Meta-Analysis

Association between matrix metalloproteinase 9 C-1562T polymorphism and the risk of coronary artery disease: an update systematic review and meta-analysis

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Keywords: coronary artery disease; myocardial infarction; matrix metalloproteinase 9; polymorphism; meta-analysis

Received: November 30, 2016 Accepted: December 08, 2017 Published: December 15, 2017

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ABSTRACT

Polymorphism (rs3918242) in the MMP9 gene has been reported to be associated with coronary artery disease (CAD). This study aims to investigate a more accurate estimation of the relationship between CAD and rs3918242 polymorphism by a meta-analysis method. We systematically searched studies on the association of rs3918242 polymorphism and CAD in PubMed, Web of Science, the Cochrane Library, Wanfang Data and CNKI. We used Stata 12.0 and RevMan 5.3 software to perform the meta-analyses. A total of 37 case-control studies involving 13,035 CAD patients and 11,372 non-CAD controls were included. A statistically significant association between rs3918242 polymorphism and CAD was observed in allelic model (Odds ratio (OR) 1.34; 95% confidence interval (CI) 1.20–1.50; p < 0.00001), recessive model (OR 1.43; 95% CI 1.17–1.75; p = 0.0004), and in dominant model (OR 1.36; 95% CI 1.20–1.53; p < 0.00001). Moreover, we also found that there is a statistically significant association between rs3918242 polymorphism and myocardial infarction (MI) in Asians with allelic model (OR 1.66; 95% CI 1.29–2.14; p < 0.0001), recessive model (OR 2.29; 95% CI 1.44–3.63; p = 0.004), and dominant (OR 1.74; 95% CI 1.29–2.35; p = 0.0003) model. A similar result in Caucasians with allelic model (OR 1.14; 95% CI 1.02–1.27; p = 0.02), and in dominant (OR 1.17; 95% CI 1.04–1.32; p = 0.01) model. Our meta-analysis suggested that the MMP9 T allele is a risk factor for CAD and MI.

INTRODUCTION

Current studies have well documented that the interaction between various environmental factors and certain genetic polymorphisms may lead to CAD [1]. Many association studies between polymorphisms of matrix metalloproteases (MMPs) gene and CAD have been carried out [2, 3]. These studies showed that MMPs is associated with a higher risk of plaque rupture/

atherosclerosis and adverse cardiovascular events in patients undergoing CAD [4].

Matrix metallopeptidases 9 (MMP9) has been focused on the value of degrade a wide range of extracellular matrix proteins in patients [5]. MMP 9 is regulated primarily at the transcription level and posttranslational by activation of the zymogen and by inhibition of the endogenous inhibitor TIMP-1[6]. Although various studies between MMP9 and CAD have been reported, the conclusions are not consistent. The MMP9 C-1562T (rs3918242) in the promoter region is of special interest, which was considered a close association with CAD by many studies. Up to now, lots of case-control studies and systematic reviews on the relation between rs3918242 and CAD were carried out. However, the conclusions were inconsistent. Based on these observations, to investigate a more accurate estimation of the relationship between CAD and rs3918242, we conducted an update meta-analysis.

RESULTS

Study characteristics

A total of 37 studies [7–41] including 13,035 cases and 11,372 controls were identified in this meta-analysis. The Figure 1 show that the study selection process. Supplementary Table 1 and Table 1 have summarized the main characteristics of included studies. In all studies, the genotype frequencies in controls were in consistent with HWE. The results of NOS showed that the methodological quality of be included studies were mostly good (6–9 stars).

Meta-analysis

Table 2 presents a principal results of this studies. For the rs3918242 polymorphism, heterogeneity was found in the allelic ($I^2 = 66\%$, p < 0.00001) and dominant ($I^2 = 65\%$, p < 0.00001) models, but not in the recessive model ($I^2 = 22\%$, p = 0.13). Therefore, We performed a random-effects and fixed-effects method to merge the ORs. The meta-analysis results showed that significant statistical association between rs3918242 polymorphism and the risk of CAD in allelic (OR 1.34; 95% CI 1.20–1.55; p < 0.00001), recessive (OR 1.43; 95% CI 1.20–1.55; p < 0.00001), and dominant (OR 1.36; 95% CI 1.20–1.53; p < 0.00001) models.

In addition, a subgroup analysis was conducted according to ethnics. In Caucasians, no significant statistical association between rs3918242 polymorphism and CAD either in allelic (OR 1.11; 95% CI 0.99–1.25; p = 0.07) or recessive (OR 1.06; 95% CI 0.80–1.40; p = 0.70) models. But significant statistical association was observed in dominant (OR1.13; 95% CI 1.01–1.26; p = 0.03) model. In Asians, significant statistical association was found between rs3918242 and CAD in allelic contrast (OR 1.45; 95% CI 1.25–1.69; p < 0.00001), recessive(OR 1.94; 95% CI 1.45–2.58; p < 0.00001) and dominant (OR 1.48; 95% CI 1.25–1.75; p < 0.00001) models (Figures 2–7).

Sensitivity analyses

We excluded individual studies one at a time and recalculated the pooled p or OR for the remaining

studies. The results proved that the ORs were not changed obviously, which suggested that this results are stable.

Publication bias

Egger's test and Funnel plot were conducted to evaluate the publication bias of all contrast models. No obvious bias was found in our study. No obvious asymmetry was found in the funnel plot for the allelic, recessive and dominant genetic models (Figure 8). Further, Egger's test be used to detect the whole publication bias. No statistically significant of publication bias was detected in allelic (p = 0.592), recessive (p = 0.103) and dominant (p = 0.683) models. The same was true in the subgroup analysis.

