Association between myeloperoxidase rs2333227 polymorphism and susceptibility to coronary heart disease

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Coronary heart disease (CHD) accounts for the most morbidity and mortality all over the world [1]. Heritable factors account for 30–60% of the susceptibility to coronary heart disease, and therefore genotypic variants are potential modifiers of predisposition to coronary heart disease. Our previous study demonstrated that apolipoprotein A1 polymorphism was associated with coronary artery disease [2]. Recently, researchers have revealed myeloperoxidase (MPO) as a new potential mutation associated with the pathogenesis of CHD [3]. In Piedrafita *et al.*'s study, MPO rs2333227 was reported to be associated with significantly decreased transcriptional activity due to the disruption of an SP1 (specificity protein-1)-binding site in an Alu hormone-responsive element [4]. To date, there have been many researchers studying the association between MPO rs2333227 and coronary heart disease. But the results were not consistent. Given the conflicting evidence on this issue, we conducted the present meta-analysis of all available studies to evaluate the association between MPO rs2333227 genetic polymorphism and the risk of coronary heart disease.

We performed our meta-analysis according to the "Meta-analysis Of Observational Studies in Epidemiology" (MOOSE) proposal [5]. To identify eligible studies for this meta-analysis, two investigators (Yi-Qing Zhang and Yu-Feng Jiang) searched the PubMed, Web of Science, Embase, CNKI (Chinese National Knowledge Infrastructure) and WanFang database in all languages up to March 31, 2017, combined with a manual search of reference lists from identified studies. For the article search, the following combination of medical subject heading or suitable key words was used: coronary heart disease, coronary artery disease, ischemic heart disease, angina or myocardial infarction and myeloperoxidase rs2333227 and polymorphism. The inclusion criteria were preestablished: 1) case-control designed studies; 2) studies that evaluated the association of myeloperoxidase polymorphism and susceptibility to CHD; 3) provided detailed information on genotype frequency and 4) studies that provided sufficient data to calculate odds ratios (ORs) and 95% confidential intervals for extraction. Useful data in all eligible studies were extracted by two authors (Yi-Qing Zhang and Yu-Feng Jiang). Conflicts were discussed with a third investigator (Ya-Feng Zhou). Study quality was assessed according to the 9-point Newcastle-Ottawa Scale (NOS) [6]. We performed Hardy-Weinberg equilibrium (HWE) tests

to evaluate the controls in all the included studies in this meta-analysis. We combined ORs and 95% confidence intervals (95% CI) under a fixed or random effect model to evaluate the association between myeloperoxidase polymorphism and susceptibility to CHD according to the I^2 value. To identify the potential heterogeneity, we also conducted subgroup analyses according to ethnicity, source of control, study sample size and disease subtypes (including stable angina pectoris (SAP), defined as chest pain with typical features occurring at predictable levels of exertion, and acute coronary syndrome (ACS), which occurs when an atherosclerotic plaque disrupts and results in activation of thrombocytes and coagulation factors and ultimately the formation of a thrombus). Five genetic models – allele, recessive, dominant, additive and codominant models – were used in subgroup and overall analyses. We performed a sensitivity analysis to identify latent alternation of the overall meta result by combining ORs repeatedly with omission of each study. Publication bias was shown by calculating Egger's test and drawing Begg's funnel plot, and there was no statistically significant publication bias ($p > 0.05$). All statistical tests were performed with Stata version 14.0 (Stata Corporation, USA).

Eventually, there were nineteen studies [7–25] containing 4008 cases and 3460 controls eligible for this meta-analysis. The sample sizes ranged from 128 to 2471 of all eligible studies, containing 3554 Asian ($n = 13$) and 3914 Caucasian ($n = 6$), and all but three [13, 18, 19] of them conformed to the Hardy-Weinberg equilibrium test. Moreover, all eligible studies were checked by NOS and scores were more than 6 points, showing the studies to be of high quality. Studies' characteristics are presented in Table I.

