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Relationships of *OPG* Genetic Polymorphisms with Susceptibility to Cardiovascular Disease: A Meta-Analysis

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The aim of this meta-analysis was to determine whether genetic polymorphisms in the osteoprotegerin (*OPG*) gene contribute to increased risk of cardiovascular disease (CVD).

Material/Methods: Electronic databases were searched carefully without any language restriction. Analyses of data were conducted using STATA software. Odds ratios (OR) and 95% confidence intervals (95%CI) were also calculated.

Results: Seven clinical case-control studies that enrolled 1170 CVD patients and 1194 healthy subjects were included. The results indicated that *OPG* gene polymorphism might be closely associated with susceptibility to CVD, especially for rs2073617 T>C and rs2073618 G>C polymorphisms. Ethnicity-stratified analysis indicated that genetic polymorphism in the *OPG* were closely related with the pathogenesis of CVD among Asians (all $P<0.001$), but no obvious relationship was found among Caucasians (all $P>0.05$).

Conclusions: Our meta-analysis provided quantitative evidence that *OPG* gene polymorphism may be closely related to an increased risk of CVD, especially for rs2073617 T>C and rs2073618 G>C polymorphisms.

MeSH Keywords: Cardiovascular Diseases • Meta-Analysis • Polymorphism, Genetic • RANK Ligand

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Background

Cardiovascular disease (CVD), a leading cause of death worldwide, refers to any disease that affects the human cardiovascular system, primarily including cardiac diseases, vascular diseases of the brain and kidney, and peripheral arterial disease [1]. It is reported that CVD accounts for approximately 30% of all deaths worldwide, and the mortality rates of CVD vary between developed countries and low- and middle-income countries [2]. Furthermore, it has been estimated that approximately 82,600,000 American adults have 1 or more types of CVD, and about half of those people are over 60 years old [3]. Typically, CVD is a multifactorial disease caused by a combination of genetic and non-genetic factors [4,5]. Though massive environmental factors have been established in CVD, including smoking, unhealthy diet, reduced physical activity, obesity, stress, diabetes, hypertension, behavior, and lifestyle changes, genetic factors also have been demonstrated to be vital in the pathogenesis of CVD [4,6–8]. Growing evidence has indicated that genetic polymorphisms of some special genes play vital roles in the pathogenesis of CVD [9,10]. During the past decades, epidemiological studies have documented that osteoprotegerin (OPG), which is normally produced in vascular smooth muscle and endothelial cells, might be strongly related to the development of CVD [5,11].

OPG is a secreted basic glycoprotein that is a part of tumor necrosis factor (TNF) receptor super-family [12]. OPG was observed to be synthesized by osteoblasts and is found in a variety of organs and tissues, such as kidney, heart, lung, bone, and vessel wall [13]. By binding to the receptor activator of nuclear factor-γB ligand (RANKL), OPG can modulate bone resorption, functioning as a decoy receptor. It is also important for the survival, differentiation, and activation of osteoclasts and can regulate osteoblast-osteoclast cross-talks and bone homeostasis [14]. Recently, serum OPG level was demonstrated to be correlated with the severity of atherosclerosis, particularly with the progression of CVD [5,15]. This was partly because arterial wall calcification may be related to reduced bone mineral density and increased incidence of fractures [16,17]. Bone metabolism involves alternate cycles of bone resorption and formation, and the RANKL-OPG system may be beneficial in the maturation of osteoclasts [18]. The potential relationship between OPG and calcification in arterial walls was investigated in several experimental studies, which illustrated that *OPG* gene knockout mice also have aortic calcification and osteoporosis at the same time [19]. In this regard, OPG may play a crucial role in arterial wall calcification, and thus contribute to the development of CVD. More importantly, genetic polymorphisms related to alteration in expression of OPG may also be predisposing factors for the risk of CVD [11,14]. The human *OPG* gene is located on chromosome 8q23-24; it spans approximately 29 kb and consists of 5 exons [20]. Many

