0.570 (0.481–0.674)	<.001	13	2199	1842	.025	48.7%
	Control source							
	HB	0.655 (0.558–0.768)	<.001	31	10,318	7633	<.001	59.7%
	PB	0.763 (0.708–0.822)	<.001	12	3767	12,630	.039	46.3%
	Sample size							
	≥500 in Asian subgroup	0.737 (0.639–0.850)	<.001	8	2701	2437	.569	0.00%
	<500 in Asian subgroup	0.521 (0.451–0.603)	<.001	20	2962	2665	.288	13.4%
	≥1000 in Caucasian subgroup	0.915 (0.804–1.041)	.424	5	5909	12,609	.289	19.8%
	<1000 in Caucasian subgroup	0.798 (0.590–1.081)	.145	7	1287	1715	.267	21.3%
Dominant genetic model	Whole population	0.703 (0.633–0.781)	<.001	43	14,085	20,263	<.001	71.9%
	Ethnicity							
	Asian subgroup	0.645 (0.595–0.700)	<.001	28	5663	5102	.034	35.4%
	Caucasian subgroup	0.857 (0.730–1.007)	.060	12	7196	14,324	<.001	76.9%
	Other	0.849 (0.567–1.271)	.425	3	1226	837	.094	57.6%
	Geographical location							
	South China	0.647 (0.577–0.726)	<.001	11	2607	2661	.049	45.5%
	North China	0.623 (0.546–0.711)	<.001	13	2199	1842	.107	34.4%
	Control source							
	HB	0.667 (0.576–0.771)	<.001	31	10,318	7633	<.001	77.0%
	PB	0.842 (0.776–0.913)	<.001	12	3767	12,630	.073	40.2%
	Sample size							
	≥500 in Asian subgroup	0.747 (0.664–0.840)	<.001	8	2701	2437	.644	0.00%
	<500 in Asian subgroup	0.566 (0.506–0.633)	<.001	20	2962	2665	.143	25.7%
	≥1000 in Caucasian subgroup	0.974 (0.790–1.200)	.805	5	5909	12,609	<.001	85.7%
	<1000 in Caucasian subgroup	0.740 (0.634–0.863)	<.001	7	1287	1715	.331	12.9%
Homogenetic model	Whole population	0.573 (0.488–0.672)	<.001	43	14,085	20,263	<.001	68.2%
	Ethnicity							
	Asian subgroup	0.505 (0.450–0.566)	<.001	28	5663	5102	.013	41.4%
	Caucasian subgroup	0.903 (0.791–1.031)	.132	12	7196	14,324	.034	47.5%
	Other	0.801 (0.347–1.849)	.603	3	1226	837	.017	75.3%
	Geographical location							
	South China	0.518 (0.441–0.609)	<.001	11	2607	2661	.293	15.9%
	North China	0.410 (0.301–0.560)	<.001	13	2199	1842	.005	57.5%
	Control source							
	HB	0.535 (0.434–0.659)	<.001	31	10,318	7633	<.001	71.9%
	PB	0.661 (0.522–0.839)	.001	12	3767	12,630	.009	55.9%
	Sample size							
	≥500 in Asian subgroup	0.635 (0.540–0.746)	<.001	8	2701	2437	.576	0.00%
	<500 in Asian subgroup	0.401 (0.341–0.472)	<.001	20	2962	2665	.116	28.3%
	≥1000 in Caucasian subgroup	0.846 (0.685–1.044)	.514	5	5909	12,609	.039	60.4%
	<1000 in Caucasian subgroup	0.716 (0.525–0.977)	.035	7	1287	1715	.221	27.2%
Heterogenetic model	Whole population	0.761 (0.693–0.837)	<.001	43	14,085	20,263	<.001	60.2%
	Ethnicity							
	Asian subgroup	0.707 (0.649–0.770)	<.001	28	5663	5102	.265	13.3%
	Caucasian subgroup	0.870 (0.741–1.021)	.088	12	7196	14,324	<.001	74.3%
	Other	0.935 (0.762–1.147)	.516	3	1226	837	.424	0.00%

(*continued*)

Table 3

(continued).