In our meta-analysis, we found that the myeloperoxidase rs2333227 polymorphism could reduce the risk of coronary heart disease in Asians but not in Caucasians (Figure 1). Although there was a significant association in the overall population, high inter-study heterogeneity was observed. After conducting subgroup analysis by ethnicity, the results grew in disparity in Asians and Caucasians with lowered individual heterogeneity, which means ethnicity might be a confounding factor in this study. In the stratified analysis of population, we noted that A allele in the Asian population is significantly related to lower risk of CHD, but not in Caucasians. This may reflect differences in genetic background and gene-environment interaction. In addition, in terms of research characteristics, the allele frequency of control in the Asian population (28.3% on average) and Caucasian population (with an average frequency of 23.0%) was significantly different. As a result, results in Caucasians should be carefully explained, and further larger studies in Caucasians are needed to further evaluate the correlation. We also conducted subgroup analysis on CHD subtypes. There were three studies reporting data on subtypes. Results were shown in Table II. According to the analysis, we found the same condition in SAP and ACS subtypes. Three studies did not fit the HWE test in the control group. After omission of these studies during the sensitivity analysis, it did not alter the conclusions made in the meta-analysis. To evaluate the publication bias of literature, we performed Begg's funnel plot and Egger's test. There is no apparent asymmetry in the shape of the funnel plots. Subsequently, the symmetry of funnel plots and statistical evidence in Egger's test indicated that in overall analyses there was no publication bias under the allele model (Egger's test, $p = 0.73$). As a result, our meta-analysis results ought to be reliable.

In general, coronary heart disease is a complicated disease, which is mainly caused by atherosclerosis and relevant to many genes and environment factors [26]. At present the therapy of coronary heart disease still involves drugs and interventional treatment. The genetic therapy of coronary heart disease remains to be explored. Since Nikpoor reported that myeloperoxidase polymorphism may be associated with coronary heart disease [8], there has been a research upsurge, but the results are varied and controversial. Meta-analysis as a powerful statistical technique could improve the reliability of the inconsistent results and find out the reason for the variation. In order to estimate the relationship between MPO RS2333227 polymorphism and susceptibility to CHD, we thus did this updated meta-analysis. The myeloperoxidase gene is located on chromosome 17q23–q24, a functional polymorphism located in the promoter region of this gene that affects its transcription [8]. Myeloperoxidase plays an important role in pro-atherosclerosis [27, 28] by decreasing nitric oxide bioavailability, oxidizing low-density lipoprotein, generating dysfunctional high-density lipoprotein and other pathways [29].

Myeloperoxidase gene polymorphism, which has been reported to be able to alter an SP1 transcription factor binding site, is a G to A replacement at a site 463 bp upstream of the transcription start site. Moreover, the presence of an A rather than G at this site disrupts the binding site for SP1 and reduces the expression of MPO enzyme in the cell [4]. Therefore, it seems that A in the 463 site will slow down the process of atherosclerosis. To date there have been no genome-wide association studies relevant to myeloperoxidase rs2333227. Previous meta-analyses [30–33] re-