DISCUSSION

Our meta-analysis showed that rs3918242 polymorphism was linked with an increased risk of CAD in Asians. More available evidence supports the fact that the rs3918242 as a risk factor association with MI both in Asian and Caucasian populations. MMP-9 might be particularly important in matrix degradation and the subsequent atherosclerotic plaque rupture because of its extensive substrate specificity and distal position in the proteolytic cascade reaction [42]. Loftus et al. reported that MMP-9 concentration and activity were significantly higher in unstable atherosclerotic plaque with intense inflammatory cell infiltration, hence contributing to the plaque rupture ultimately [43]. Opstad et al. suggested that patients with previous MI were associated with the higher MMP-9 gene expression [32]. The current study data from animal experiment, observation of circulating markers and expression investigations on atherosclerotic tissue, has indicated a role of MMP-9 in atherosclerosis. However, the association of rs3918242 polymorphism with CAD and MI risks remains inclusive, although several meta-analysis research (Wang et al. [42], Abilleira et al. [44], Juan et al. [45]) have been published. Wang [42] performed a meta-analysis which included sixteen case-control studies to evaluate the association between rs3918242 and CAD. Subgroup analysis was performed according to different races and outcome(CAD or MI). The final conclusion suggested that an obvious ethnic difference. MMP-9 C1562T polymorphism was associated with CAD or MI in East Asians. But not to west Asians or western populations. Abilleira [43] presented a study of available data from five studies and did not find association of MMP9 polymorphism with CAD. Also, they did not have further specific analysis and subgroup analysis. Juan [44] collected all publications on the association between rs3918242 polymorphism and MI which included 7 researchs. Their data showed that the rs3918242 is a risk factor for white populations, but not for Asian populations.

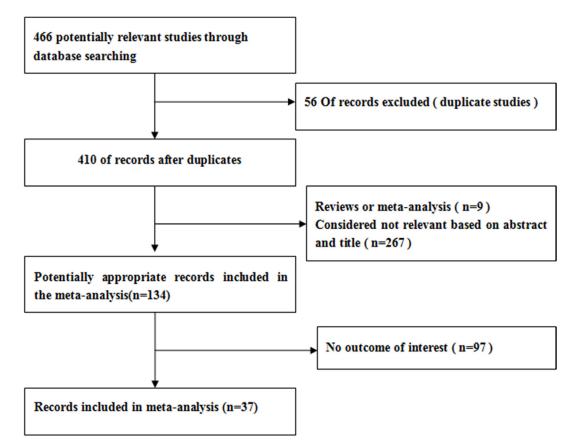


Figure 1: Flow chart of meta-analysis for exclusion /inclusion of individual studies.

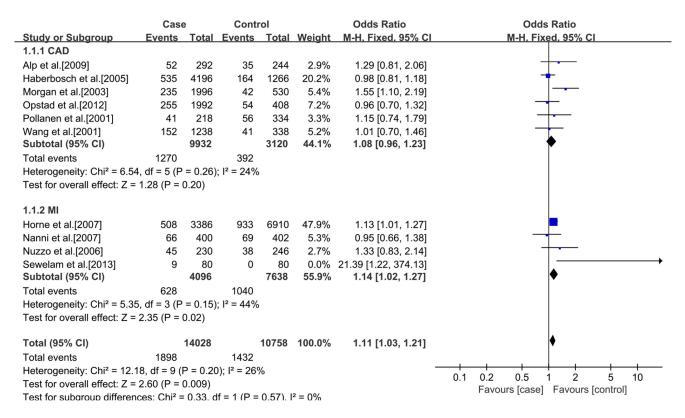


Figure 2: Forest plot of the meta-analysis of the association between MMP-9 C-1562T(rs3918242) and CAD or MI risks in an allele genetic model in Caucasians subgroup.

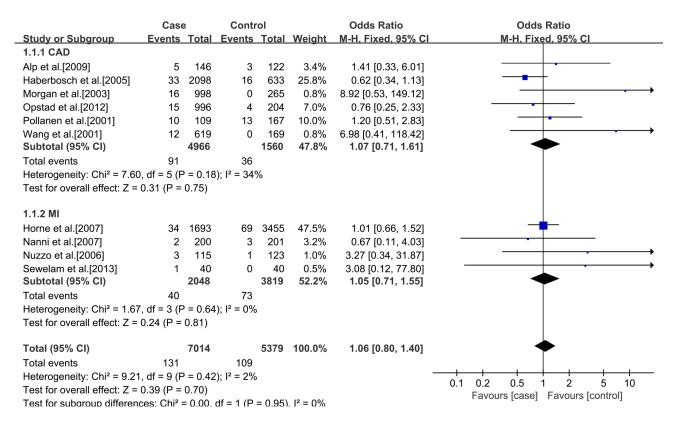


Figure 3: Forest plot of the meta-analysis of the association between MMP-9 C-1562T(rs3918242) and CAD or MI risks in a recessive genetic model in Caucasians subgroup.