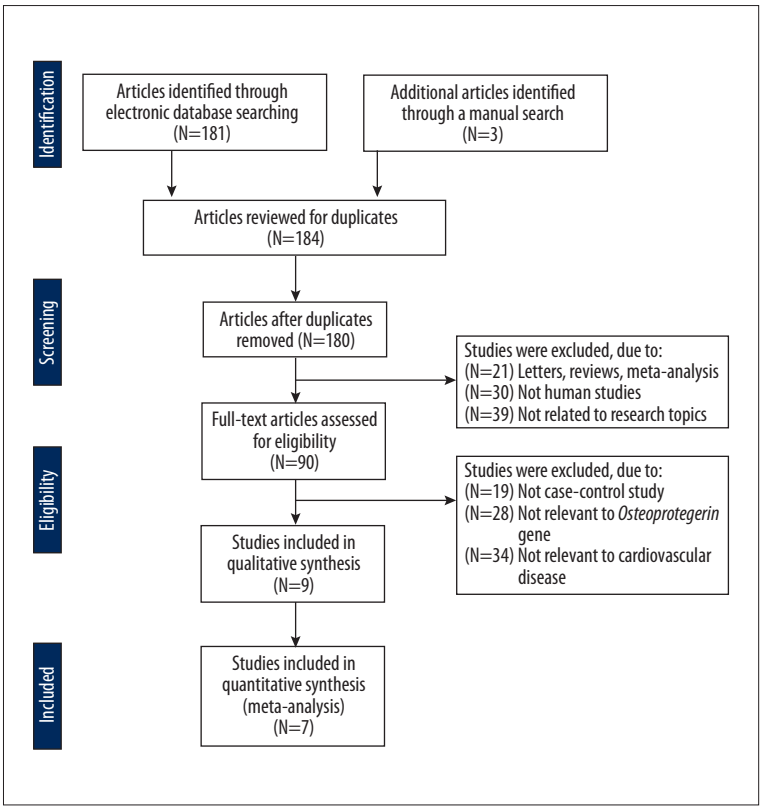

Figure 1. Flow chart shows study selection procedure. Seven case-control studies were included in this meta-analysis.

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Table 1. Main characteristics and methodological quality of all eligible studies.

First author	Year	Language	Disease	Number		Gender (M/F)		Age (years)		Genotype methods	SNP	NOS score
				Case	Control	Case	Control	Case	Control			
Luo ZR [28]	2012	Asians	ACS	360	360	216/144	210/150	66.0 ±5.0	60.0 ±10.0	PCR–RFLP	rs2073617 T>C	8
											rs2073618 G>C	
Hong WL [27]	2012	Asians	ACS	69	65	–	–	70.1 ±10.9	63.7 ±10.8	PCR–LDR	rs2073618 G>C	5
Celczynska-Bajew L [22]	2011	Caucasians	CAD	31	30	0/31	0/30	66 (39~82)	71 (56~84)	Minisequencing	rs2073618 G>C	6
Fang K [23]	2010	Asians	CHD	150	150	106/44	95/55	64.0 ±10.0	58.0 ±10.0	PCR–RFLP	rs2073617 T>C	7
											rs2073618 G>C	
Xu L [24]	2009	Asians	CHD	48	102	–	–	–	–	PCR–RFLP	rs2073617 T>C	5
Ohmori R [13]	2006	Asians	CAD	405	126	405/0	126/0	63.0 ±9.0	59.0 ±10.0	TaqMan assay	rs2073617 T>C	8
											rs2073617 T>C	
Soufi M [14]	2004	Caucasians	CAD	107	361	107/0	361/0	58.5 ±8.9	–	TaqMan assay	rs2073617 T>C	7
											rs2073618 G>C	

M – male; F – female; SNP – single-nucleotide polymorphisms; NOS – Newcastle-Ottawa Scale; CAD – coronary artery disease; ACS – acute coronary syndrome; CHD – coronary heart disease; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; PCR-LDR – PCR-ligase detection reaction.

reports have focused on the relation between genetic polymorphisms in *OPG* gene and susceptibility to CVD, especially for rs2073617 T>C and rs2073618 G>C polymorphisms [13,21,22]. However, the results from relevant studies were inconclusive and contradictory [23,24]. Therefore, we performed this meta-analysis to examine the connection between *OPG* genetic polymorphisms and pathogenesis of CVD.

Material and Methods

Literature search and selection criteria

The Cochrane Library Database, MEDLINE, EMBASE, the Chinese Biomedical Database (CBM), and Web of Science databases were searched carefully without any language restriction. The following keywords and MeSH terms were used: ("genetic polymorphism" or "SNP" or "variation" or "single nucleotide polymorphism" or "polymorphism" or "mutation" or "variant") and ("osteoprotegerin" or "TNFRSF11B" or "OPG" or "osteoclastogenesis inhibitory factor" or "follicular dendritic cell-derived receptor-1" or "FDCR-1 protein" or "tumor necrosis factor receptor 11b") and ("coronary artery disease" or "acute coronary syndrome" or "myocardial infarction" or "coronary arteriosclerosis" or "MI" or "CAD" or "CHD" or "ischemic heart disease" or "ACS" or "cardiovascular disease" or "CVD"). Moreover, a manual search was carried out to acquire other potential studies.