Table I. Characteristics of the studies included for meta-analysis

Author	Year	Country	Ethnicity	Age [years]		Gender (M/F)		Comorbidities	Source of controls	Geno-typing method	Poly-mor-phism	NOS score	HWE test
				Case	Control	Case	Control						
Nikpoor *et al.* [8]	2001	Canada	Caucasian	59.3 (9.6)	56.8 (11.3)	177/52	92/125	HTN, HLP, diabetes, smoking	PB	PCR-RFLP	G463A	9	0.23
Lin *et al.* [9]	2006	China	Asian	58.2 (10.4)	51.6 (9.3)	80/25	79/26	HTN, HLP, diabetes, smoking	HB	PCR-RFLP	G463A	7	0.18
Honghong [10]	2006	China	Asian	60.1 (11.3)	53.6 (10.5)	138/33	60/51	HTN, HLP, diabetes, smoking	HB	PCR-RFLP	G463A	7	0.35
Grahl *et al.* [11]	2007	Sweden	Caucasian	55 (22–70)		Male: 61%		HTN, diabetes	PB	PCR-RFLP	G463A	8	0.94
Hui *et al.* [12]	2007	China	Asian	62.7 (11.5)	61.9 (9.9)	47/13	43/26	HTN, diabetes, smoking	HB	PCR-RFLP	G463A	7	0.50
Quanzhong *et al.* [13]	2008	China	Asian	51.5 (5.8)	50.7 (6.4)	65/69	65/80	HTN, HLP, diabetes, smoking	HB	PCR-RFLP	G463A	7	< 0.001
Zhong *et al.* [14]	2009	China	Asian	52.3 (7.0)	52.9 (7.4)	131/98	125/105	HLP, diabetes, smoking	HB	PCR-RFLP	G463A	7	0.96
Zotova *et al.* [15]	2009	Sweden	Caucasian	61.0 (6.8)	61.0 (6.2)	852/361	1054/507	HTN, HLP, diabetes, smoking	PB	PCR-RFLP	G463A	7	0.20
Hua *et al.* [16]	2009	China	Asian	51.2 (5.1)	50.6 (4.8)	95/56	46/30	HTN, HLP, diabetes, smoking	HB	PCR-RFLP	G463A	9	0.47
Lijing [17]	2009	China	Asian	70.2 (8.7)	69.5 (9.7)	114/106	55/50	HTN, HLP, diabetes, smoking	HB	PCR-RFLP	G463A	9	0.62
Yongsheng *et al.* [18]	2010	China	Asian	65.0 (9.5)	62.0 (7.4)	106/86	54/42	Not referred	HB	PCR-RFLP	G463A	9	0.003
Aihua *et al.* [19]	2010	China	Asian	64.5 (9.8)	55.9 (8.5)	126/99	36/34	HTN, HLP, diabetes	HB	PCR-RFLP	G463A	8	0.03
Ergen *et al.* [20]	2011	Turkish	Caucasian	58.2 (11.1)	63.4 (17.5)	76/24	46/54	HTN, HLP, diabetes, smoking	PB	PCR-RFLP	G463A	9	0.6
Lili *et al.* [21]	2011	China	Asian	63.4 (11.3)	63.6 (5.8)	164/139	178/150	HTN, diabetes, CAD	HB	PCR-RFLP	G463A	8	0.12
Zhangchao [22]	2011	China	Asian	63.0 (10.4)	58.3 (10.6)	173/123	36/56	HTN, HLP, diabetes, smoking	HB	PCR-RFLP	G463A	9	0.51
Reynold *et al.* [7]	2003	Netherlands	Caucasian	53.0 (8.2)	53.0 (8.9)	93/57	94/55	HTN, HLP, diabetes, smoking	PB	PCR-RFLP	G463A	8	0.56
Natarajan *et al.* [23]	2016	Indian	Asian	53.0 (8.2)	53.0 (8.9)	93/57	194/55	HTN, HLP, diabetes, smoking	PB	PCR-RFLP	G463A	7	0.31
Reddy *et al.* [24]	2016	Indian	Asian	65.3 (4.2)	62.3 (7.4)	48/22	48/22	Diabetes	PB	PCR-RFLP	G463A	7	0.10
Mohammadi *et al.* [25]	2015	Iran	Caucasian	72.9 (5.3)	73.2 (6.6)	237/201	246/204	HTN, diabetes, CAD	HB	PCR-RFLP	G463A	7	0.12

Case-control design was used in all the included studies. PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism, year – publication year, NOS – Newcastle-Ottawa scale, HWE – Hardy–Weinberg equilibrium, HB – hospital-based, PB – population based, HLP – hyperlipidemia, HTN – hypertension.