	Case	•	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
1.1.1 CAD							
Alp et al.[2009]	47	146	32	122	2.7%	1.34 [0.78, 2.27]	
Haberbosch et al.[2005]	502	2098	148	633	20.1%	1.03 [0.84, 1.27]	+
Morgan et al.[2003]	219	998	42	265	6.0%	1.49 [1.04, 2.14]	
Opstad et al.[2012]	240	996	50	204	7.3%	0.98 [0.69, 1.39]	_
Pollanen et al.[2001]	31	109	43	167	2.8%	1.15 [0.67, 1.97]	
Wang et al.[2001]	140	619	41	169	5.8%	0.91 [0.61, 1.36]	
Subtotal (95% CI)		4966		1560	44.7%	1.09 [0.95, 1.26]	•
Total events	1179		356				
Heterogeneity: Chi ² = 4.89	, df = 5 (F	9 = 0.43); I ² = 0%	,			
Test for overall effect: Z =	1.28 (P =	0.20)					
1.1.2 MI							
Horne et al.[2007]	474	1693	864	3455	47.4%	1.17 [1.02, 1.33]	=
Nanni et al.[2007]	64	200	66	201	5.2%	0.96 [0.63, 1.46]	
Nuzzo et al.[2006]	42	115	37	123	2.6%	1.34 [0.78, 2.30]	
Sewelam et al.[2013]	8	40	0	40	0.0%	21.18 [1.18, 380.90]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		2048		3819	55.3%	1.17 [1.04, 1.32]	◆
Total events	588		967				
Heterogeneity: Chi ² = 4.94	, df = 3 (F	9 = 0.18); I ² = 39 ⁶	%			
Test for overall effect: Z =	2.56 (P =	0.01)					
Total (95% CI)		7014		5379	100.0%	1.14 [1.04, 1.25]	◆
Total events	1767		1323				
Heterogeneity: Chi ² = 10.2	8, df = 9 (P = 0.3	3); l² = 12	2%			
Test for overall effect: Z =	2.76 (P =	0.006)					
Test for subaroup difference	ces: Chi² :	= 0.52.	df = 1 (P	= 0.47)	. I² = 0%		Favours [case] Favours [control]

Figure 4: Forest plot of the meta-analysis of the association between MMP-9 C-1562T(rs3918242) and CAD or MI risks in a dominant genetic model in Caucasians subgroup.

Table 1: Characteristics of included studies

Reference	Year	Ethnicity			Ca	se						Control		
			N	0	Genotype (<i>n</i>)	all	ele	Ν		Genotype (n))	all	ele
				СС	СТ	TT	С	Т		CC	СТ	TT	С	Т
Wang et al.	2001	Caucasian	619	479	128	12	1086	152	169	128	41	0	297	41
Pollanen et al.	2001	Caucasian	109	78	21	10	177	41	167	124	30	13	278	56
Cho et al.	2002	Asian	63	48	15	0	111	15	67	63	4	0	130	4
Kim et al.	2002	Asian	131	99	32	0	230	32	117	85	32	0	202	32
Morgan et al.	2003	Caucasian	998	779	203	16	1761	235	265	223	42	0	488	42
Haberbosch et al.	2005	Caucasian	2098	1596	469	33	3661	535	633	485	132	16	1102	164
Chen et al.	2005	Asian	78	57	21	0	135	21	81	73	8	0	154	8
Tang et al.	2005	Asian	101	73	27	1	173	29	105	91	13	1	195	15
Meng et al.	2006	Asian	117	91	26	0	208	26	99	80	18	1	178	20
Nuzzo et al.	2006	Caucasian	115	73	39	3	185	45	123	86	36	1	208	38
Horne et al.	2007	Caucasian	1693	1219	440	34	2878	508	3455	2591	795	69	5977	933
Nanni et al.	2007	Caucasian	200	136	62	2	334	66	201	135	63	3	333	69
Chen et al.	2007	Asian	150	97	48	5	242	58	70	61	6	3	128	12
Chen et al.	2007	Asian	110	92	13	5	197	23	70	61	6	3	128	12
Wang et al.	2007	Asian	64	46	17	1	109	19	84	66	18	0	150	18
Koh et al.	2008	Asian	206	151	52	3	354	58	173	142	31	0	315	31
Zhang et al.	2008	Asian	92	67	22	3	156	28	95	83	12	0	178	12
Alp et al.	2009	Caucasian	146	99	42	5	240	52	122	90	29	3	209	35
Wu et al.	2009	Asian	791	628	155	8	1411	171	689	545	143	1	1233	145
Wu et al.	2009	Asian	370	289	77	4	655	85	689	545	143	1	1233	145
Fallah et al.	2010	Asian	145	77	57	11	211	79	157	62	76	19	200	114
Zhi et al.	2010	Asian	762	585	174	3	1344	180	555	442	110	3	994	116
Gao et al.	2010	Asian	96	49	38	9	136	56	78	59	18	1	136	20
Ma et al.	2010	Asian	347	251	83	13	585	109	403	346	53	4	745	61
Yong et al.	2010	Asian	128	97	30	1	224	32	106	92	14	0	198	14
Ghaderian et al.	2011	Asian	234	177	47	10	401	67	200	141	53	6	335	65
Wang et al.	2011	Asian	352	261	80	11	602	102	421	355	61	5	771	71
Opstad et al.	2012	Caucasian	996	756	225	15	1737	255	204	154	46	4	354	54
Wang et al.	2012	Asian	384	286	87	11	659	109	451	373	72	6	818	84
Spurthi et al.	2012	Asian	100	40	47	13	127	73	100	48	46	6	142	58
Han et al.	2012	Asian	91	65	25	1	155	27	101	75	25	1	175	27
Sewelam et al.	2013	Caucasian	40	32	7	1	71	9	40	40	0	0	80	0
Yang et al.	2013	Asian	240	186	47	7	419	61	200	161	35	4	357	43
Wu et al.	2013	Asian	258	193	56	9	442	74	153	131	22	0	284	22
Xu et al.	2013	Asian	382	268	109	5	645	119	466	361	103	2	825	107
Lu et al.	2014	Asian	168	102	62	4	266	70	208	156	50	2	362	54
Yuan et al.	2014	Asian	61	48	11	2	107	15	55	38	16	1	92	18

In order to obtain reliable conclusion, we implemented an update meta-analysis involving 37 studies to provide the relationship between rs3918242 and CAD or MI risks. The study revealed that rs3918242 possibly increased the risk of MI in both Asian and Caucasian populations. As compared with the former

studies [43–45], our findings has a lot of novelty. Firstly, although lots of studies and systematic review have reported this association, the conclusions were inconsistent or inconclusive. Therefore, our research is urgent and meaningful. Secondly, our meta-analysis is superior to the others, due to the far larger number of

participants (37 included studies with 13,035 cases and 11,372 controls) which were from all over the world. The substantially large sample size ensures the reliability of the results. Thirdly, subgroup analysis was further conducted according to different races.

