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PRISMA-combined Myeloperoxidase -463G/A gene polymorphism and coronary artery disease

A meta-analysis of 4744 subjects

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Abstract

Background: *Myeloperoxidase (MPO)* -463G/A gene polymorphism may be associated with an increased risk of developing coronary artery disease (CAD). Studies on the subject, however, do not provide a clear consensus. This meta-analysis was performed to explore the relationship between *MPO* gene -463G/A polymorphism and CAD risk.

Methods: This meta-analysis combines data from 4744 subjects from 9 independent studies. By using fixed or random effect models, the pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were assessed.

Results: Our analysis found a significant association between *MPO* gene -463G/A polymorphism and CAD in the whole population under all genetic models: allelic (OR: 0.68, 95% CI: 0.54–0.85, $P=0.0009$), recessive (OR: 0.41, 95% CI: 0.22–0.76, $P=0.005$), dominant (OR: 0.682, 95% CI: 0.534–0.871, $P=0.002$), homozygous (OR: 0.36, 95% CI: 0.16–0.79, $P=0.01$), heterozygous genetic model (OR: 0.832, 95% CI: 0.733–0.945, $P=0.004$), and additive (OR: 0.64, 95% CI: 0.46–0.90, $P=0.01$), especially in the Chinese subgroup ($P<0.05$). On the contrary, we found no such relationship in the non-Chinese subgroup ($P>0.05$).

Conclusion: The *MPO* gene -463G/A polymorphism is associated with CAD risk, especially within the Chinese population. The A allele of *MPO* gene -463G/A polymorphism might protect the people from suffering the CAD risk.

Abbreviations: A = adenine, ACS = acute coronary syndrome, Apo A-I = ApolipoproteinA-I, CAD = coronary artery disease, CIs = confidence intervals, Cl- = chloride anion, G = guanine, H_2O_2 = hydrogen peroxide, HOCl = hypochlorous acid, HWE = Hardy–Weinberg equilibrium, LDL/HDL = low and high-density lipoprotein, MPO = myeloperoxidase, ORs = odds ratios, ox-LDL = oxidized low density lipoprotein, SP1 = specificity protein 1.

Keywords: -463G/A, coronary artery disease, gene, myeloperoxidase, polymorphism

1. Introduction

Coronary artery disease (CAD) describes a family of ischemic diseases characterized by the occlusion of the coronary artery lumen by atheromatous plaque. Plaque from acute coronary syndrome (ACS) patients has increased levels of myeloperoxidase (MPO) and its oxidative products,[1] suggesting that MPO may be involved in the atherosclerotic process.

MPO, a member of the heme-peroxidase superfamily, is secreted by activated phagocytes and plays a crucial role in the antimicrobial innate immune response.[2] It has a 150-kDa homodimeric structure consisting of two 15-kDa light chains and 2 variable-weight heavy chains with a prosthetic heme group.[3] The primary reaction catalyzed by MPO is the degradation of hydrogen peroxide (H_2O_2) to hypochlorous acid (HOCl) and

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Y-YL and HW contribute equally to this work.

Authorship: Conceived and designed the meta-analysis: YL and LW. Performed the meta-analysis: YL and HW. Analyzed the data: YL, JQ, and CZ. Contributed material/analysis tools: YL. Wrote the manuscript: YL. Reference collection and data management: YL and JW. Statistical analyses and paper writing: YL, HK, and ZY. Study design: YL and XL.

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chloride anion (Cl-). Although HOCL has strong anti-microbial and detoxification properties, it can also cause oxidative damage to host tissue. MPO is secreted primarily by myelocytes, with up to 95% of the circulating MPO found in the blood vessels are derived from neutrophils.