Inclusion criteria were: (1) studies focus on the relations between *OPG* gene polymorphism and susceptibility to CVD; (2) all patients should be diagnosed with any type of cardiovascular diseases, such as coronary artery disease (CAD), acute coronary syndrome (ACS), and ischemic heart disease (IHD); (3) the genotype frequencies of control subjects should follow Hardy-Weinberg equilibrium (HWE); (4) sufficient data about frequency of *OPG* polymorphisms must be provided. Articles that did not fit these inclusion criteria were eliminated.

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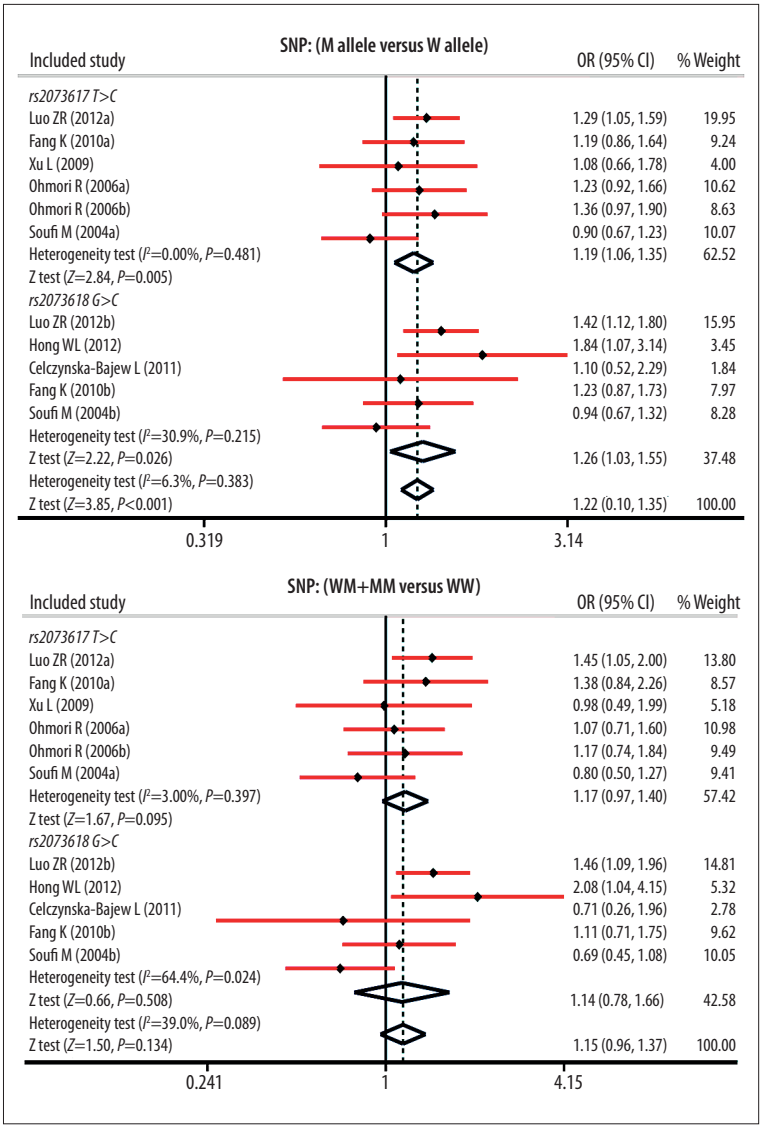

Figure 2. Forest plots for the influences of *OPG* genetic polymorphisms and cardiovascular disease under the allele and dominant models.

Data extraction

The following information from included studies was extracted by 2 authors: first author's surname, publication year, language, geographical location, subject source, study design, total number of cases, sample size, the frequency of single-nucleotide polymorphisms (SNPs), detection method of genotypes, and type of disease.