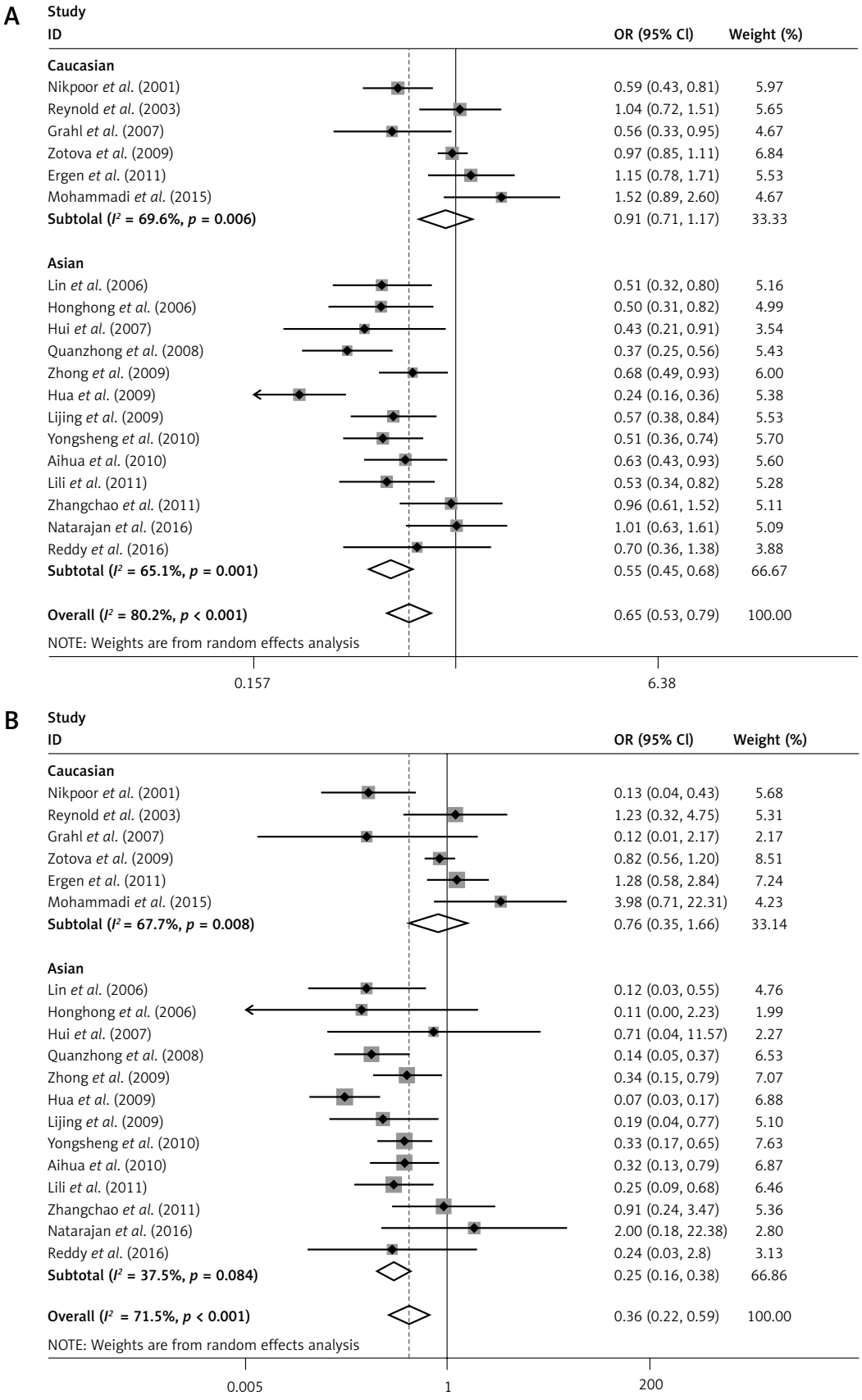
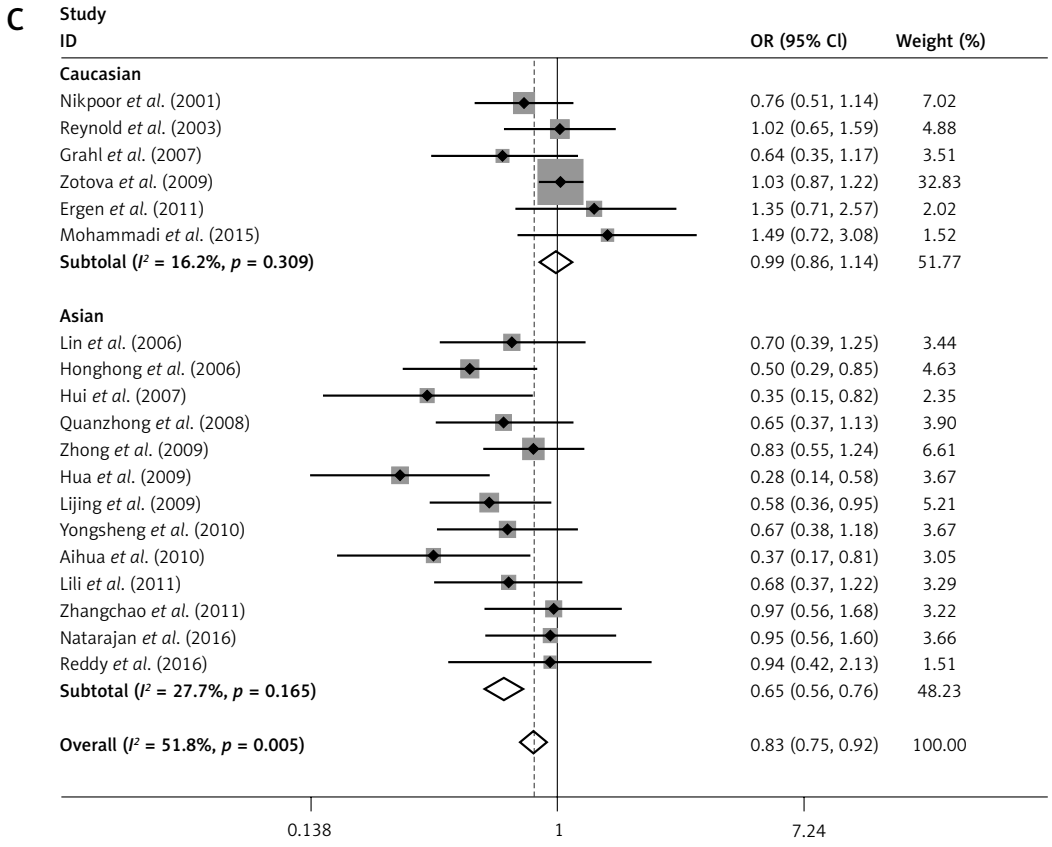


