Systematic Review and Meta-Analysis

Medicine®

OPEN

Rs10757274 gene polymorphisms in coronary artery disease

A systematic review and a meta-analysis

Lang-Biao Xu, MD[a,*], Yi-Qing Zhang, MD[a], Nan-Nan Zhang, MD[a], Biao Li, MD[a], Jia-Yi Weng, MD[a], Xiao-Yang Li, MD[a], Wen-Chao Lu, MD[a], Pei-Ran Yu, MD[a], Xi Wang, MD[a], Yuan Li, MD[a], Zhen Han, MD[a], Lu Chen, MD[a], Hong-Tao He, MD[a], Ya-Feng Zhou, PHD[b], Xue-Xing Ma, MD[a], Gui-Dong Xu, MD[a,*]

Abstract

Background: It has been reported the rs10757274 SNP (present on locus 9p21 in the gene for CDKN2BAS1) might be associated with susceptibility to coronary artery disease (CAD). Owing to mixed and inconclusive results, we conducted a meta-analysis to investigate the association between rs10757274 polymorphism and the risk of CAD.

Objectives: The present study aimed to investigate the relationship between rs10757274 polymorphism and the risk of CAD.

Methods: All studies of the rs10757274 SNP with CAD that were published between 2007 and 2018 were retrieved from the PubMed database. Meta-analysis was performed with Stata 14.0 software. The effect size of the rs10757274 SNP with CAD risk was assessed based on the odds ratios (ORs) with calculation of 95% confidence interval (CI).

Results: Eleven studies including 52,209 subjects (cases: 7990, controls: 44,219) were included in the final data combination. Pooled overall analyses showed that rs10757274 (allele model: $P < .001$; dominant model: $P < .001$; recessive model: $P < .001$; Heterozygote codominant: $P = .002$; Homozygote codominant: $P < .001$) polymorphisms were significantly associated with the likelihood of CAD. Significant heterogeneity between individual studies appears in all 5 models. Further subgroup analyses revealed that rs10757274 polymorphisms were all significantly correlated with the likelihood of CAD and no heterogeneity were observed in West Asians.

Conclusions: Our findings indicated that rs10757274 polymorphisms may serve as genetic biomarkers of CAD, especially in West Asians.

Abbreviations: CAD = coronary artery disease, CAD = coronary artery disease, CI = confidence interval, MI = myocardial infarction, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: confidence interval (CI), coronary artery disease(CAD), gene polymorphism, Hardy Weinberg equilibrium (HWE), meta-analysis, odds risk(OR), rs10757274

1. Introduction

Coronary artery disease (CAD) still leads the causes of morbidity and mortality worldwide.[1] The accurate mechanisms responsible for the incidence of CAD are still unclear, which is influenced by numerous factors.[2,3] The risk factors such as hypertension, diabetes mellitus, abnormal serum cholesterol(LDL and HDL), cigarette smoking, high alcohol consumption, age, stress, family history of CAD, and obesity affect the development and security of CAD.[4,5,6,7,8] Genetic factors have been defined as an important risk contributor for the pathogenesis of CAD,[9,10] but the responsible molecular and genetic determinants remain largely unidentified.

Genome-wide association studies (GWAS) and candidate gene studies have reported that CDKN2BAS (cyclin-dependent kinase inhibitor 2B antisense RNA) is a risk gene for CAD susceptibility.[11,12,13] CDKN2BAS encodes an antisense non-coding RNA, and is located near the *CDKN2A-CDKN2B* gene. The precise function of CDKN2BAS is unknown, but it regulates the expression of neighboring protein-coding genes, like *CDKN2A*, *CDKN2B*, and *MTAP*, that enhance the progression of atherosclerosis by influencing vascular remodeling, thrombogenesis, and plaque stability.[14,15] Therefore, CDKN2BAS

Editor: Jacek Bil.

The ethical approval is not required since this study is based on published studies.

The authors report no conflicts of interest.

[a] Department of Cardiology, Suzhou Municipal Hospital, Nanjing Medical University, [b] Department of Cardiology, the First Affiliated Hospital of Soochow University, Suzhou City 215006, Jiang su Province, PR China.

[*] Correspondence: Gui-Dong Xu, Lang-Biao Xu, Department of Cardiology, Suzhou Municipal Hospital, Nanjing Medical University, Suzhou City 215000, Jiang su Province, PR China (e-mail: 1070027667@qq.com.cn, 18351037236@163.cn).

How to cite this article: Xu LB, Zhang YQ, Zhang NN, Li B, Weng JY, Li XY, Lu WC, Yu PR, Wang X, Li Y, Han Z, Chen L, He HT, Zhou YF, Ma XX, Xu GD. Rs10757274 gene polymorphisms in coronary artery disease: A systematic review and a meta-analysis. Medicine 2020;99:3(e18841).