There are several possible metabolic and molecular mechanisms to explain our conclusion. Zhang [46] have suggested that the C-1562T polymorphic locus is important for the regulatory element that the mutation appeared to be a binding site for a transcription repressor protein and T-allelic promoter had a higher promoter activity. Moreover, more evidences have indicated that the MMP-9 have associated with cell migration and proliferation [47]. More important, the overexpression and activity of MMP-9(rs3918242) was monitored in unstable atherosclerotic plaques [48]. These evidences were in line with our results.

Several limitations should to be pointed out. Risk of bias and unobservable heterogeneity may disturb the results. Included studies of language limit to English and Chinese, missing some studies by other languages. Some hardly to be avoided publication bias might exist. Such as some factors like age, gender, individual conditions, environment and experimental method are different, those might influence the interpretation of result in our metaanalysis.

In conclusion, the meta-analysis provided evidence that MMP9 rs3918242 polymorphism was significantly associated with CAD/ MI in Asian populations. The same of available evidence supports the fact that the

	Cas	е	Conti	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 CAD							
Chen et al-b.[2007]	23	220	12	140	2.5%	1.25 [0.60, 2.59]	
Cho et al.[2002]	15	126	4	134	1.4%	4.39 [1.42, 13.62]	· · · · · · · · · · · · · · · · · · ·
Fallah et al.[2010]	79	290	114	314	4.6%	0.66 [0.46, 0.93]	
Gao et al.[2010]	56	192	20	156	3.3%	2.80 [1.59, 4.92]	
Han et al.[2012]	27	182	27	202	3.2%	1.13 [0.63, 2.01]	
Kim et al.[2002]	32	262	32	234	3.5%	0.88 [0.52, 1.48]	
Lu et al.[2014]	70	336	54	416	4.4%	1.76 [1.20, 2.60]	
Meng et al.[2006]	26	234	20	198	3.0%	1.11 [0.60, 2.06]	
Spurthi et al.[2012]	73	200	58	200	4.2%	1.41 [0.92, 2.14]	
Wang et al.[2007]	19	128	18	168	2.7%	1.45 [0.73, 2.90]	
Wu et al-a.[2009]	171	1582	145	1378	5.3%	1.03 [0.82, 1.30]	+
Wu et al.[2013]	74	516	22	306	3.7%	2.16 [1.31, 3.56]	
Xu et al.[2013]	119	764	107	932	5.1%	1.42 [1.07, 1.88]	
Yang et al.[2013]	61	480	43	400	4.2%	1.21 [0.80, 1.83]	
Yong et al.[2010]	32	256	14	212	2.8%	2.02 [1.05, 3.90]	
Yuan et al.[2014]	15	122	18	110	2.5%	0.72 [0.34, 1.50]	
Zhang et al.[2008]	28	184	12	190	2.6%	2.66 [1.31, 5.41]	
Zhi et al.[2010]	180	1524	116	1110	5.3%	1.15 [0.90, 1.47]	†
Subtotal (95% CI)		7598		6800	64.4%	1.35 [1.12, 1.62]	•
Total events	1100		836				
Heterogeneity: Tau ² = 0.	09; Chi² =	48.56, 0	df = 17 (P	< 0.000	01); l ² = 65%	6	
Test for overall effect: Z	= 3.16 (P	= 0.002					
1.1.2 MI							
Chen et al-a.[2007]	58	300	12	140	2.8%	2.56 [1.32, 4.93]	
Chen et al.[2007] Chen et al.[2005]	21	156	8	162	2.8%	2.99 [1.28, 6.98]	
	67	468	65	400	4.5%	0.86 [0.59, 1.25]	
Ghaderian et al.[2011]	58	400	31	346	4.5% 3.9%		
Koh et al.[2008]		694		806	3.9% 4.7%	1.66 [1.05, 2.64]	
Ma et al.[2010]	109 29	202	61 15	210	2.8%	2.28 [1.63, 3.17]	
Tang et al.[2005]		704	71	842	2.8% 4.8%	2.18 [1.13, 4.20]	
Wang et al.[2011]	102 109	768	84	902	4.8% 4.9%	1.84 [1.33, 2.54] 1.61 [1.19, 2.18]	
Wang et al.[2012] Wu et al-b.[2009]	85	740	04 145	1378	4.9% 5.0%		
Subtotal (95% CI)	60	4444	145	5186	35.6%	1.10 [0.83, 1.47] 1.66 [1.29, 2.14]	•
Total events	638		492				
Heterogeneity: $Tau^2 = 0$.		27.15		= 0.0007	′); ² = 71%		
Test for overall effect: Z					,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
Total (95% CI)		12042		11986	100.0%	1.45 [1.25, 1.69]	•
Total events	1738	12042	1328	11500	100.070	1.45 [1.25, 1.05]	↓ ▼
Heterogeneity: Tau ² = 0.		02 01		< 0.000	01). 12 - 60		
0,		,		< 0.00C	joij; i- – 69	7/0	0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z			,	- 0.48	12 - 42 20/		Favours [case] Favours [control]
Test for subaroup differe	nces: Chi	- = 1.76.	dt = 1 (P)	= 0.18)	. 1~ = 43.3%		

Figure 5: Forest plot of the meta-analysis of the association between MMP-9 C-1562T(rs3918242) and CAD or MI risks in an allele genetic model in Asians subgroup.