The *MPO* gene, located in the 17q23.1, spans 14.638 kb and contains 12 exons and 11 introns.[4] The *MPO* -463G/A gene polymorphism involves a substitution of a guanine (G) for an adenine (A) in the upstream promoter region and acts in the cis-acting element for specificity protein 1 (SP1), a transcription factor. Four Glu repetitive sequences are included in the cis-acting element. The G nucleotide in this *MPO* -463G/A gene polymorphism establishes the central binding site for the SP1 transcription factor that can induce up to a 25-fold increase in *MPO* gene transcription. Substitution of this central guanine with adenine significantly decreases the *MPO* gene transcription by reducing the promoter's binding affinity, providing a plausible mechanism of how *MPO* gene transcription could influence CAD susceptibility.[5]

Many studies on the association between the *MPO* -463G/A gene polymorphism and CAD have been conducted, but have not provided a clear consensus. In 2006, Hao and Lu[6] also identified the G allele as an independent risk factor for CAD and the A allele as protective against CAD in the Chinese population, an effect attributed to the polymorphism's impact on transcription. Similarly, Nikpoor et al[7] found the A allele of the *MPO* -463G/A gene polymorphism to be associated with fewer CAD cases and concluded that the *MPO* gene -463 G/A polymorphism influences the CAD risk. On the contrary, Lin and Zhang[8] found no significant association of *MPO* -463G/A gene polymorphism with CAD in a separate Chinese population.

Given the lack of consensus on the relationship between *MPO* -463G/A gene polymorphism and CAD, we produced the current meta-analysis of 2454 CAD patients and 2290 controls.[9]

2. Methods

2.1. Publication search and inclusion criteria

The current study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. The terms "coronary heart disease," "myeloperoxidase," "coronary artery disease," "coronary heart disease," and "polymorphism" were used to collect studies. The China Biological Medicine Database, China National Knowledge Infrastructure, Embase, PubMed, and the Web of Science were searched. Retrieved studies were published between 2001 and 2011 with the latest paper updated on February 21, 2017.

The selected studies had to conform to the following criteria: Assessment of the *MPO* -463G/A gene polymorphism and CAD; Diagnosis of CAD conducted in a manner consistent with criteria proposed by World Health Organization in 1979; and Genotypes in the control group follow the Hardy–Weinberg equilibrium (HWE).

2.2. Data extraction

Data were extracted as per a standardized protocol. Studies published in duplicates, those that did not meet inclusion criteria, and those with insufficient data were removed from the study. Overlapping data sets applied in separate publications were applied singly. The extracted data comprised the following items: the first author's name, publication year, region, number of genotypes, genotyping, matching criteria, total number of cases and controls.

2.3. Statistical analysis

In the present meta-analysis, 6 genetic models as the allelic (A allele distribution frequency of *MPO* -463G/A gene polymorphism), recessive (AA vs GA+GG), dominant (AA+GA vs GG), homozygous (AA vs GG), heterozygous (GA vs GG), and additive genetic models (A vs G) were used. The odds ratio (OR) and their corresponding 95% confidence interval (CI) were used to compare the relationship between *MPO* -463G/A gene polymorphism and CAD. The Chi-square based Q-test was used to calculate the heterogeneity between studies and the significance was set at $P < 0.05$ level.[10] The heterogeneity variation was evaluated by calculating the inconsistency index I^2. If heterogeneity was detected, the random-effects model (Der Simonian and Laird method) would be used to estimate the pooled OR.[11] If no heterogeneity is detected, the fixed-effects model (Mantel–Haenszel method) would be adopted.[12] The pooled OR would be determined by using the Z test with significance set at $P < 0.05$ level.

The HWE was evaluated by using the Fisher exact test and the significance was set at $P < 0.05$ level. Potential publication bias would be estimated by using funnel plot. The Egger linear regression test on the natural logarithm scale of the OR was used to assess the funnel plot asymmetry and the significance was set at $P < 0.05$ level.[13] The STATA 12.0 software (StataCorp, College Station, TX) and review manager 5.0 were used to perform the statistical analysis.

3. Results

3.1. Studies and populations

Among the 19 papers produced from our initial search, 9 papers met the inclusion criteria. In total, data were extracted from 2454 CAD patients and 2290 controls (Table 1).[6–8,14–19] Patients

Table 1

Characteristics of the investigated studies of the association between *MPO* -463G/A gene polymorphism and CAD.