Received: 17 May 2019 / Received in final form: 27 October 2019 / Accepted: 20 December 2019

http://dx.doi.org/10.1097/MD.0000000000018841

expression plays a crucial role in the development of CAD by altering the dynamics of vascular cell proliferation. In addition, single nucleotide polymorphisms (SNPs) in CDKN2BAS are connected with the risk of multiple diseases, such as CAD[12,14,16] type 2 diabetes,[17] ischemic stroke,[18] and periodontitis.[19]

It has been reported that Gene rs10757274 A/G (present on locus 9p21 in the gene for CDKN2BAS) Polymorphism might be association with the susceptibility to CAD. Several studies have demonstrated a strong association of rs10757274 with CAD in Pakistani,[14] Caucasian,[20] and South-West Iranian[21] population. However, 1 previous study found no association of rs10757274 with CHD in a Han Chinese population (Shenzhen).[22] The results of these studies were controversial. Thus, we performed the present meta-analysis to better evaluate gene rs10757274 polymorphisms in CAD.

2. Material and methods

2.1. Study selection

To identify all the articles that examined the association of rs10757274 SNP (present on locus 9p21 in the gene for CDKN2BAS) polymorphisms with coronary artery disease, we conducted a comprehensive search of PubMed, Web of Science, Cochrane library, and EMBASE (the last search update was January 6, 2019). Search terms included rs10757274 or rs10757274 A/G; gene polymorphism, or genetic mutation and myocardial infarct, myocardial infarction, coronary artery disease, coronary heart disease, myocardial ischemia, ischemic heart disease, ischemic cardiomyopathy, angina, angina pectoris, acute coronary syndrome, acute coronary syndrome (ACS), coronary calcification, coronary flow reserve, ischemic heart failure, heart failure. We also screened references of the retrieved articles and review articles by a hand search. Studies in this meta-analysis had to meet the following inclusion criteria:

1. evaluation of the association between rs10757274 A/G polymorphisms and CAD;
2. case-control study;
3. studies focusing on humans;
4. detailed genotype data could be acquired to calculate the odds ratios (ORs) and 95% confidence intervals (CIs).

Exclusion criteria:

1. duplication of previous publications;
2. comment, review, and editorial;
3. family-based studies of pedigrees;
4. study with no detailed genotype data.

When there were multiple publications from the same population, only the largest study was included. Study selection was performed by 2 investigators independently, according to the inclusion and exclusion criteria by screening the title, abstract, and full text. Any dispute was solved by discussion.

2.2. Data extraction

For each study that met our criteria, the following information was collected: first author, year of publication, country of origin, ethnicity, criteria of diagnosis, number of cases and controls, genotype distribution, genotyping methods and allele frequency, the criteria of CAD, Hardy-Weinberg equilibrium, number of cases and controls, and genotype frequency in cases, and controls for rs10757274. All the searching work and data extraction work were conducted by 2 independent investigators. If dissent existed, they would recheck the original data of the included studies and have a discussion to reach a consensus. If the dissent still existed, the third investigator would be involved to adjudicate the disagreements.

2.3. Quality assessment

The quality of the included studies was assessed by 2 authors separately according to the methodological quality assessment scale. In this scale, 5 items—representativeness of cases, source of controls, sample size, quality control of genotyping methods, and Hardy-Weinberg equilibrium (HWE) —were carefully checked. The quality score ranges from 0 to 10, and a high score means good quality of the study. Two investigators scored the studies

Table 1

Characteristics of the studies included in the meta-analysis.

Authors	Year	Country	Ethnicity	Case/control (n)	Cases			Controls		
					AA	AG	GG	AA	AG	GG
Shahid[23]	2018	Pakistan	East-Asian	404/219	107	186	111	60	115	44
Aleyasin[24]	2017	Iran	West-Asian	111/100	13	41	57	12	54	34
Golchin[25]	2017	Iran	West-Asian	103/102	16	47	40	29	51	22
Zhang[26]	2014	China	East-Asian	502/308	118	264	120	101	158	49
Zhuang[27]	2012	China	East-Asian	95/110	15	47	33	35	56	19
Kumar.J[28]	2011	India	East-Asian	310/439	116	135	59	144	210	85
Talmud[29]	2008	UK	Caucasian	264/2430	53	138	73	680	1186	564
Dehghan-CHD[30]	2008	Holland	Caucasian	588/6251	184	273	131	1834	3107	1310
Dehghan-MI[30]	2008	Holland	Caucasian	412/6247	133	197	82	1832	3106	1309
Mcpherson-ohs1[31]	2007	Canada	Caucasian	322/312	49	148	125	85	149	78
Mcpherson-ohs2[31]	2007	Canada	Caucasian	304/326	56	140	108	85	161	80
McPherson-aric[31]	2007	Canada	Caucasian	1037/7743	230	525	282	2063	3822	1858
McPherson-cchs[31]	2007	Canada	Caucasian	1525/9053	393	792	340	2752	4543	1758
McPherson-dhsv[31]	2007	Canada	Caucasian	154/527	27	85	42	147	258	122
McPherson-ohs3[31]	2007	Canada	Caucasian	647/847	121	333	193	228	418	201
Ayman a[32]	2015	Arabia	West-Asian	236/152	41	102	93	30	72	50
Scheffold[33]	2011	Germany	Caucasian	976/9053	208	515	253	2752	4543	1758

CHD = coronary heart disease, MI = myocardial infarction, year = publication year.