Table 2: Results From a meta-analysis of the association between CAD and matrix metalloproteinase 9 C-1562T polymorphism

								Gen	otype		
Polymorphism	and Subgroup		No. of Studies	No. of Cases	No. of Controls	T/C		TT/CT+C	С	CT+TT	/CC
						OR and 95% CI	P Value	OR and 95% CI	P Value	OR and 95% CI	P Value
	All popula	tion	37	13035	11372	1.34 (1.20, 1.50)	< 0.00001	1.43 (1.17, 1.75)	0.0004	1.36 (1.20, 1.53)	< 0.00001
Ethnicity	Caucasia	an	10	7014	5379	1.11 (0.99, 1.25)	0.07	1.06 (0.80, 1.40)	0.70	1.13 (1.01, 1.26)	0.03
	Asian		27	6021	5993	1.45 (1.25, 1.69)	< 0.00001	1.94 (1.45, 2.58)	< 0.00001	1.48 (1.25, 1.75)	< 0.00001
	Caucasian	CAD	6	4966	1560	1.08 (0.96, 1.23)	0.20	1.07 (0.71, 1.61)	0.75	1.09 (0.95, 1.26)	0.20
	Caucasian	MI	4	2048	3819	1.14 (1.02, 1.27)	0.02	1.05 (0.71, 1.55)	0.81	1.17 (1.04, 1.32)	0.01
Outcome	Asian	CAD	18	3799	3400	1.35 (1.12, 1.62)	0.002	1.73 (1.20, 2.51)	0.004	1.35 (1.11, 1.65)	0.003
	i ssan	MI	9	2222	2593	1.66 (1.29, 2.14)	< 0.0001	2.29 (1.44, 3.63)	0.004	1.74 (1.29, 2.35)	0.0003