Genetic model	Group analysis	Pooled OR (95% CI)	*P* value	Literature number	CAD size	Control size	$P_{heterogeneity}$	I^2, %
	Geographical location							
	South China	0.702 (0.622–0.793)	<.001	11	2607	2661	.081	40.1%
	North China	0.693 (0.602–0.798)	<.001	13	2199	1842	.540	0.00%
	Control source							
	HB	0.727 (0.637–0.830)	<.001	31	10,318	7633	<.001	68.0%
	PB	0.867 (0.796–0.944)	.001	12	3767	12,630	.384	6.20%
	Sample size							
	≥500 in Asian subgroup	0.707 (0.649–0.770)	<.001	8	2701	2437	.776	0.00%
	<500 in Asian subgroup	0.638 (0.567–0.718)	<.001	20	2962	2665	.331	10.0%
	≥1000 in Caucasian subgroup	0.989 (0.804–1.218)	.920	5	5909	12,609	<.001	84.1%
	<1000 in Caucasian subgroup	0.746 (0.635–0.877)	<.001	7	1287	1715	.450	0.00%

CI = confidence interval, HB = hospital-based, OR = odds ratio, PB = population-base.

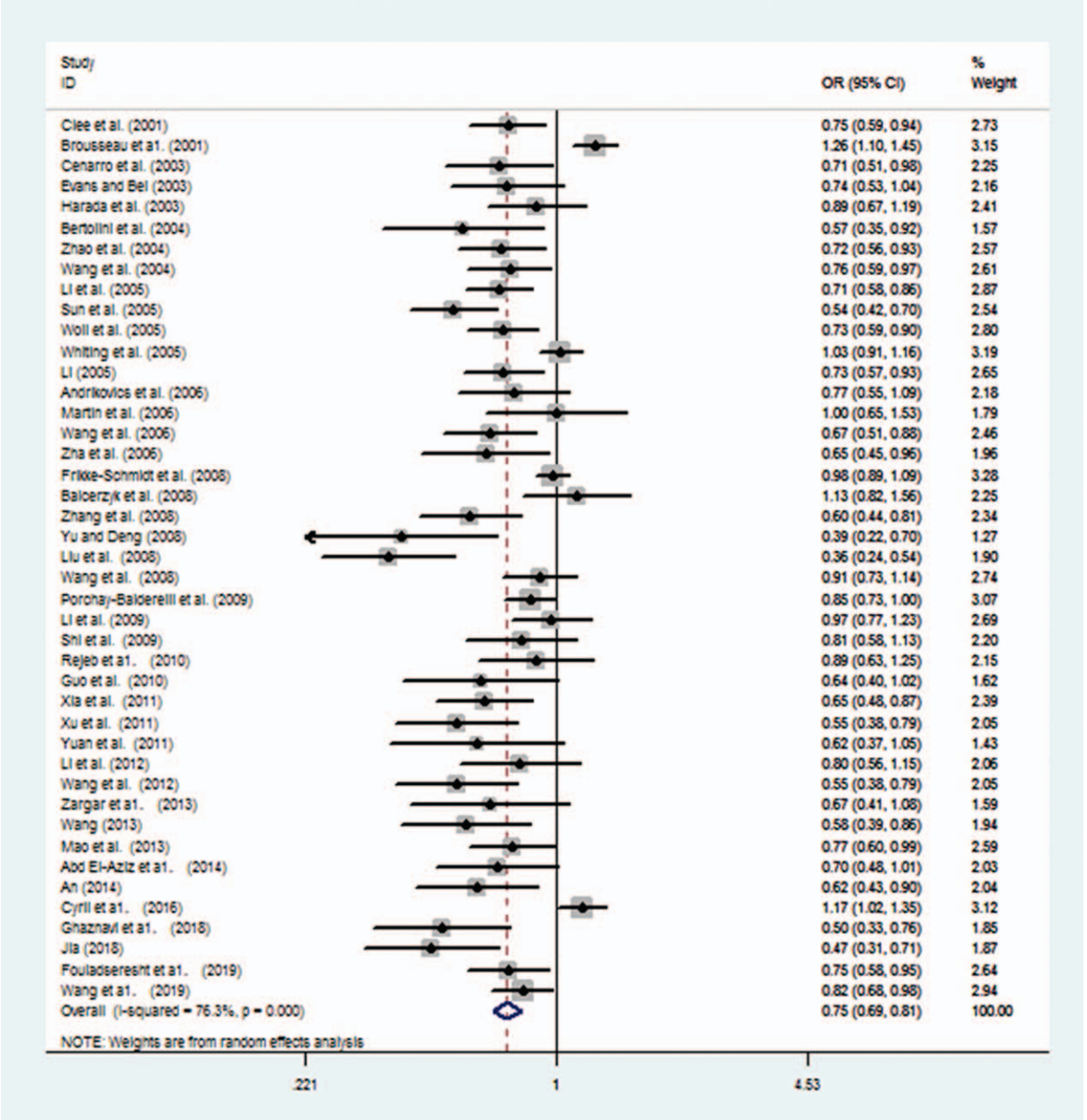

Figure 2. Meta-analysis with a random-effects model for the overall association between rs2230806 and CAD under the allele model.

Table 4

Results of sensitivity analysis of rs2230806 in allele model.

Study omitted	Cases/controls (n)	Crude OR (95% CI)
Clee et al (2001)	432/358	0.745 (0.685–0.810)
Brousseau et a1 (2001)	1014/1013	0.736 (0.682–0.795)
Cenarro et al (2003)	216/158	0.746 (0.686–0.810)
Evans and Bei (2003)	114/629	0.745 (0.685–0.810)
Harada et al (2003)	273/137	0.741 (0.682–0.806)
Bertolini et al (2004)	97/97	0.748 (0.689–0.813)
Zhao et al (2004)	236/251	0.745 (0.686–0.810)
Wang et al (2004)	222/278	0.744 (0.685–0.809)
Li et al (2005)	396/417	0.746 (0.686–0.811)
Sun et al (2005)	224/248	0.753 (0.693–0.816)