Figure 1. Subgroup meta-analysis by ethnicity of the relationship between the MPO rs2333227 polymorphism and CHD risk. **A** – Allele model: A vs. G. **B** – Homozygote model: AA vs. GG



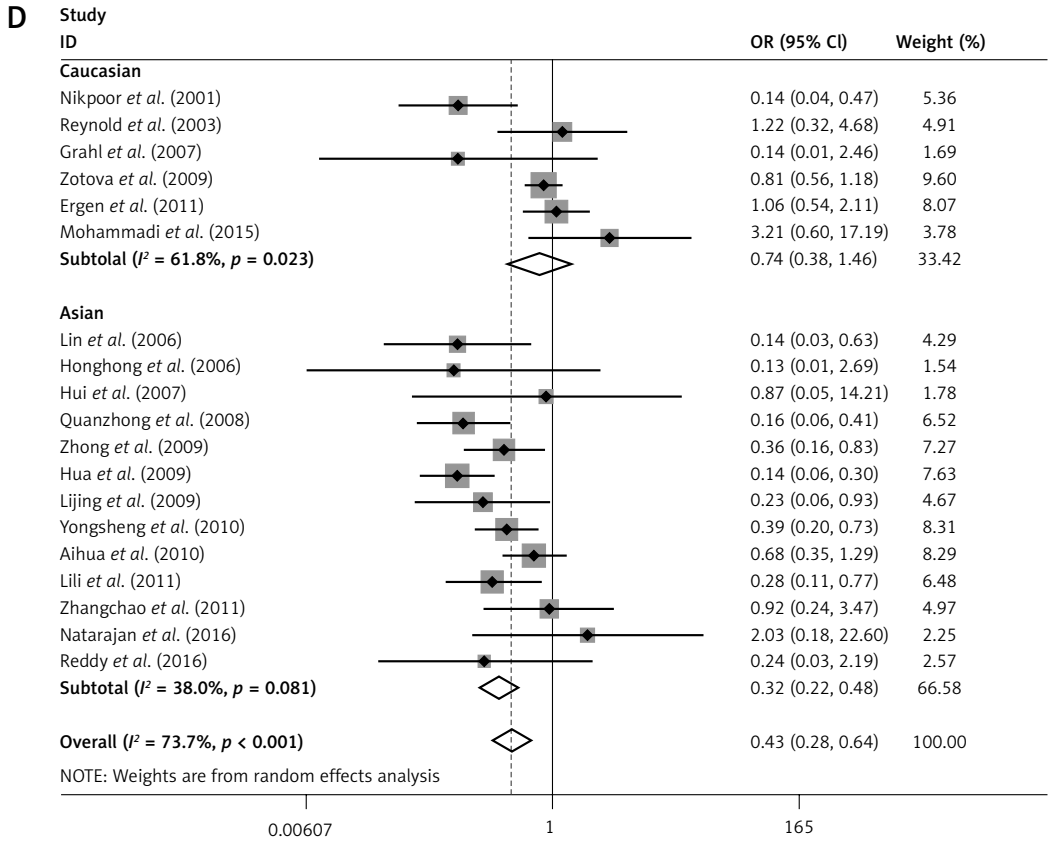


Figure 1. Cont. **C** – Heterozygote model: GA vs. GG. **D** – Recessive model: AA vs. GA+GG