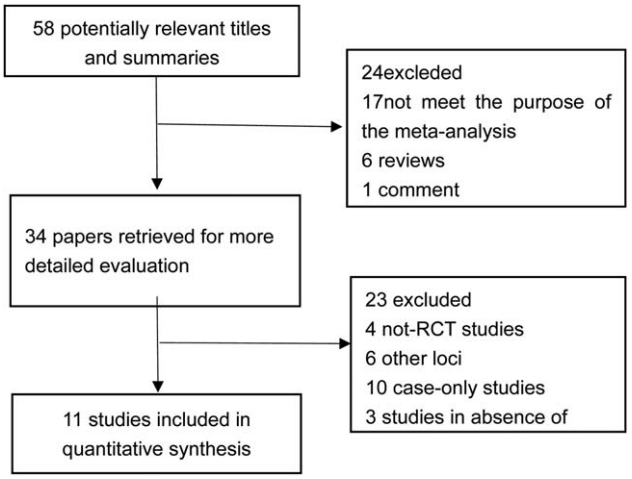

Figure 1. Study selection process.

independently and solved disagreement through discussion (Table 1).[23–33]

2.4. Statistical analysis

The strength of association between rs10757274 A/G polymorphisms and CAD was measured by the odds ratio (OR) corresponding to a 95% confidence interval (CI) according to the method of Woolf.[34] Heterogeneity between studies was assessed by Cochran χ^2-based Q statistic test.[35] Where the P value for heterogeneity was less than .1, a random-effects model using the DerSimonian and Laird method[36] was used to pool the results; otherwise, a fixed-effects model using the Mantel-Haenszel method was adopted.[37] In order to better evaluate the extent of heterogeneity between studies, the I^2 test was also used. This statistic yields results ranging from 0% to 100% (I^2 = 0%–25%, no heterogeneity; I^2 = 25%–50%, moderate heterogeneity; I^2 = 50%–75%, large heterogeneity; I^2 = 75%–100%, extreme heterogeneity).[38]

For the rs10757274 A/G promoter polymorphism, we investigated associations between the genetic variant and coronary artery disease risk in allelic contrast (G vs A), homozygote comparison (GG vs AA), heterozygote comparison (AG vs AA), dominant (AG/GG vs AA) and recessive (GG vs AG/AA) models, respectively. The significance of the pooled OR was determined by the Z-test ($P < .05$ suggests a significant association). Subgroup analyses were also conducted by ethnicity of participants. HWE was tested by the χ^2 test at a significant level of $P < .05$.[39] Publication bias was investigated by Begg funnel plot[37] and by Egger linear regression test.[38] Sensitivity analysis was also performed to evaluate the stability of the meta-analysis, All analyses were performed using STATA version 14.0 (StataCorp LP, College Station, Texas).