Woll et al (2005)	838/257	0.745 (0.685–0.810)
Whiting et al (2005)	2468/834	0.737 (0.678–0.801)
Li (2005)	264/278	0.745 (0.685–0.810)
Andrikovics et al (2006)	150/193	0.744 (0.685–0.809)
Martin et al (2006)	100/100	0.741 (0.682–0.805)
Wang et al (2006)	234/198	0.747 (0.688–0.811)
Zha et al (2006)	112/108	0.747 (0.688–0.812)
Frikke-Schmidt et al (2008)	1107/7858	0.737 (0.677–0.803)
Balcerzyk et al (2008)	178/180	0.738 (0.679–0.802)
Zhang et al (2008)	162/186	0.749 (0.690–0.814)
Yu and Deng (2008)	49/72	0.752 (0.693–0.816)
Liu et al (2008)	113/155	0.758 (0.700–0.820)
Wang et al (2008)	321/294	0.740 (0.681–0.805)
Porchay-Balderelli et al (2009)	482/2647	0.741 (0.680–0.807)
Li et al (2009)	365/246	0.739 (0.680–0.804)
Shi et al (2009)	132/157	0.743 (0.684–0.808)
Rejeb et a1 (2010)	212/104	0.742 (0.683–0.806)
Guo et al (2010)	71/83	0.747 (0.688–0.811)
Xia et al (2011)	227/162	0.748 (0.688–0.812)
Xu et al (2011)	141/109	0.750 (0.691–0.815)
Yuan et al (2011)	60/55	0.747 (0.688–0.811)
Li et al (2012)	150/100	0.744 (0.684–0.808)
Wang et al (2012)	141/109	0.750 (0.691–0.815)
Zargar et a1 (2013)	120/100	0.746 (0.687–0.811)
Wang (2013)	103/114	0.749 (0.690–0.813)
Mao et al (2013)	377/178	0.744 (0.684–0.809)
Abd El-Aziz et a1 (2014)	116/119	0.746 (0.687–0.811)
An (2014)	126/119	0.748 (0.689–0.812)
Cyril et a1 (2016)	990/618	0.736 (0.679–0.798)
Ghaznavi et a1 (2018)	100/100	0.751 (0.692–0.815)
Jia (2018)	96/98	0.752 (0.694–0.816)
Fouladseresht et a1 (2019)	272/258	0.744 (0.685–0.810)
Wang et a1 (2019)	484/488	0.742 (0.682–0.808)

CI = confidence interval, OR = odds ratio.