E

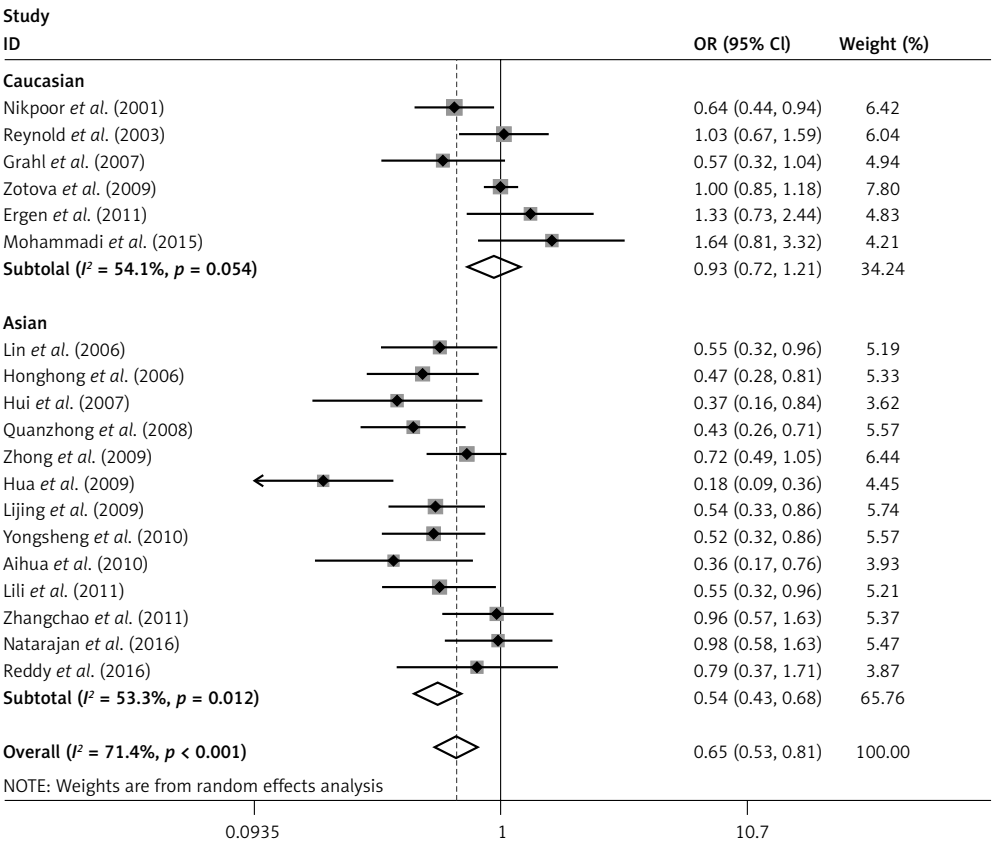


Figure 1. Cont. **E** – Dominant model: AA+GA vs. GG

garding to myeloperoxidase rs2333227 polymorphism and coronary heart disease gave controversial results. Compared to them, our meta-analysis has some strengths. First, we included more studies and as a result had a larger sample size in this study. Second, we performed HWE tests and sensitivity analysis to eliminate the possible bias. In addition, we did stratified analysis on the source of control to consider whether comorbidities could influence the results.

However, some limitations did exist. First, three studies did not fit the HWE test in the control group. After omission of these studies during the sensitivity analysis, it did not alter the conclusions made in the meta-analysis. Secondly, there were no studies including Africans. Third, the genetic susceptibility may also depend on the coincidence of several gene polymorphisms acting together, which may influence the results.

Our meta-analysis demonstrated that the myeloperoxidase rs2333227 polymorphism could reduce the risk of coronary heart disease. Myeloperoxidase, as a kind of superoxide enzyme in the activated neutrophils, monocytes and macrophages in human atherosclerotic plaque, may be a promising gene therapy site of coronary heart disease in the future. However, more case-control studies are needed for further validation, and to reinforce the results of the present meta-analysis.

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Conflict of interest

The authors declare no conflict of interest.