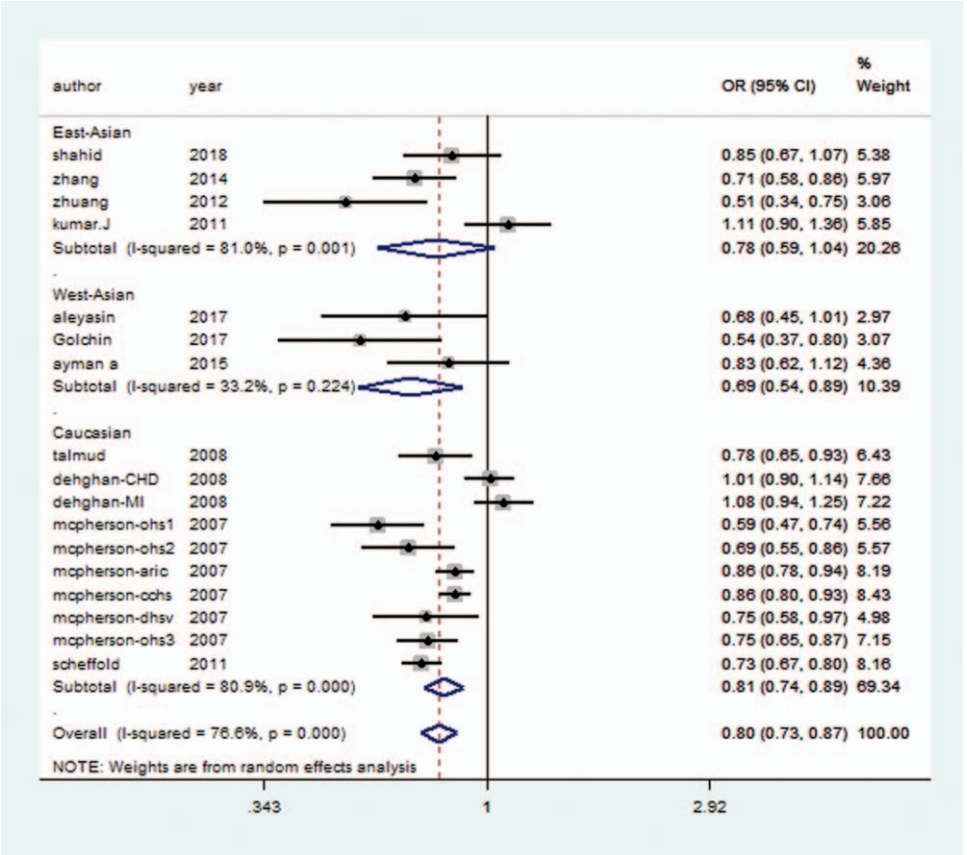

Figure 2. Forrest plot of allelic model for overall comparison of rs10757274 polymorphisms and CAD.

3. Result

3.1. Characteristics of included studies

In total, 11 articles were identified according to inclusion and exclusion criteria. The detailed screening process was shown in Figure 1.

3.2. Meta-analysis results

For the rs10757274 A/G polymorphism and its relationship to CAD, significant heterogeneity between individual studies appears obvious in all 5 models. Therefore, the random-effect model (DerSimonian and Laird) was applied in all 5 models. There was a statistically significant association between rs10757274A/G polymorphism and CAD risk under the 5 models, the allele model (OR = 0.80, 95% CI: 0.73–0.87, *Pv* < .001) (Fig. 2); the dominant model (OR = 0.75, 95% CI: 0.65–0.86, *Pv* < .001) (Fig. 3); the recessive model (OR = 0.74, 95% CI: 0.67–0.83, *Pv* < .001); heterozygote model (OR = 0.82, 95% CI: 0.72–0.93, *Pv* = .002) and homozygote model (OR = 0.64, 95% CI: 0.54–0.75, *Pv* < .001) (Table 2).

Having higher heterogeneity in all of models, we further performed subgroup analysis by ethnicity of participants (East Asians, West Asians, and Caucasian). The results showed that significant heterogeneity was still observed in East Asians and Caucasian. Additionally no heterogeneity was observed in West Asians and a statistically significant association was observed between rs10757274A/G polymorphism and CAD risk in all subgroups.

3.3. Sensitivity analysis

The results of sensitivity analysis (Fig. 6) showed that the pooled OR were not considerably affected by omitting any individual study using the 5 genetic models, which confirmed that the results of this meta-analysis were reliable and stable.

3.4. Publication bias

Publication biases were evaluated by Begg funnel plot (Fig. 5) and Egger linear regression test (Fig. 4). We did not find obvious asymmetry of funnel plots in any comparisons, which indicated that our findings were unlikely to be impacted by severe publication biases.

4. Discussion

Our study was a report to pool published case-control studies to estimate the association between CDKN2BAS rs10757274 A/G polymorphism and susceptibility to CAD. Our results of meta-analysis showed that there were significant statistically associations between rs10757274 polymorphism with CAD under all genetic models, we found A allele that had a lower risk of CAD as compared to G allele. To explore the source of heterogeneity, we