				CAD			Control				
Author	Year	Region	Ethnicity	GG	GA	AA	GG	GA	AA	Matching criteria	Sample size (CAD/control)
Zotova et al[14]	2009	Sweden	Non-Chinese	682	368	47	854	488	72	Age, sex, ethnicity	1097/1414
Nikpoor et al[7]	2001	Canada	Non-Chinese	151	75	3	120	78	19	Age, sex, ethnicity	229/217
Li and Bao[15]	2007	China	Chinese	68	10	1	48	20	1	Age, sex, ethnicity	79/69
Ergen et al[16]	2011	Turkey	Non-Chinese	27	52	21	33	47	20	Age, sex, BMI, ethnicity	100/100
Zhang [17]	2009	China	Chinese	148	69	3	55	44	6	Age, sex, ethnicity	220/105
Lin and Zhang [8]	2011	China	Chinese	217	70	9	66	22	3	BMI, ethnicity	296/91
Hao and Lu[6]	2006	China	Chinese	68	35	2	53	39	13	Age, sex, ethnicity	105/105
Han and Shen[18]	2007	China	Chinese	101	49	7	39	28	11	Age, ethnicity	157/78
Zhang and Ma[19]	2006	China	Chinese	135	36	0	71	38	2	Age, ethnicity	171/111

Case–control study design and PCR-RFLP genotyping method were used in all of the above studies.
BMI = body mass index, CAD = coronary artery disease, MPO = myeloperoxidase, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, Year = publication year.

Table 2

Summary of meta-analysis of association of *MPO* -463G/A gene polymorphism and CAD.

Genetic model	Pooled OR (95% CI)	Z value	P	Literature number	CAD size	Control size	$P_{heterogeneity}$ (I^2%)
Allelic genetic model	0.68 (0.54–0.85)	3.32	0.0009*	9	2454	2290	0.0004* (72.0%)
Chinese subgroup	0.58 (0.47–0.71)	5.09	3.58×10^{-7}*	6	1028	559	0.31 (16.0%)
Non-Chinese subgroup	0.85 (0.62–1.18)	0.95	0.34	3	1426	1731	0.02* (76.0%)
Recessive genetic model	0.41 (0.22–0.76)	2.84	0.005*	9	2454	2290	0.004* (64.0%)
Chinese subgroup	0.29 (0.16–0.55)	3.81	0.0001a*	6	1028	559	0.38 (6.0%)
Non-Chinese subgroup	0.58 (0.24–1.41)	1.20	0.23	3	1426	1731	0.01* (78.0%)
Dominant genetic model	0.682 (0.534–0.871)	3.06	0.002*	9	2454	2290	0.007* (61.8%)
Chinese subgroup	0.573 (0. 452–0.725)	4.64	3.48×10^{-6}*	6	1028	559	0.37 (7.3%)
Non-Chinese subgroup	0.883 (0. 642–1.213)	0.77	0.441	3	1426	1731	0.09 (58.5%)
Homo genetic model	0.36 (0.16 -0.79)	2.56	0.01*	9	2454	2290	0.0002* (73.0%)
Chinese subgroup	0.24 (0.11–0.50)	3.77	0.0002*	6	1028	559	0.26 (24.0%)
Non-Chinese subgroup	0.61 (0.16–2.34)	0.72	0.47	3	1426	1731	0.001* (85.0%)
Hetero genetic model	0.832 (0.773–0.945)	2.84	0.004*	9	2454	2290	0.057 (47.1%)
Chinese subgroup	0.629 (0.498–0.793)	3.91	9.23×10^{-5}*	6	1028	559	0.4 (2.6%)
Non-Chinese subgroup	0.934 (0.803–1.086)	0.88	0.377	3	1426	1731	0.322 (11.7%)
Additive genetic model	0.64 (0.46–0.90)	2.59	0.01*	9	2454	2290	<0.00001* (84.0%)
Chinese subgroup	0.53 (0.36–0.79)	3.16	0.002*	6	1028	559	0.004a* (71.0%)
Non-Chinese subgroup	0.91 (0.49–1.69)	0.29	0.77	3	1426	1731	<0.0001a* (90.0%)