	Case	•	Conti	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.1.1 CAD							
Chen et al-b.[2007]	5	110	3	70	5.0%	1.06 [0.25, 4.60]	
Cho et al.[2002]	0	63	0	67		Not estimable	
Fallah et al.[2010]	11	145	19	157	24.0%	0.60 [0.27, 1.30]	
Gao et al.[2010]	9	96	1	78	1.4%	7.97 [0.99, 64.31]	
Han et al.[2012]	1	91	1	101	1.3%	1.11 [0.07, 18.02]	· · · ·
Kim et al.[2002]	0	131	0	117		Not estimable	
Lu et al.[2014]	4	168	2	208	2.5%	2.51 [0.45, 13.89]	
Meng et al.[2006]	0	117	1	99	2.3%	0.28 [0.01, 6.94]	• • •
Spurthi et al.[2012]	13	100	6	100	7.4%	2.34 [0.85, 6.43]	
Wang et al.[2007]	1	64	0	84	0.6%	3.99 [0.16, 99.63]	· · · ·
Wu et al-a.[2009]	8	791	1	689	1.5%	7.03 [0.88, 56.34]	
Wu et al.[2013]	9	258	0	153	0.9%	11.69 [0.68, 202.27]	
Xu et al.[2013]	5	382	2	466	2.5%	3.08 [0.59, 15.95]	
Yang et al.[2013]	7	240	4	200	6.0%	1.47 [0.42, 5.10]	
Yong et al.[2010]	1	128	0	106	0.8%	2.51 [0.10, 62.15]	· · · · ·
Yuan et al.[2014]	2	61	1	55	1.5%	1.83 [0.16, 20.76]	
Zhang et al.[2008]	3	92	0	95	0.7%	7.47 [0.38, 146.64]	
Zhi et al.[2010]	3	762	3	555	4.9%	0.73 [0.15, 3.62]	
Subtotal (95% CI)	-	3799	-	3400	63.4%	1.73 [1.20, 2.51]	•
Total events	82		44			• • •	
Heterogeneity: Chi ² = 17.	.88. df = 1	5 (P =	0.27): l ² =	= 16%			
Test for overall effect: Z =	,		//				
1.1.2 MI							
	5	150	3	70	5.6%	0.77 [0.18, 3.32]	
Chen et al-a.[2007]	5 0	150 78	3	70 81	5.6%	0.77 [0.18, 3.32] Not estimable	
Chen et al-a.[2007] Chen et al.[2005]	0	78	0	81		Not estimable	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011]	0 10	78 234	0 6	81 200	8.8%	Not estimable 1.44 [0.52, 4.04]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008]	0 10 3	78 234 206	0 6 0	81 200 173	8.8% 0.8%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010]	0 10 3 13	78 234 206 347	0 6 0 4	81 200 173 403	8.8% 0.8% 5.1%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Tang et al.[2005]	0 10 3 13 1	78 234 206 347 101	0 6 0 4 1	81 200 173 403 105	8.8% 0.8% 5.1% 1.4%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Fang et al.[2005] Wang et al.[2011]	0 10 3 13 1 11	78 234 206 347 101 352	0 6 0 4 1 5	81 200 173 403 105 421	8.8% 0.8% 5.1% 1.4% 6.3%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012]	0 10 3 13 1	78 234 206 347 101 352 384	0 6 0 4 1	81 200 173 403 105 421 451	8.8% 0.8% 5.1% 1.4% 6.3% 7.6%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009]	0 10 3 13 1 11 11	78 234 206 347 101 352 384 370	0 6 0 4 1 5 6	81 200 173 403 105 421 451 689	8.8% 0.8% 5.1% 1.4% 6.3% 7.6% 1.0%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97] 7.52 [0.84, 67.52]	
1.1.2 MI Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events	0 10 3 13 1 11 11	78 234 206 347 101 352 384	0 6 0 4 1 5 6	81 200 173 403 105 421 451	8.8% 0.8% 5.1% 1.4% 6.3% 7.6%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events	0 10 3 13 1 11 11 4 58	78 234 206 347 101 352 384 370 2222	0 6 0 4 1 5 6 1 26	81 200 173 403 105 421 451 689 2593	8.8% 0.8% 5.1% 1.4% 6.3% 7.6% 1.0%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97] 7.52 [0.84, 67.52]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI)	0 10 3 13 1 11 11 4 58 68, df = 7 (78 234 206 347 101 352 384 370 2222 (P = 0.5	0 6 0 4 1 5 6 1 26 88); I ² = 0	81 200 173 403 105 421 451 689 2593	8.8% 0.8% 5.1% 1.4% 6.3% 7.6% 1.0%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97] 7.52 [0.84, 67.52]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2000] Mang et al.[2005] Wang et al.[2011] Wu et al-b.[2009] Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5.6 Test for overall effect: Z =	0 10 3 13 1 11 11 4 58 68, df = 7 (78 234 206 347 101 352 384 370 2222 (P = 0.5	0 6 0 4 1 5 6 1 26 88); I ² = 0	81 200 173 403 105 421 451 689 2593 %	8.8% 0.8% 5.1% 1.4% 6.3% 7.6% 1.0%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97] 7.52 [0.84, 67.52]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5.6 Test for overall effect: Z = Total (95% CI)	0 10 3 13 1 11 11 4 58 88, df = 7 (= 3.52 (P =	78 234 206 347 101 352 384 370 2222 (P = 0.5 = 0.000	0 6 0 4 1 5 6 1 26 8); ² = 0 4)	81 200 173 403 105 421 451 689 2593 %	8.8% 0.8% 5.1% 1.4% 6.3% 7.6% 1.0% 36.6%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97] 7.52 [0.84, 67.52] 2.29 [1.44, 3.63]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2000] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5.6 Test for overall effect: Z = Total (95% CI) Total events	0 10 3 13 11 11 11 4 58 88, df = 7 (f = 3.52 (f) =	78 234 206 347 101 352 384 370 2222 (P = 0.5 = 0.000 6021	0 6 0 4 1 5 6 1 26 88); I ² = 0 4) 70	81 200 173 403 105 421 451 689 2593 %	8.8% 0.8% 5.1% 1.4% 6.3% 7.6% 1.0% 36.6%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97] 7.52 [0.84, 67.52] 2.29 [1.44, 3.63]	
Chen et al-a.[2007] Chen et al.[2005] Ghaderian et al.[2011] Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5.6 Test for overall effect: Z = Total (95% CI)	0 10 3 13 1 11 11 4 58 88, df = 7 (= 3.52 (P = = 3.52 (P = = 140 .81, df = 2	78 234 206 347 101 352 384 370 2222 (P = 0.5 = 0.000 6021	0 6 0 4 1 5 6 1 26 88); I ² = 0 4) 70 0.36); I ² =	81 200 173 403 105 421 451 689 2593 %	8.8% 0.8% 5.1% 1.4% 6.3% 7.6% 1.0% 36.6%	Not estimable 1.44 [0.52, 4.04] 5.97 [0.31, 116.34] 3.88 [1.25, 12.02] 1.04 [0.06, 16.85] 2.68 [0.92, 7.80] 2.19 [0.80, 5.97] 7.52 [0.84, 67.52] 2.29 [1.44, 3.63]	0.1 0.2 0.5 1 2 5 10 Favours [case] Favours [control]

Figure 6: Forest plot of the meta-analysis of the association between MMP-9 C-1562T(rs3918242) and CAD or MI risks in a recessive genetic model in Asians subgroup.

rs3918242 is a risk factor for MI in Caucasian populations. Larger studies with the consideration of more influence factors and better study designs are still required to further evaluate the connection of MMP9 rs3918242 polymorphism with CAD/MI susceptibility.

MATERIALS AND METHODS

Literature search

All studies that researched the association between the rs3918242 polymorphism and CAD were identified by comprehensive computer-based searches of PubMed, Web of Science, the Cochrane Library, Wanfang Data and China National Knowledge Infrastructure (CNKI). The language was limited to English and Chinese articles before Feb.2016. The following keywords were used : #1 matrix metalloproteinase [MeSH]; #2 matrix metalloproteinase 9 [MeSH]; #3 polymorphism [MeSH]; #4 mutation [MeSH]; #5 variation [MeSH]; #6 genotype [MeSH]; #7 coronary artery disease [MeSH]; #8 coronary heart disease [MeSH]; #9 myocardial Infarction [MeSH]; #10 ischemic cardiovascular disease[MeSH]. The retrieval strategy is #1 or #2 and #3 or #4 or #5 or #6 and #7 or #8 or #9 or #10.