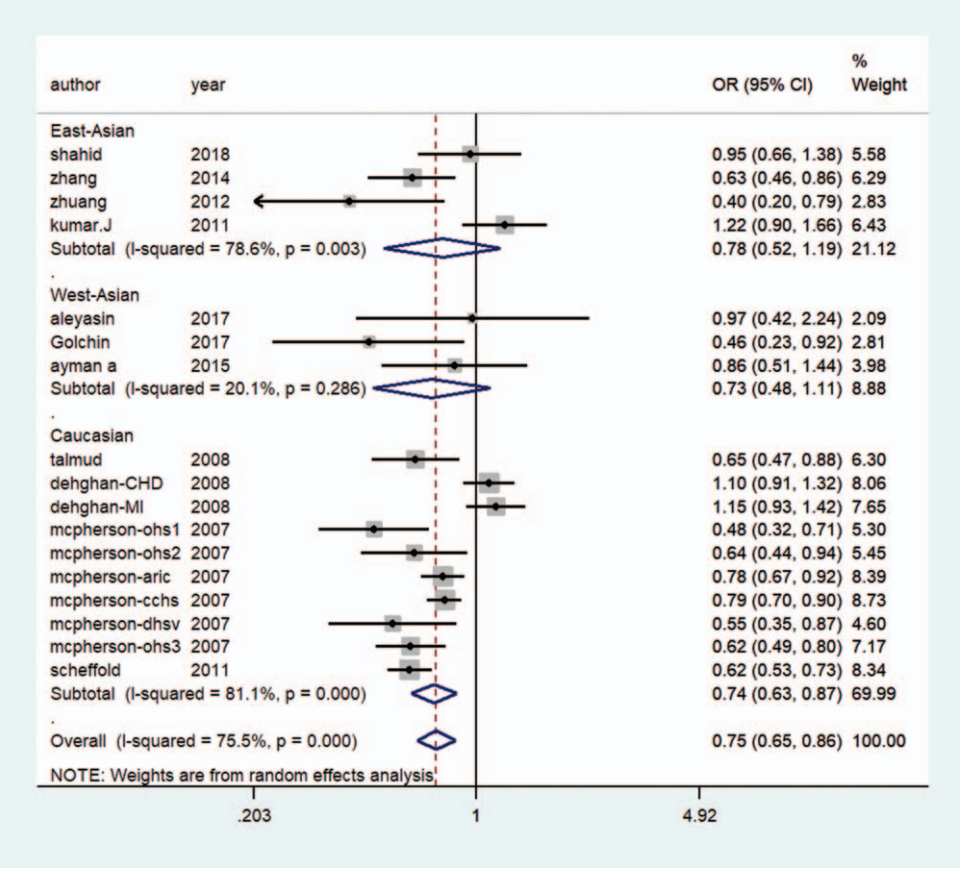

Figure 3. Forrest plot of dominant model for overall comparison of rs10757274 polymorphisms and CAD.

Table 2

Results of meta-analysis for rs10757274 polymorphisms and CAD risks.

Study Groups	Allele contrast model		Dominant model		Recessive model	
	OR (95% CI)	P_V	OR (95% CI)	P_V	OR (95% CI)	P_V
Total	0.8 (0.73–0.87)	<.001	0.75 (0.65–0.86)	<.001	0.74 (0.67–0.83)	<.001
Ethnicity						
East-Asian	0.78 (0.59–1.04)	.089	0.78 (0.52–1.19)	.25	0.67 (0.47–0.94)	.021
West-Asian	0.69 (0.54–0.89)	.004	0.73 (0.48–1.11)	.142	0.57 (0.40–0.81)	.002
Caucasian	0.81 (0.74–0.89)	<.001	0.74 (0.63–0.87)	<.001	0.78 (0.71–0.87)	<.001

Study groups	Heterozygote codominant		Homozygote codominant	
	OR (95% CI)	P_V	OR (95% CI)	P_V
Total	0.82 (0.72–0.93)	.002	0.64 (0.54–0.75)	<.001
Ethnicity				
East-Asian	0.89 (0.62–1.28)	.534	0.60 (0.34–1.04)	.070
West-Asian	0.91 (0.59–1.40)	.659	0.54 (0.32–0.94)	.028
Caucasian	0.79 (0.68–0.91)	.001	0.66 (0.54–0.80)	<.001

CI = confidence interval, OR = odds ratio.

further performed subgroup publication bias and sensitivity analyses. The result of subgroup analysis showed that a statistically significant association was observed between rs10757274A/G polymorphism and CAD risk in East Asians, West Asians, and Caucasian. Moreover, we also found that no heterogeneity was observed in West Asians. Sensitivity analysis did not identify any sources of heterogeneity. It suggested that there was no evidence of publication bias among the studies using all of the genetic models.

Many genome-wide association studies have identified a great number of genetic loci, suggesting that common genetic variants contribute to the CAD development.[40] A large number of polymorphisms at novel loci play a critical role for CAD.[41] The rs10757274 is one of the most intensively examined polymorphisms of CDKN2B-AS gene at 9p21 locus.

The genetic/molecular basis of 9p21 genetic variation on CAD risk is unknown. The 9p21.3 locus is located outside of annotated genes. A role for CDKN2A and CDKN2B, which play an important role in regulation of the cell cycle and lie in relatively close proximity,[42] appears to be excluded by resequencing studies of McPherson et al.[11] Subsequently, Broadbent et al[43] reported that the 9p21 high-risk haplotype collocates with a large antisense noncoding RNA gene, which is expressed in tissues and cell types affected by atherosclerosis and which might act as an important growth regulatory element.