Additive genetic model: total A vs total G; Allelic genetic model: distribution of A allelic frequency of *MPO* gene -463G/A polymorphism; CAD = coronary artery disease; CAD size = the total number of CAD cases; CI = confidence interval; control size: the total number of control group; Dominant genetic model: AA+GA vs GG; hetero genetic model: heterozygous genetic model, GA vs GG; homo genetic model: homozygous genetic model: AA vs GG; OR = odds ratio; recessive genetic model: AA vs GA+GG; MPO = myeloperoxidase.

* $P < 0.05$.

were from China, Sweden, Canada, and Turkey and were of either Chinese or non-Chinese descent. Of the 10 studies removed from our initial search, 2 papers were duplicates and 3 were reviews on the topic. Two other papers did not address either *MPO* -463G/A gene polymorphism or CAD. Three studies were excluded for deviating from HWE.[20–22]

3.2. Pooled analyses

There was a significant association between *MPO* gene -463G/A polymorphism and CAD in the whole population under allelic (OR: 0.68, 95% CI: 0.54–0.85, $P = 0.0009$), recessive (OR: 0.41, 95% CI: 0.22–0.76, $P = 0.005$), dominant (OR: 0.682, 95% CI: 0.534–0.871, $P = 0.002$), homozygous (OR: 0.36, 95% CI: 0.16–0.79, $P = 0.01$), heterozygous genetic model (OR: 0.832, 95% CI: 0.733–0.945, $P = 0.004$), and additive genetic models (OR: 0.64, 95% CI: 0.46–0.90, $P = 0.01$) (Table 2, Figs. 1–6).

Under the heterozygous genetic model, no heterogeneity was detected in the whole population. Although the whole population displayed significant heterogeneity under all genetic models ($P_{heterogeneity} < 0.05$), heterogeneity was only detected under the