Statistical analysis

Statistical data were analyzed with STATA statistical software (Version 12.0, College Station, TX, USA). Odds ratios (OR) and corresponding 95% confidence intervals (95%CI) were estimated. The significance of pooled data and ORs were evaluated by *Z* test. Heterogeneity between reports was analyzed using the Cochran's *Q*-statistic and I^2 tests [25]. A *P* value <0.05 or I^2 >50% means studies were heterogeneous, in which case the random-effects model was used; otherwise, the fixed-effects model was used. Meta-regression and subgroup analyses were also applied to explore sources of heterogeneity. Sensitivity analysis was also performed. Potential publication bias was examined using Funnel plots and Egger's test [26].

Results

Study selection and characteristics of included studies

Initially, our search strategy obtained 184 articles. We screened the titles and abstracts and then removed 90 articles. After reviewing the full texts, we excluded 81 articles. In addition, 2 studies were eliminated for lack of data integrity (Figure 1). Finally, 7 clinical case-control studies that

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Table 2. Meta-analysis of the relationships of *opg* gene with the cardiovascular disease.

	M allele *vs.* W allele (allele model)			WM + MM *vs.* WW (dominant model)			MM *vs.* WW + WM (recessive model)			MM *vs.* WW (homozygous model)			MM *vs.* WM (heterozygous model)		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Overall	1.22	1.10 –1.35	<0.001	1.15	0.96 –1.37	0.134	1.49	1.24 –1.79	<0.001	1.59	1.30 –1.94	<0.001	1.52	1.20 –1.92	<0.001
SNP type															
rs2073617 T>C	1.19	1.06 –1.35	0.005	1.17	0.97 –1.40	0.095	1.37	1.07 –1.75	0.013	1.46	1.12 –1.91	0.006	1.34	1.02 –1.78	0.039
rs2073618 G>C	1.26	1.03 –1.55	0.026	1.14	0.78 –1.66	0.508	1.92	1.36 –2.71	<0.001	1.88	1.32 –2.69	0.001	1.96	1.35 –2.84	<0.001
Ethnicity															
Asians	1.30	1.17 –1.45	<0.001	1.32	1.13 –1.53	<0.001	1.54	1.25 –1.89	<0.001	1.74	1.38 –2.19	<0.001	1.41	1.13 –1.77	0.002
Caucasians	0.93	0.75 –1.16	0.540	0.74	0.55 –1.00	0.050	1.48	0.82 –2.67	0.192	1.16	0.73 –1.86	0.526	2.01	0.88 –4.56	0.096
Disease															
ACS	1.37	1.20 –1.58	<0.001	1.44	1.19 –1.74	<0.001	1.59	1.21 –2.08	0.001	1.88	1.39 –2.53	<0.001	1.43	1.04 –1.97	0.028
CAD	1.09	0.95 –1.25	0.220	0.96	0.80 –1.16	0.680	1.42	1.10 –1.82	0.007	1.37	1.04 –1.81	0.024	1.60	1.13 –2.26	0.008
Genotype method															
PCR-RFLP	1.28	1.13 –1.46	<0.001	1.35	1.13 –1.61	0.001	1.39	1.10 –1.76	0.007	1.62	1.24 –2.11	<0.001	1.25	0.97 –1.61	0.084
Non-PCR-RFLP	1.15	0.95 –1.40	0.150	0.99	0.75 –1.32	0.949	1.72	1.23 –2.40	0.002	1.59	1.10 –2.29	0.014	1.93	1.32 –2.82	0.001

OPG – osteoprotegerin; W – wild allele; M – mutant allele; WW – wild homozygote; WM – heterozygote; MM – mutant homozygote; OR – odds ratio; 95%CI – 95% confidence interval; SNP – single-nucleotide polymorphisms; CAD – coronary artery disease; ACS – acute coronary syndrome; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism.

enrolled 1170 CVD patients and 1194 healthy subjects were enrolled [13,14,22–24,27,28]. The publication years of enrolled studies ranged from 2004 to 2012. Overall, 5 studies were performed among Asians, and the other 2 studies were among Caucasians. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), Minisequencing, TaqMan assay, and PCR-ligase detection reaction (PCR-LDR) method were implemented for genotyping. Two genetic polymorphisms (rs2073617 T>C and rs2073618 G>C) in *the OPG* gene were analyzed in our meta-analysis. Genotype frequencies of controls were all in HWE (all $P>0.05$). The characteristics and methodological quality of enrolled studies are demonstrated in Table 1.