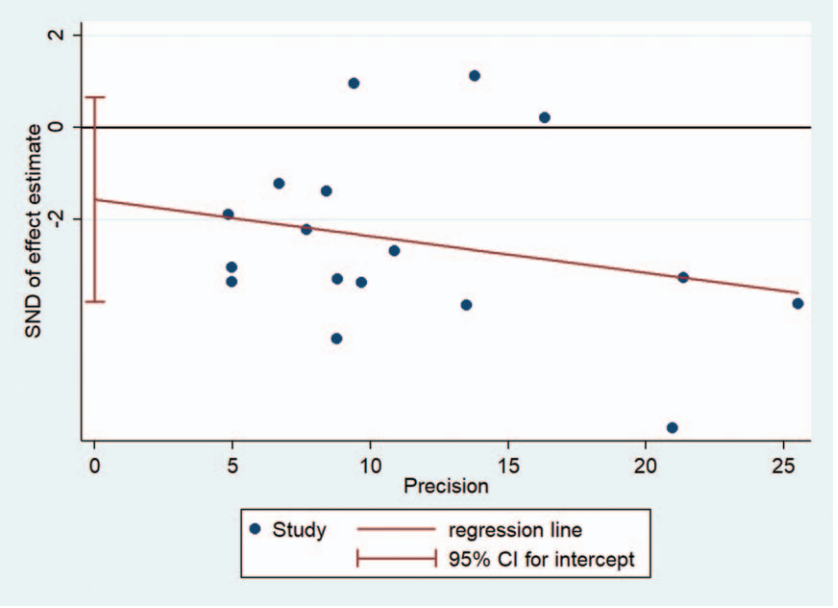

Figure 4. Egger plot for publication bias test of the rs10757274 polymorphisms and CAD.

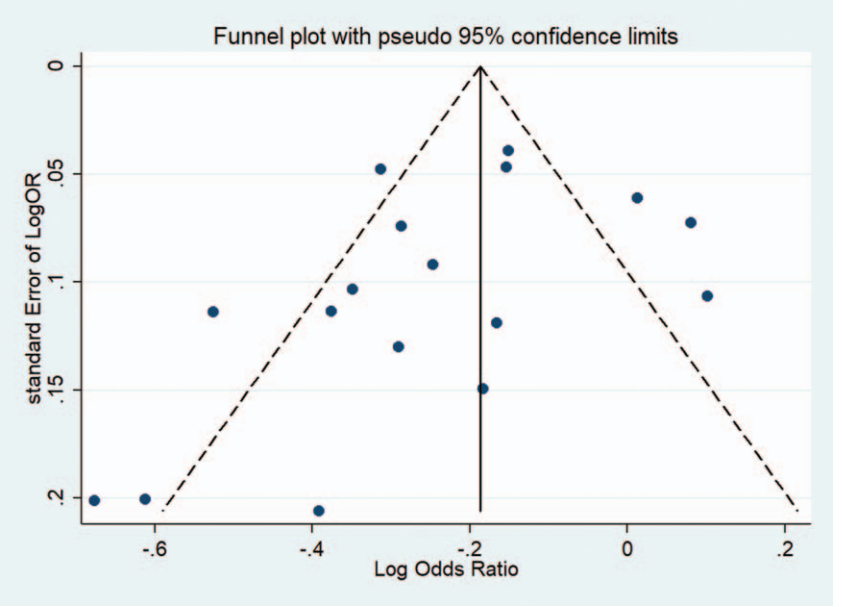

Figure 5. Funnel plot for publication bias test of the rs10757274 polymorphisms and CAD.

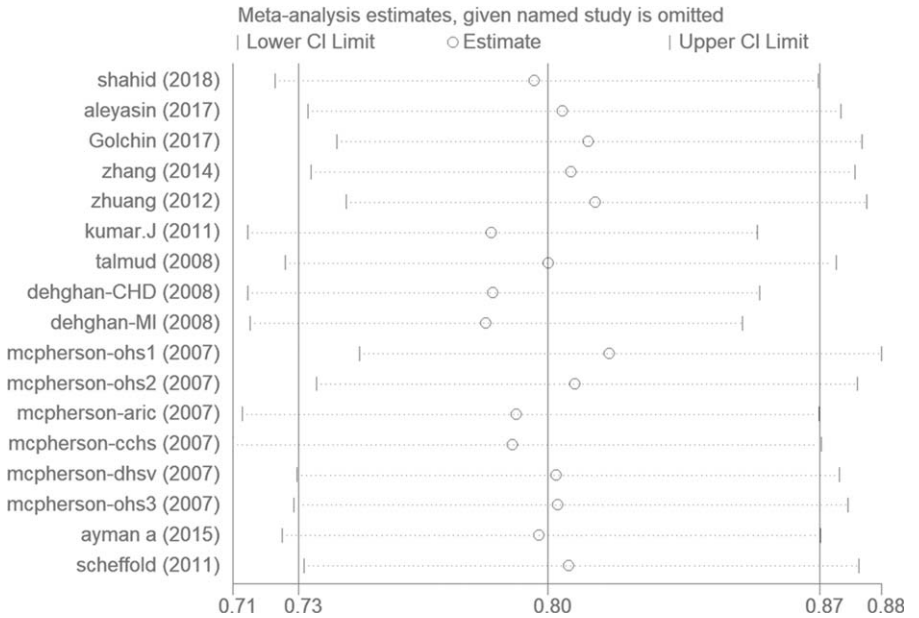

Figure 6. The results of sensitivity analysis showed that the pooled OR were not considerably affected by omitting any individual study using the 5 genetic models, which confirmed that the results of this meta-analysis were reliable and stable.