Table II. Subgroup analyses of association between myeloperoxidase 463G/A polymorphism and CHD

Subgroup		Number	Odds ratio	95% confidential interval	*P*-value	I^2 (%)
Allele model:						
Source of control	HB	12	0.56	0.44, 0.71	< 0.001	73.4
	PB	7	0.86	0.70, 1.06	0.15	56.4
Sample size	≥ 300	7	0.66	0.47, 0.93	0.02	88.0
	< 300	12	0.64	0.51, 0.82	< 0.001	68.1
Subtype	SAP	3	0.53	0.38, 0.73	< 0.001	88.1
	ACS	3	0.45	0.34, 0.59	< 0.001	86.0
Homozygote model:						
Source of control	HB	12	0.27	0.16, 0.47	< 0.001	58.1
	PB	7	0.63	0.31, 1.26	0.19	56.8
Sample size	≥ 300	7	0.34	0.14, 0.80	0.01	83.0
	< 300	12	0.39	0.21, 0.72	0.003	59.0
Subtype	SAP	3	0.22	0.10, 0.47	< 0.001	78.2
	ACS	3	0.15	0.07, 0.32	< 0.001	71.8
Heterozygote model:						
Source of control	HB	12	0.65	0.55, 0.76	< 0.001	41.7
	PB	7	0.97	0.85, 1.11	0.70	0.0
Sample size	≥ 300	7	0.90	0.79, 1.02	0.09	63.8
	< 300	12	0.71	0.60, 0.85	< 0.001	34.4
Subtype	SAP	3	0.67	0.44, 1.02	0.06	69.3
	ACS	3	0.52	0.36, 0.74	< 0.001	66.8
Recessive model:						
Source of control	HB	12	0.35	0.22, 0.56	< 0.001	54.1
	PB	7	0.64	0.35, 1.18	0.15	50.5
Sample size	≥ 300	7	0.39	0.19, 0.80	0.01	76.6
	< 300	12	0.45	0.27, 0.78	0.004	53.9
Subtype	SAP	3	0.27	0.13, 0.57	0.001	64.4
	ACS	3	0.21	0.10, 0.44	< 0.001	50.1
Dominant model:						
Source of control	HB	12	0.54	0.42, 0.70	< 0.001	62.4
	PB	7	0.90	0.74, 1.09	0.26	31.5
Sample size	≥ 300	7	0.68	0.49, 0.95	0.02	81.0
	< 300	12	0.63	0.49, 0.82	< 0.001	54.3
Subtype	SAP	3	0.57	0.38, 0.85	0.01	84.6
	ACS	3	0.45	0.32, 0.64	< 0.001	83.1

ACS – acute coronary syndrome, CHD – coronary heart disease, HB – hospital-based, PB – population-based, SAP – stable angina pectoris.

References

1. Miniño AM. Death in the United States, 2009. Nchs Data Brief 2011; 5: 1-8.
2. Langbiao X, Yafeng Z, Jialu Y, et al. Apolipoprotein A1 polymorphisms and risk of coronary artery disease: a meta-analysis. Arch Med Sci 2017; 13: 813-9.
3. Sayols-Baixeras S, Lluís-Ganella C, Lucas G, Elosua R. Pathogenesis of coronary artery disease: focus on genetic risk factors and identification of genetic variants. Appl Clin Genet 2014; 7: 15-32.
4. Piedrafita FJ, Molander RB, Vansant G, Orlova EA, Pfahl M, Reynolds WF. An Alu element in the myeloperoxidase promoter contains a composite SP1-thyroid hormone-retinoic acid response element. J Biol Chem 1996; 271: 14412-20.
5. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000; 283: 2008-12.
6. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-5.
7. Reynolds WF, Chang E, Douer D, Ball ED, Kanda V. An allelic association implicates myeloperoxidase in the etiology of acute promyelocytic leukemia. Blood 1997; 90: 2730-7.