Inclusion criteria

The diagnosis of CAD was fitted to the examination results of coronary arteriography, treadmill exercise test,

	Case	е	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 CAD					_		
Chen et al-b.[2007]	18	110	9	70	2.4%	1.33 [0.56, 3.14]	
Cho et al.[2002]	15	63	4	67	1.6%	4.92 [1.54, 15.78]	
Fallah et al.[2010]	68	145	95	157	4.2%	0.58 [0.36, 0.91]	
Gao et al.[2010]	47	96	19	78	3.2%	2.98 [1.55, 5.73]	
Han et al.[2012]	26	91	26	101	3.3%	1.15 [0.61, 2.18]	
Kim et al.[2002]	32	131	32	117	3.6%	0.86 [0.49, 1.52]	
_u et al.[2014]	66	168	52	208	4.3%	1.94 [1.25, 3.02]	
Meng et al.[2006]	26	117	19	99	3.1%	1.20 [0.62, 2.34]	
Spurthi et al.[2012]	60	100	52	100	3.7%	1.38 [0.79, 2.42]	- +-
Wang et al.[2007]	18	64	18	84	2.8%	1.43 [0.68, 3.05]	
Wu et al-a.[2009]	163	791	144	689	5.4%	0.98 [0.76, 1.26]	-+-
Wu et al.[2013]	65	258	22	153	3.8%	2.01 [1.18, 3.41]	— —
Xu et al.[2013]	114	382	105	466	5.1%	1.46 [1.07, 1.99]	
Yang et al.[2013]	54	240	39	200	4.2%	1.20 [0.75, 1.90]	- !- -
Yong et al.[2010]	31	128	14	106	3.0%	2.10 [1.05, 4.20]	
Yuan et al.[2014]	13	61	17	55	2.4%	0.61 [0.26, 1.40]	
Zhang et al.[2008]	25	92	12	95	2.7%	2.58 [1.21, 5.52]	
Zhi et al.[2010]	177	762	113	555	5.3%	1.18 [0.91, 1.54]	
Subtotal (95% CI)		3799	110	3400	64.1%	1.35 [1.11, 1.65]	•
Total events	1018		792				
Heterogeneity: Tau ² = 0.		= 45 23		P = 0.0	$(02) \cdot I^2 = 6$	32%	
Test for overall effect: Z				0.0	<i>502)</i> , 1 0	5270	
1.1.2 MI							
Chen et al-a.[2007]	53						
Chen et al.[2005]		150	9	70	27%	3 70 [1 70 8 04]	
		150 78	9 8	70 81	2.7% 2.3%	3.70 [1.70, 8.04] 3.36 [1.39, 8.15]	
Shaderian et al [2011]	21	78	8	81	2.3%	3.36 [1.39, 8.15]	
Ghaderian et al.[2011]	21 57	78 234	8 59	81 200	2.3% 4.4%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18]	
Koh et al.[2008]	21 57 55	78 234 206	8 59 31	81 200 173	2.3% 4.4% 4.0%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74]	
Koh et al.[2008] Ma et al.[2010]	21 57 55 96	78 234 206 347	8 59 31 57	81 200 173 403	2.3% 4.4% 4.0% 4.8%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005]	21 57 55 96 28	78 234 206 347 101	8 59 31 57 14	81 200 173 403 105	2.3% 4.4% 4.0% 4.8% 2.9%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011]	21 57 55 96 28 91	78 234 206 347 101 352	8 59 31 57 14 66	81 200 173 403 105 421	2.3% 4.4% 4.0% 4.8% 2.9% 4.8%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012]	21 57 55 96 28 91 98	78 234 206 347 101 352 384	8 59 31 57 14 66 78	81 200 173 403 105 421 451	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009]	21 57 55 96 28 91	78 234 206 347 101 352 384 370	8 59 31 57 14 66	81 200 173 403 105 421 451 689	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9% 5.1%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29] 1.06 [0.78, 1.44]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI)	21 57 55 96 28 91 98 81	78 234 206 347 101 352 384	8 59 31 57 14 66 78 144	81 200 173 403 105 421 451	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events	21 57 55 96 28 91 98 81 580	78 234 206 347 101 352 384 370 2222	8 59 31 57 14 66 78 144 466	81 200 173 403 105 421 451 689 2593	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9% 5.1% 35.9%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29] 1.06 [0.78, 1.44] 1.74 [1.29, 2.35]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.	21 57 55 96 28 91 98 81 580 .15; Chi ² =	78 234 206 347 101 352 384 370 2222 = 31.67,	8 59 31 57 14 66 78 144 466 df = 8 (P	81 200 173 403 105 421 451 689 2593	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9% 5.1% 35.9%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29] 1.06 [0.78, 1.44] 1.74 [1.29, 2.35]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events	21 57 55 96 28 91 98 81 580 .15; Chi ² =	78 234 206 347 101 352 384 370 2222 = 31.67,	8 59 31 57 14 66 78 144 466 df = 8 (P	81 200 173 403 105 421 451 689 2593	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9% 5.1% 35.9%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29] 1.06 [0.78, 1.44] 1.74 [1.29, 2.35]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2005] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.	21 57 55 96 28 91 98 81 580 .15; Chi² = = 3.60 (P	78 234 206 347 101 352 384 370 2222 = 31.67,	8 59 31 57 14 66 78 144 466 df = 8 (P	81 200 173 403 105 421 451 689 2593 = 0.000	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9% 5.1% 35.9%	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29] 1.06 [0.78, 1.44] 1.74 [1.29, 2.35]	
Koh et al. [2008] Ma et al. [2010] Tang et al. [2005] Wang et al. [2011] Wang et al. [2012] Wu et al-b. [2009] Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0. Total (95% CI) Total (95% CI) Total events	21 57 55 96 28 91 98 81 .15; Chi ² = = 3.60 (P 1598	78 234 206 347 101 352 384 370 2222 = 31.67, = 0.000 6021	8 59 31 57 14 66 78 144 466 df = 8 (P 3)	81 200 173 403 105 421 451 689 2593 = 0.000 5993	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9% 5.1% 35.9% 01); l ² = 75	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29] 1.06 [0.78, 1.44] 1.74 [1.29, 2.35]	
Koh et al.[2008] Ma et al.[2010] Tang et al.[2015] Wang et al.[2011] Wang et al.[2012] Wu et al-b.[2009] Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z	21 57 55 96 28 91 98 81 .15; Chi ² = = 3.60 (P 1598	78 234 206 347 101 352 384 370 2222 = 31.67, = 0.000 6021	8 59 31 57 14 66 78 144 466 df = 8 (P 3)	81 200 173 403 105 421 451 689 2593 = 0.000 5993	2.3% 4.4% 4.0% 4.8% 2.9% 4.8% 4.9% 5.1% 35.9% 01); l ² = 75	3.36 [1.39, 8.15] 0.77 [0.50, 1.18] 1.67 [1.02, 2.74] 2.32 [1.61, 3.35] 2.49 [1.22, 5.08] 1.88 [1.32, 2.67] 1.64 [1.17, 2.29] 1.06 [0.78, 1.44] 1.74 [1.29, 2.35] 5% 1.48 [1.25, 1.75]	↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓