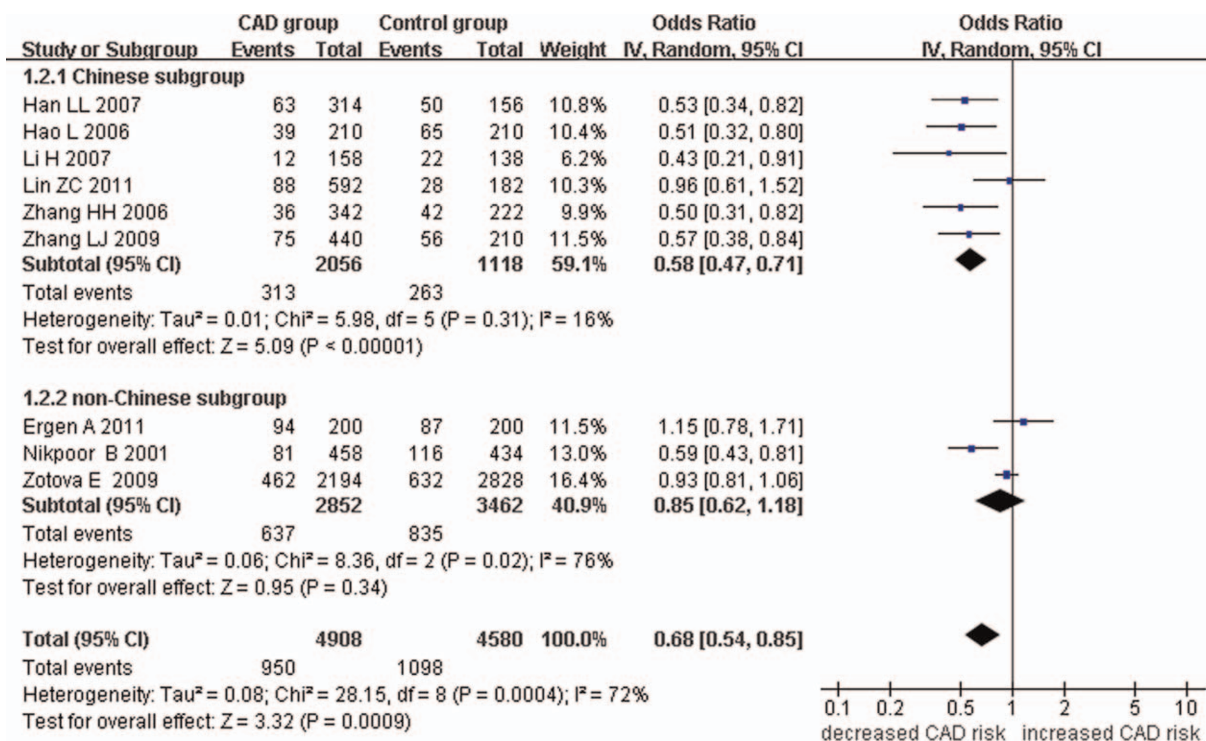

Figure 1. Forest plot of CAD associated with *MPO* -463G/A gene polymorphism stratified by ethnicity under an allelic genetic model (distribution of A allelic frequency of *MPO* -463G/A gene polymorphism). A = adenine, CAD = coronary artery disease, G = guanine, MPO = myeloperoxidase.