8. Nikpoor B, Turecki G, Fournier C, Théroux P, Rouleau GA. A functional myeloperoxidase polymorphic variant is associated with coronary artery disease in French-Canadians. Am Heart J 2001; 142: 336.
9. Lin H. Correlation between the myeloperoxidase polymorphic variant and coronary artery disease. Thesis, Shandong University. 2006. Available from: http://cdmd.cnki.com.cn/article/cdmd-10422-2006167275.htm.
10. Honghong Z. Association between the myeloperoxidase gene-463 G/A polymorphism and coronary heart disease. Thesis, Lanzhou University. 2006. Available from: http://cdmd.cnki.com.cn/Article/CDMD-10730-2006088176.htm.
11. Grahl DA, Axelsson J, Nordfors L, et al. Associations between the CYBA 242C/T and the MPO -463G/A polymorphisms, oxidative stress and cardiovascular disease in chronic kidney disease patients. Blood Purif 2007; 25: 210-8.
12. Hui L, Zongming B. Association between myeloperoxidase-463 G/Apolymorphism and coronary artery disease. Clin Cardiol 2007; 23: 825-8.
13. Quanzhong Y, Zhong C, Hua Z. Relationship between MPO -463G>A gene polymorphism and premature CHD. Jiangsu Med J 2008; 34: 1103-5.
14. Zhong C, Yin Q, Ma G, et al. Myeloperoxidase gene-463 g > a polymorphism and premature coronary artery disease. Genet Mol Biol 2009; 32: 260.
15. Zotova E, Lyrenäs L, De FU, Morgenstern R, Gigante B, Bennet AM. The myeloperoxidase gene and its influence on myocardial infarction in a Swedish population: protective role of the -129A allele in women. Coron Artery Dis 2009; 20: 322-6.
16. Hua Z, Quanzhong Y, Ruolong D. Clinical application of measurement of myeloperoxidase concentration and gene -463 G > A polymorphism in high-risk group with early-onset coronary heart disease. J Pathol Clin Res 2009; 26: 219-21.
17. Lijing Z. Study on relationship between myeloperoxidase-463 G/A polymorphism and coronary heart disease. Thesis, Fujian University. 2009. Available from: http://d.wanfangdata.com.cn/Thesis/Y1487080.
18. Yongsheng D, Zongming B, Shili W. Study on the relationship between MPO -436 G/A gene polymorphism and the degree of coronary artery stenosis. Medicine 2009; 26: 3916-7.
19. Aihua L, Juan C, Xiaochen Y. Correlation between the myeloperoxidase genetic polymorphism and coronary artery disease. Clin Cardiol 2010; 26: 25-9.
20. Ergen A, İsbir S, Timirci Ö, Tekeli A, İsbir T. Effects of myeloperoxidase -463 G/A gene polymorphism and plasma levels on coronary artery disease. Mol Biol Rep 2011; 38: 887-91.
21. Lili H, Xiaoli S, Lifang L. The relationship between MPO -463G/A genetic polymorphism and CAD susceptivity. J China Trad Chinese Med Info 2011; 3: 126-7.
22. Zhangchao L. Relationship between myeloperoxidase -463G/A polymorphism and coronary heart disease. Thesis, Hebei University. 2011. Available from: http://d.wanfangdata.com.cn/Thesis/Y1901794.
23. Natarajan S, Ponde CK, Rajani RM, Ashavaid TF. Association of variation with coronary artery disease in Indians. Biomarkers 2016; 21: 1-8.
24. Reddy DG, Rao DK, Unni VK. Myeloperoxidase variants (at SNP -463 G/A) and the risk of coronary artery disease (CAD): a case control study. 2016. Available from: http://worldwidejournals.in/ojs/index.php/ijar/article/view/7774.
25. Mohammadi P, Soleimani S, Sharifi Z. Association between G-436 A (rs2333227) polymorphism at myeloperoxidase gene promoter andcoronary artery disease risk in Iranian patients. Surgery 2015; 140: 836-7.
26. Karakas M, Koenig W, Zierer A, et al. Myeloperoxidase is associated with incident coronary heart disease independently of traditional risk factors: results from the MONICA/KORA Augsburg study. J Intern Med 2012; 271: 43-50.
27. Hoy A, Leininger-Muller B, Kutter D, Siest G, Visvikis S. Growing significance of myeloperoxidase in non-infectious diseases. Clin Chem Lab Med 2002; 40: 2-8.
28. Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol 2005; 25: 1102-11.
29. Karakas M, Koenig W, Zierer A, et al. Myeloperoxidase is associated with incident coronary heart disease independently of traditional risk factors: results from the MONICA/KORA Augsburg study. J Intern Med 2012; 271: 43-50.
30. Chen L, Zhao S, Cheng G, Shi R, Zhang G. Meta-analysis of myeloperoxidase gene polymorphism and coronary artery disease susceptibility. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2014; 39: 217-31.
31. Chang C, Gao B, Zheng L, Mao J, Jiang G. The myeloperoxidase -463G/A polymorphism and coronary artery disease risk: a meta-analysis of 1938 cases and 1990 controls. Clin Biochem 2013; 46: 1644-8.
32. Tang N, Wang Y, Mei Q. Myeloperoxidase G-463A polymorphism and susceptibility to coronary artery disease: a meta-analysis. Gene 2013; 523: 152-7.
33. Li YY, Wang H, Qian J, et al. PRISMA-combined myeloperoxidase -463G/A gene polymorphism and coronary artery disease: a meta-analysis of 4744 subjects. Medicine 2017; 96: e6461.