Figure 7: Forest plot of the meta-analysis of the association between MMP-9 C-1562T(rs3918242) and CAD or MI risks in a dominant genetic model in Asians subgroup.

clinical symptoms combined with electrocardiogram, as well as some other inspection project, for example echocardiography and myocardial perfusion imaging. The inclusion criteria for eligible studies were as follows: (1) independent case-control studies using either a hospitalbased or a population-based design; (2) the studies of MMP9 C-1562T polymorphism and CAD risk; (3) the studies has an intact original data on genotype distribution and a comprehensive statistical index, sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); (4) no repeat published data.

Exclusion criteria

We excluded studies if (1) reviews, editorials, and articles with insufficient information; (2) the genotype distribution in the control group non-conformity the Hardy-Weinberg equilibrium.

Data extraction

Two authors independently extracted the data. The extracted information included the first author's name,

publication year, study population, number of genotypes, genotyping methods, allele frequency of cases and controls, sample sizes in the cases and controls, sex and age of cases and controls. Disagreement was resolved by consensus. If these two authors could not reach a consensus, the result was reviewed by a third author.

Quality assessment

To determine the methodological quality of the included studies, we used the Newcastle–Ottawa scale [49], which uses a "star" rating system to judge the quality of observational studies. The NOS ranges between zero (worst) up to nine stars (best). Two authors assessed the quality of included studies independently and solved disagreement through discussion.

Statistical analysis

The association between rs3918242 polymorphism and CAD, which in our meta-analysis were compared by using the OR and its corresponding to 95% CI. Hardy– Weinberg equilibrium (HWE) was assessed by Chi-square

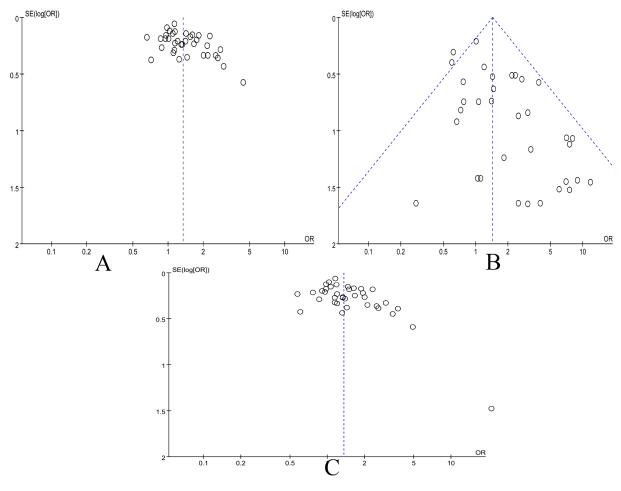


Figure 8: Funnel plot of the association between MMP-9 C-1562T(rs3918242) and CAD risk in all populations. (A) The allele genetic model in all populations. (B) The recessive genetic model in all populations. (C) The dominant genetic model in all populations.

test in control groups, and P < 0.05 was considered a significant departure from HWE. Heterogeneity between studies was assessed by I² test, p < 0.10 and I² > 50% indicated evidence of heterogeneity. If heterogeneity existed among the studies, the random effects model was used to estimate the pooled OR (the DerSimonian and Kacker method). Otherwise, the fixed effects model was adopted (the Mantel-Haenszel method) [50, 51]. The associations between the genetic variant and CAD risk of pooled ORs were performed for a recessive genetic model, dominant genetic model and allelic contrast. Z test was used to determine the pooled OR and significance was set at p < 0.05. Besides, subgroup analyses were stratified by ethnicity and outcome. The potential publication bias was checked by using funnel plots and Egger's test [52]. The statistical analysis was performed by using Review Manager 5.30 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen) and Stata 12.0 software (StataCorp, College Station, TX, USA). A two-tailed *p* < 0.05 was considered significant.

Author contributions

MMZ, XX and SYZ conceived the study, participated in the design, collected the data, performed statistical analyses, and drafted the manuscript. XQH, XWC and WH conceived the study and revised manuscript. HW participated in the design, and helped to draft the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS AND FUNDING

This study was supported by Luoyang Science and Technology Projects (No. 1201050A-1) and the project of Henan Science and Technology (NO.122300410234).

CONFLICTS OF INTEREST

The authors declared that they have no competing interests.

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