of *ABCA1* gene becomes a research hotspot in the genetic mechanism of CAD. Currently, several meta-analyses evaluating the association between *ABCA1* polymorphism and CAD have been published.[65–70] Besides, a large number of epidemiological studies have also been conducted. For instance, the study of Clee et al[14] reported that the frequent R219K variant was associated with a decreased severity of atherosclerosis, decreased risk of coronary events, decreased TG, and increased HDL-C, suggesting the variant is associated with a gain of normal *ABCA1* function and increased RCT. In another study, Evanset et al[17] also suggested that the R219K polymorphism either directly or as a result of linkage disequilibrium with additional functional variant, had a protective effect against CAD and was associated with lower plasma triglycerides in subgroups of patients with hyperlipidaemia. While in the study of Brousseau et al[15] we found that the mutant allele might cause a decrease in the HDL level and promote the development of CAD. Therefore, the possible role of rs2230806 in CAD is still debatable or even the opposite.

Based on combined analyses of 34,348 participants, our study demonstrated that the K allele of rs2230806 was significantly associated with decreased risk of CAD, especially under the recessive and homogenetic models. In addition, statistical result showed rs2230806 is significantly associated with CAD in Asian population, marginally significant in Caucasian and not significant in other group. The reason for racial difference phenomenon may be attributed to allele frequency and other factors, such as lifestyle discrepancy and so on.

Due to significant heterogeneity under five genetic models in the whole population, subgroup analysis was needed to explore the source of heterogeneity. After subgroup analysis by ethnicity, geographical location, the source of control population, and the sample size in the Asian and Caucasian, we observed that the protective effect of allele from small sample subgroups in Asian population was greater than that of large sample subgroups under all 5 genetic models, the same in Caucasian population. One possible explanation is small sample effect.[71] We also found the main contributors of heterogeneity resulted from the large population in Caucasians. In addition, the statistical result mild alters after removing the large sample population of Caucasians 1 by 1 based on sensitivity analysis. Moreover, the heterogeneity from North China is greater than South China possibly due to genetic regulation in different regions and diverse living habits. After the source of control population, significant heterogeneity was observed in the hospital-based subgroup because such control subjects from a special group might not represent the general population.

Our finding is slightly different from the previous meta-analysis by Ma et al, Jiang et al, Yin et al.[68–70] Current meta-analysis studies showed the role of rs2230806 in Asian populations is consistent with previous studies, and there is controversy in the Caucasian population. Ma et al indicated rs2230806 is a protective role for CAD risk both in Asians (OR = 0.76, 95% CI = 0.68–0.85) and Caucasians (OR = 0.89, 95% CI = 0.81–0.99). Jiang et al showed the polymorphism was significantly associated with decreased risk of CAD in Asian population (OR = 0.70, 95% CI = 0.61–0.81) not Caucasians (OR = 0.91, 95% CI = 0.80–1.04). Similarly, Yin et al also found the same result in Asian population (OR = 0.66, 95% CI = 0.59–0.74) and Caucasians (OR = 0.90, 95% CI = 0.76–1.07). Our meta-analysis included the largest sample size, and the result was consistent with Jiang et al and Yin et al, but we further stratified the Caucasian population according to the sample size, the association analysis, and heterogeneity results were significantly different. Statistics analysis found that the above results in the Caucasian population *P* value swinged around.05, the size of the sample may play a key role. Then, considering that HWE may have an impact on heterogeneity and all of our included samples meet the HWE. In addition, due to the ethnic differences in publication bias, we examine the bias in Asian and Caucasian population separately.

However, several drawbacks existed in our meta-analysis. First, CAD is a complex disease affected by many factors such as multiple microeffect genes, linkages between gene loci and gene–environment interactions. The positive association between the polymorphism of a certain gene and the disease only plays a weak role in the development of CAD. Second, disease subtypes or clinical pathological features are not considered. Third, all