Several limitations exist in our research. Firstly, only 11 studies were included this research analysis involving a total of 52,209 subjects. Therefore, more studies with a larger sample sizes should be included to enhance the reliability and stability of the meta-analysis. In addition, the interference of factors, such as environmental and genetic factors, and pharmaceuticals, requires further study. Finally, we did not analysis the association between the rs10757274 polymorphism and different subtypes, as myocardial infarction, angina, and other subtypes, due to lacking sufficient statistical data in the literatures.

The results of the current meta-analysis implied that rs10757274 polymorphisms may serve as genetic biomarkers of CAD, especially in West Asians. Considering the limitations discussed, our conclusion needed further verification by high quality studies with larger sample sizes and rigorous designs.

Author contributions

Conceptualization: Gui-Dong Xu, Ya-Feng Zhou.

Data curation: Gui-Dong Xu, Ya-Feng Zhou.
Formal analysis: Gui-Dong Xu, Ya-Feng Zhou, Yuan Li.
Funding acquisition: Gui-Dong Xu.
Investigation: Lang-Biao Xu, Nan-Nan Zhang, Biao Li.
Methodology: Lang-Biao Xu, Gui-Dong Xu, Jia-Yi Weng.
Project administration: Gui-Dong Xu, Xue-Xing Ma, Xiao-Yang Li, Wen-Chao Lu.
Resources: Xue-Xing Ma.
Software: Lang-Biao Xu, Yi-Qing Zhang, Hong-Tao He.
Supervision: Gui-Dong Xu, Lu Chen.
Validation: Gui-Dong Xu, Ya-Feng Zhou, Zhen Han.
Visualization: Gui-Dong Xu, Ya-Feng Zhou.
Writing – original draft: Lang-Biao Xu.
Writing – review & editing: Lang-Biao Xu.