Quantitative data synthesis

As presented in Figure 2, our study showed that *OPG* rs2073617 T>C and rs2073618 G>C polymorphisms had statistical significance in the allele model (rs2073617 T>C: OR=1.19, 95%CI: 1.06~1.35, $P=0.005$; rs2073618 G>C: OR=1.26, 95%CI: 1.03~1.55, $P=0.026$), but not in dominant models (both $P>0.05$). In Table 2, we summarized the results for the correlations between *OPG* gene polymorphism and susceptibility of CVD. Our findings demonstrated that *OPG* genetic polymorphisms were associated with an increased risk of CVD (M allele *vs.* W allele: OR=1.22, 95%CI: 1.10~1.35, $P<0.001$; MM *vs.* WW+WM: OR=1.49, 95%CI: 1.24~1.79, $P<0.001$; MM *vs.* WW: OR=1.59, 95%CI: 1.30~1.94, $P<0.001$; MM *vs.* WM: OR=1.52, 95%CI: 1.20~1.92, $P<0.001$; respectively.

To comprehensively evaluate the influence of *OPG* genetic polymorphisms on the pathogenesis of CVD, we also carried out subgroup analysis based on ethnicity, disease, and genotyping method. Ethnicity-stratified subgroup analysis showed that genetic polymorphisms in the *OPG* gene were closely related with the development of CVD among Asians (all $P<0.001$; respectively) but not among Caucasians (all $P>0.05$) (Figure 3). Furthermore, the results of subgroup analysis base on type of disease and genotyping method illustrated that there was a positive correlation in most subgroups.

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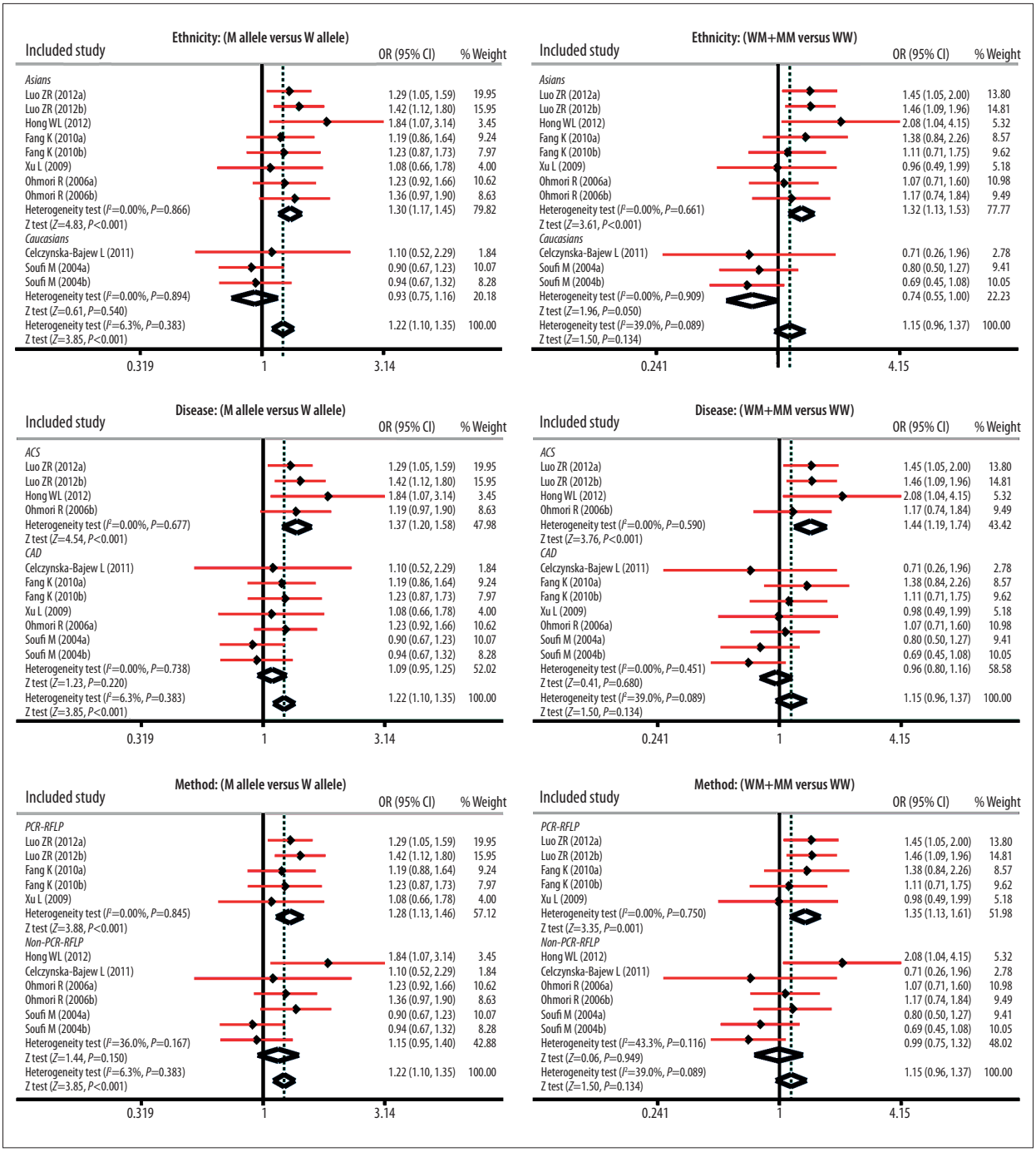