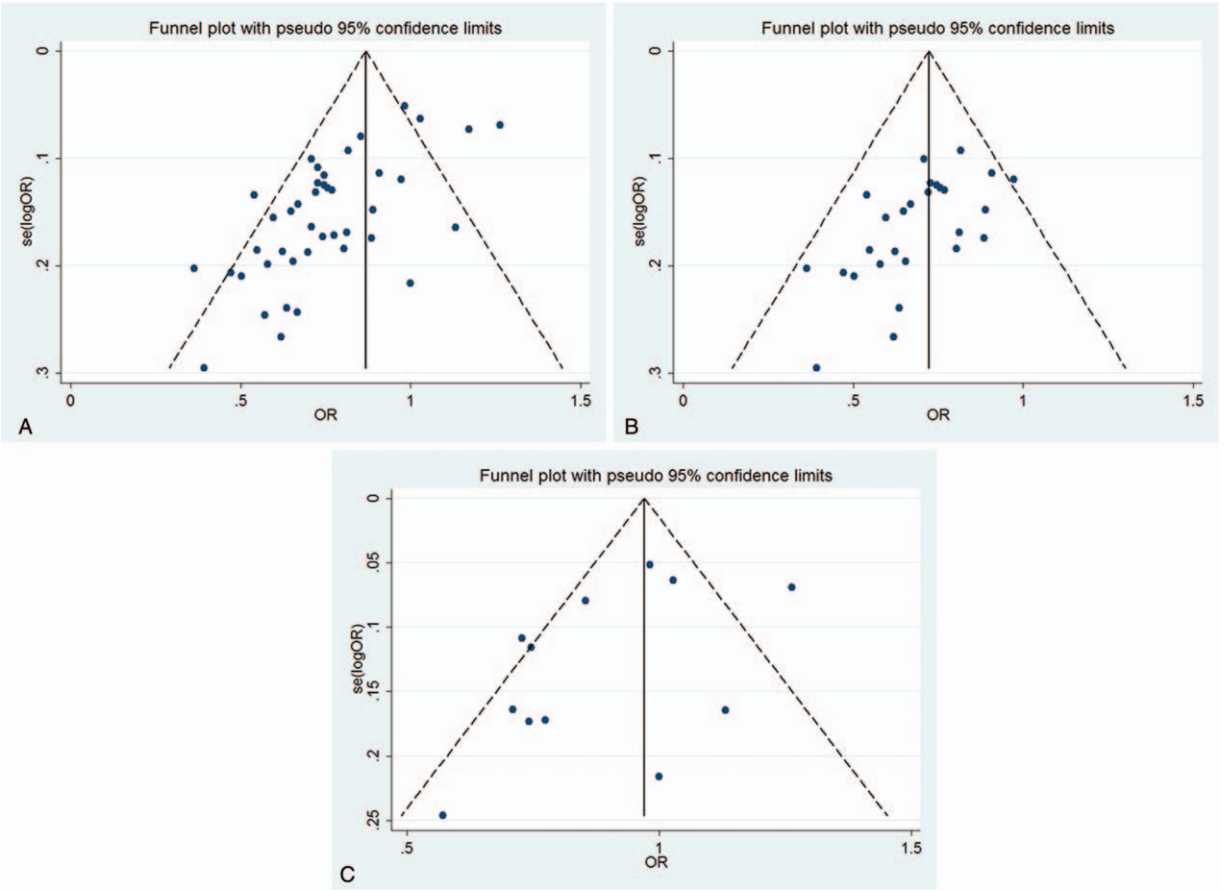

Figure 3. Forest plot for publication bias test between rs2230806 and CAD in the allelic model. A, Overall population. B, Asian population. C, Caucasian population.

eligible studies were published in English or Chinese, which might cause potential language bias. Last, heterogeneity may have an impact on our analysis.

5. Conclusion

In conclusion, the K allele of rs2230806 was significantly associated with decreased risk of CAD, especially in Asian populations and small sample Caucasians. However, in the light of the limitations in our meta-analysis, further large-scale multicenter study is needed to evaluate gene–gene and gene–environment interaction.

Author contributions

Data curation: Qian Fan, Yanfang Zhu.
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Methodology: Qian Fan, Yanfang Zhu, Fang Zhao.
Software: Qian Fan, Yanfang Zhu.
Validation: Fang Zhao.
Conceptualization: Qian Fan, Fang Zhao.
Funding acquisition: Qian Fan.
Project administration: Qian Fan, Fang Zhao.
Writing – original draft: Qian Fan.
Writing – review & editing: Qian Fan, Fang Zhao.

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