References

[1] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.
[2] Zou JG, Ma YT, Xie X, et al. The association between CYP1A1 genetic polymorphisms and coronary artery disease in the Uygur and Han of China. Lipids Health Dis 2014;13:145.
[3] Schaefer LE, Nechemias C. Endogenous hormones, lipid metabolism, and coronary artery disease. Prog Cardiovasc Dis 1965;7:449–64.
[4] van Hateren KJ, Bilo HJ. Hypertension control and cardiovascular outcomes among patients with diabetes and coronary artery disease. JAMA 2010;304:1672.
[5] Dunn JP, Ipsen J, Elsom KO, et al. Risk factors in coronary artery disease, hypertension and diabetes. Am J Med Sci 1970;259:309–22.
[6] Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 1998;316:823–8.
[7] Connelly PW, Stachenko S, MacLean DR, et al. The prevalence of hyperlipidemia in women and its association with use of oral contraceptives, sex hormone replacement therapy and nonlipid coronary artery disease risk factors. Canadian Heart Health Surveys Research Group. Can J Cardiol 1999;15:419–27.
[8] Li XL, Hong LF, Luo SH, et al. Impact of admission triglyceride for early outcome in diabetic patients with stable coronary artery disease. Lipids Health Dis 2014;13:73.
[9] Topol EJ, Smith J, Plow EF, et al. Genetic susceptibility to myocardial infarction and coronary artery disease. Hum Mol Genet 2006;15:R117–23.
[10] Wang Q. Molecular genetics of coronary artery disease. Curr Opin Cardiol 2005;20:182–8.
[11] Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. N Engl J Med 2007;357:443–53.
[12] AbdulAzeez S, Al-Nafe AN, Al-Shehri A, et al. Intronic polymorphisms in the CDKN2B-AS1 gene are strongly associated with the risk of myocardial infarction and coronary artery disease in the Saudi population. Int J Mol Sci 2016;17:
[13] Wellcome Trust Case Control CGenome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–78.
[14] Nawaz SK, Noreen A, Rani A, et al. Association of the rs10757274 SNP with coronary artery disease in a small group of a Pakistani population. Anatol J Cardiol 2015;15:709–15.
[15] Holdt LM, Sass K, Gabel G, et al. Expression of Chr9p21 genes CDKN2B(p15(INK4b)), CDKN2A (p16(INK4a), p14(ARF)) and MTAP in human atherosclerotic plaque. Atherosclerosis 2011;214:264–70.
[16] Huang Y, Ye H, Hong Q, et al. Association of CDKN2BAS polymorphism rs4977574 with coronary heart disease: a case-control study and a meta-analysis. Int J Mol Sci 2014;15:17478–92.
[17] Wang MH, Li J, Yeung VS, et al. Four pairs of gene-gene interactions associated with increased risk for type 2 diabetes (CDKN2BASKCNJ11), obesity (SLC2A9-IGF2BP2, FTO-APOA5), and hypertension (MC4R-IGF2BP2) in Chinese women. Meta gene 2014;2:384–91.
[18] Heckman MG, Soto-Ortolaza AI, Diehl NN, et al. Genetic variants associated with myocardial infarction in the PSMA6 gene and Chr9p21 are also associated with ischaemic stroke. Eur J Neurol 2013;20:300–8.
[19] Schaefer AS, Richter GM, Dommisch H, et al. CDKN2BAS is associated with periodontitis in different European populations and is activated by bacterial infection. J Med Genet 2011;48:38–47.
[20] McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. Science 316:1488–91.
[21] Foroughmand AM, Nikkhah E, Galehdari H, et al. Association study between coronary artery disease and rs1333049 and rs10757274 polymorphisms at 9p21 locus in South-West Iran. Cell J 17:89–98.
[22] Liu YH, Zhou YW, Yang JA, et al. Gene polymorphisms associated with susceptibility to coronary artery disease in Han Chinese people. Genet Mol Res 2014;13:2619–27.
[23] Shahid SU, Shabana NA, Rehman A, et al. GWAS implicated risk variants in different genes contribute additively to increase the risk of coronary artery disease (CAD) in the Pakistani subjects. Lipids Health Dis 2018;17:89.
[24] Aleyasin SA, Navidi T, Davoudi S. Association between rs10757274 and rs2383206 SNPs as genetic risk factors in Iranian patients with coronary artery disease. J Tehran Heart Cent 2017;12:114–8.
[25] Mafi Golchin M, Ghaderian SMH, Akhavan-Niaki H, et al. Analysis of two CDKN2B-AS polymorphisms in relation to coronary artery disease patients in North of Iran. Int J Mol Cell Med 2017;6:31–7.
[26] Zhang LW, Li JP, Duan FF, et al. Interaction of type 2 diabetes mellitus with chromosome 9p21 rs10757274 polymorphism on the risk of myocardial infarction: a case-control study in Chinese population. BMC Cardiovasc Disord 2014;14:170Published 2014 Nov 27.
[27] Zhuang J, Peng W, Li H, et al. Methylation of p15INK4b and expression of ANRIL on chromosome 9p21 are associated with coronary artery disease. PLoS One 2012;7:e47193.
[28] Kumar J, Yumnam S, Basu T, et al. Association of polymorphisms in 9p21 region with CAD in North Indian population: replication of SNPs identified through GWAS. Clin Genet 2011;79:588–93.
[29] Talmud PJ, Cooper JA, Palmen J, et al. Chromosome 9p21.3 coronary heart disease locus genotype and prospective risk of CHD in healthy middle-aged men. Clin Chem 2008;54:467–74.
[30] Dehghan A, van Hoek M, Sijbrands EJ, et al. Lack of association of two common polymorphisms on 9p21 with risk of coronary heart disease and myocardial infarction; results from a prospective cohort study. BMC Med 2008;6:30.
[31] McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. Science 2007;316:1488–91.
[32] El-Menyar AA, Rizk NM, Al-Qahtani A, et al. The cardiovascular implication of single nucleotide polymorphisms of chromosome 9p21 locus among Arab population. J Res Med Sci 2015;20:346–52.
[33] Scheffold T, Kullmann S, Huge A, et al. Six sequence variants on chromosome 9p21.3 are associated with a positive family history of myocardial infarction: a multicenter registry. BMC Cardiovasc Disord 2011;11:9.
[34] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007;28:105–14.
[35] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
[36] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[37] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[38] Egger M, Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[39] Lindley D. Statistical inference concerning Hardy-Weinberg equilibrium. Bayesian Stat 1988;3:307–26.
[40] Khera AV, Kathiresan S. Genetics of coronary artery disease: discovery, biology and clinical translation. Nat Rev Genet 2017; 18:331–44.
[41] Vitali C, Khetarpal SA, Rader DJ. HDL cholesterol metabolism and the risk of CHD: new insights from human genetics. Curr Cardiol Rep 2017;19:132.
[42] McPherson R, Pertsemlidis A, Kavaslav N, et al. A common allele on chromosome 9 associated with coronary heart disease. Science 2007; 316:1488–91.
[43] Broadbent HM, Peden JF, Lorkowski S, et al. Susceptibility to coronary artery disease and diabetes is encoded by distinct, tightly linked SNPs in the ANRIL locus on chromosome 9p. Hum Mol Genet 2008;17:806–14.