Figure 3. Subgroup analyses for the influences of *OPG* genetic polymorphisms and cardiovascular disease under the allele and dominant models.

Univariate and multivariate meta-regression analyses indicated that ethnicity may be a potential source of heterogeneity (Table 3). Sensitivity analysis revealed the overall pooled estimates were not be influenced by any single study (Figure 4). Funnel plots revealed no presence of obvious asymmetry (Figure 5). No publication bias was shown in Egger's test (all P>0.05).

Discussion

Our findings showed that both rs2073617 and rs2073618 polymorphisms in the *OPG* gene were related with an increased risk of CVD, suggesting that *OPG* genetic polymorphism may be involved in the development of CVD. However, the exact mechanism of *OPG* genetic polymorphism in the progression of CVD

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Table 3. Univariate and multivariate meta-regression analyses of potential source of heterogeneity.

Heterogeneity factors	Coefficient	SE	z	P	95%CI	
					LL	UL
Publication year						
Univariate	0.036	0.015	2.34	0.019	0.006	0.067
Multivariate	0.029	0.041	0.71	0.480	–0.051	0.109
SNP type						
Univariate	0.064	0.110	0.58	0.559	–0.151	0.280
Multivariate	0.074	0.113	0.65	0.513	–0.148	0.296
Ethnicity						
Univariate	–0.334	0.124	–2.69	0.007	–0.576	–0.091
Multivariate	–0.293	0.182	–1.61	0.107	–0.650	0.063
Disease						
Univariate	–0.233	0.098	–2.37	0.018	–0.426	0.040
Multivariate	–0.076	0.139	–0.55	0.586	–0.347	0.196
Genotyping method						
Univariate	–0.121	0.100	–1.21	0.226	–0.317	0.075
Multivariate	0.210	0.203	1.04	0.300	–0.187	0.607

SE – standard error; 95%CI – 95% confidence interval; UL – upper limit; LL – lower limit; SNP – single-nucleotide polymorphisms.

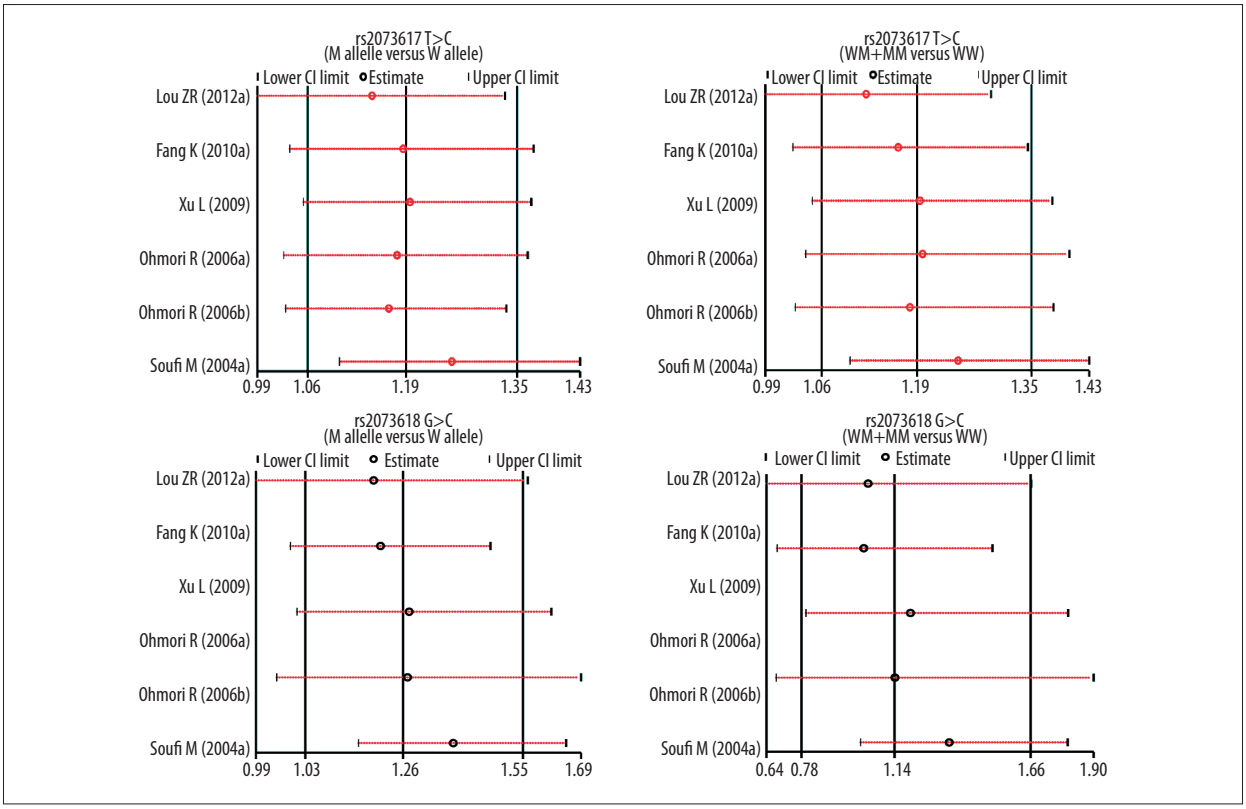

Figure 4. Sensitivity analysis for the influences of *OPG* genetic polymorphisms and cardiovascular disease under the allele and dominant models.

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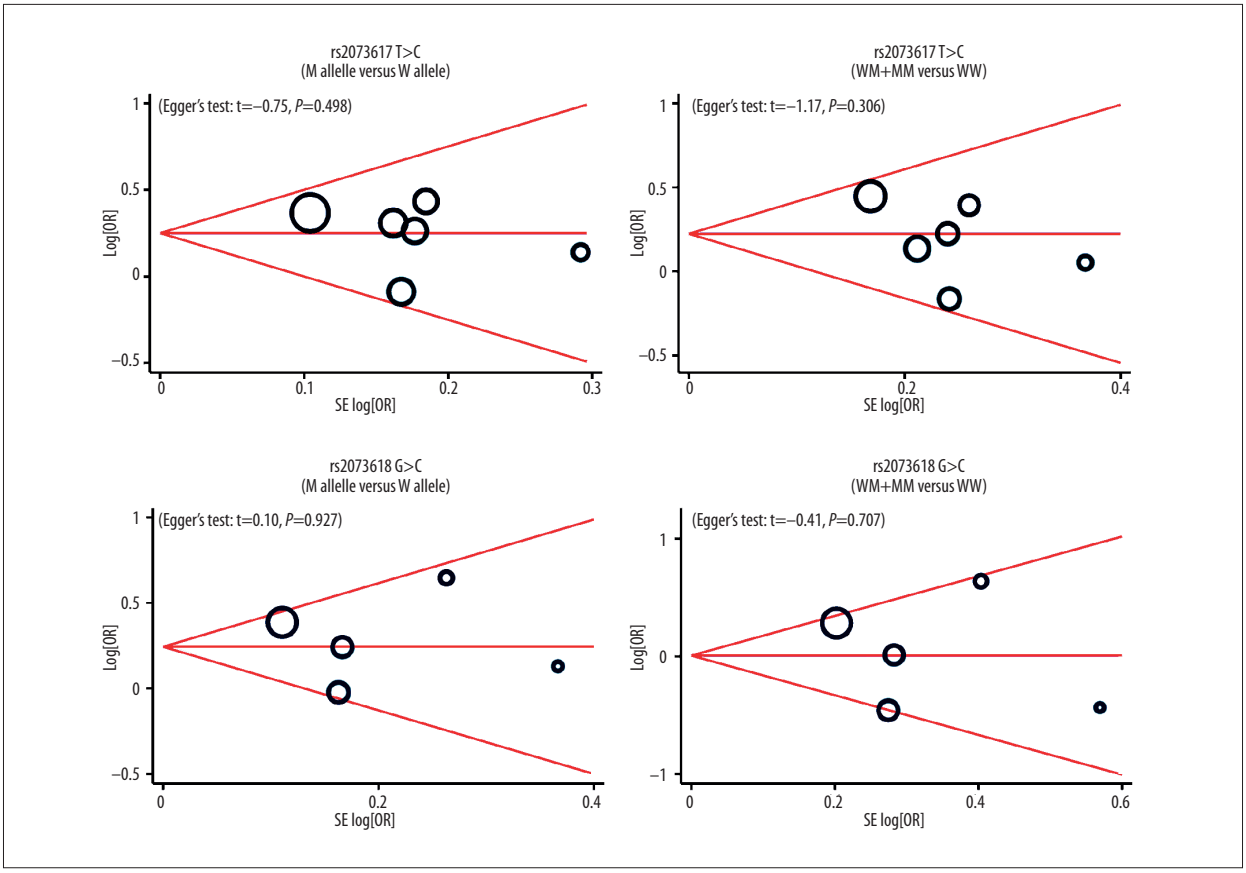

Figure 5. Funnel plot of publication biases on the relationships between genetic polymorphisms and cardiovascular disease under the allele and dominant models.

is still unclear. Clinically, OPG is a vital factor in bone remodeling, and in addition to its role in the skeletal system, it also is crucial in the development of inflammatory diseases and vascular disease [29,30]. Furthermore, it is well established that the RANK/RANKL/OPG system plays an important role in many metabolic pathways and it is involved in the regulation of bone and endothelial metabolism [22]. Since *OPG* knockout mice concurrently exhibit arterial calcification of the great arteries, *OPG* has become a critical candidate gene for the development of CVD [31]. Moreover, elevated OPG concentrations have been documented to be related with the severity of unstable angina, peripheral artery disease and heart failure, vulnerable carotid plaques, symptomatic carotid stenosis, and acute myocardial infarction [32–34]. Consequently, we hypothesized that *OPG* genetic polymorphism, which may lead to alteration of OPG expression, might be related to the pathogenesis of CVD. The polymorphisms of T950C (rs2073617 T>C) and G1181C (rs2073618 G>C) in the *OPG* gene have been investigated in our meta-analysis [13,35]. The G1181C polymorphism, located in the upstream region of exon 1, encodes the signal peptide of the OPG and causes a lysine substituted to asparagine, and the T950C polymorphism is on the promoter of *OPG* [36]. Sequence variations in the *OPG* promoter in cooperation with polymorphisms in the exon encoding for the signal peptide of this secretory protein may function synergistically in regulation of intracellular trafficking, transcription, or secretion of OPG protein [14]. Our results are consistent with a previous study that revealed that subjects with C allele in the promoter region (TC and CC) may have higher circulating levels of OPG; moreover, genetic variations in the *OPG* may confer an increased risk of CVD [35]. Ohmori et al. also supported that the 950TC/1181GC and 950CC/1181CC haplotypes were more prevalent in men with CAD than those without CAD [13]. Ethnicity-stratified analysis suggested that *OPG* polymorphism was obviously related to the development of CVD among Asians, revealing that ethnicity difference may be a causative factor influencing heterogeneity between studies. The above results demonstrate unambiguously that genetic polymorphisms in the *OPG* might be affected by ethnic differences closely related to the pathogenesis of CVD.

There were also some limitations which should be acknowledged. At first, owing to the small number of studies, we did not obtain all desired information from all documents. Consequently, our general findings may lack broad applicability and should be considered preliminary. Secondly, we could not obtain original data from the enrolled reports. However,

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our study had distinct inclusion criteria in the literature search. Future study results based on more rigorous statistical analyses may result in more credible conclusions.

Conclusions

In brief, our meta-analysis provided quantitative evidence that *OPG* genetic polymorphisms might be closely related to an increased risk of CVD, especially for rs2073617 T>C and rs2073618 G>C polymorphisms. Thus, *OPG* genetic polymorphisms may be considered as a potential candidate in early prediction of CVD. Nevertheless, due to several study limitations, large sample-size reports with more integral data are needed to acquire a more representative statistical analysis.

Competing interests

None.

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