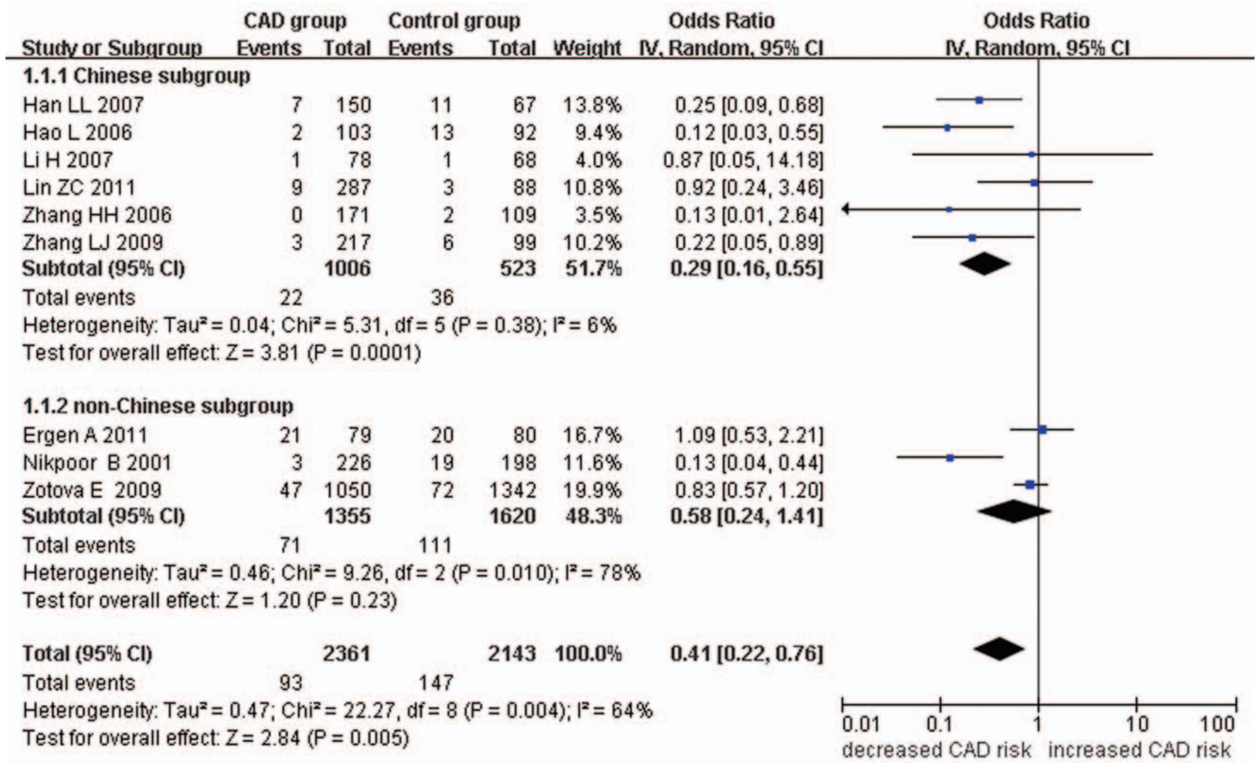

Figure 2. Forest plot of CAD associated with *MPO* -463G/A gene polymorphism stratified by ethnicity under a recessive genetic model (AA vs GA+GG). A=adenine, CAD=coronary artery disease, G=guanine, MPO=myeloperoxidase.

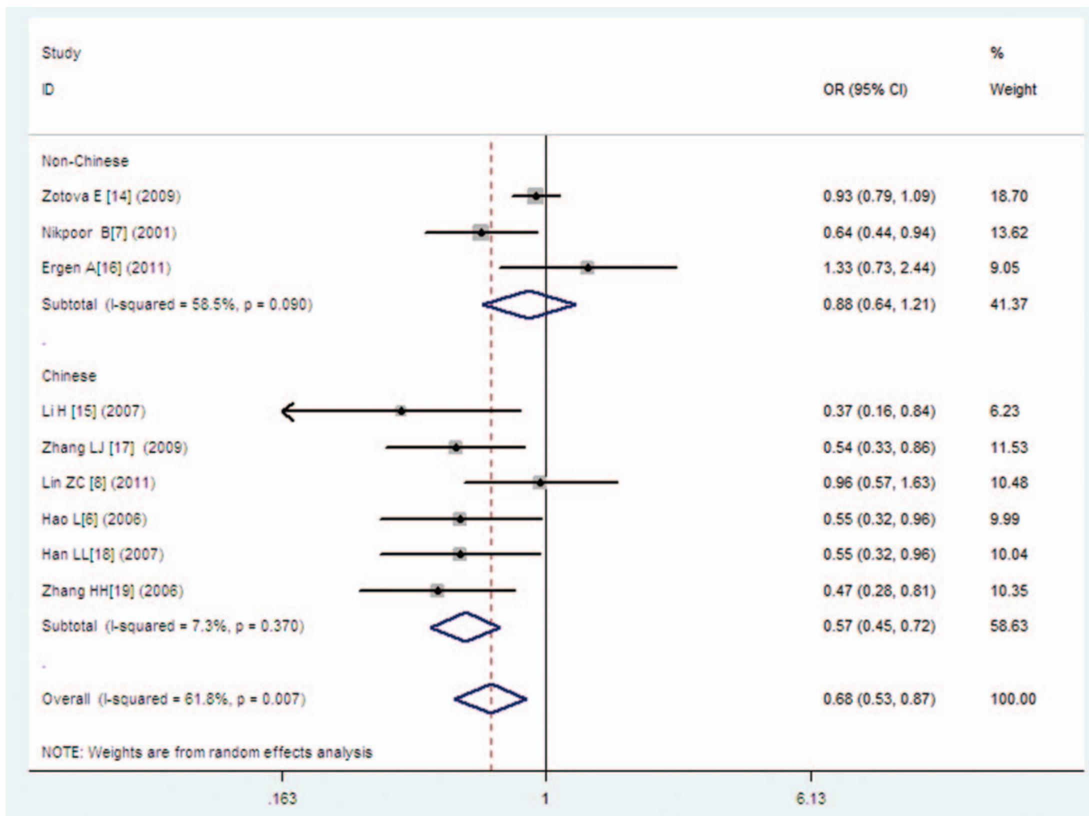

Figure 3. Forest plot of CAD associated with *MPO* -463G/A gene polymorphism stratified by ethnicity under a dominant genetic model (AA+GA vs GG). A=adenine, CAD=coronary artery disease, G=guanine, MPO=myeloperoxidase.

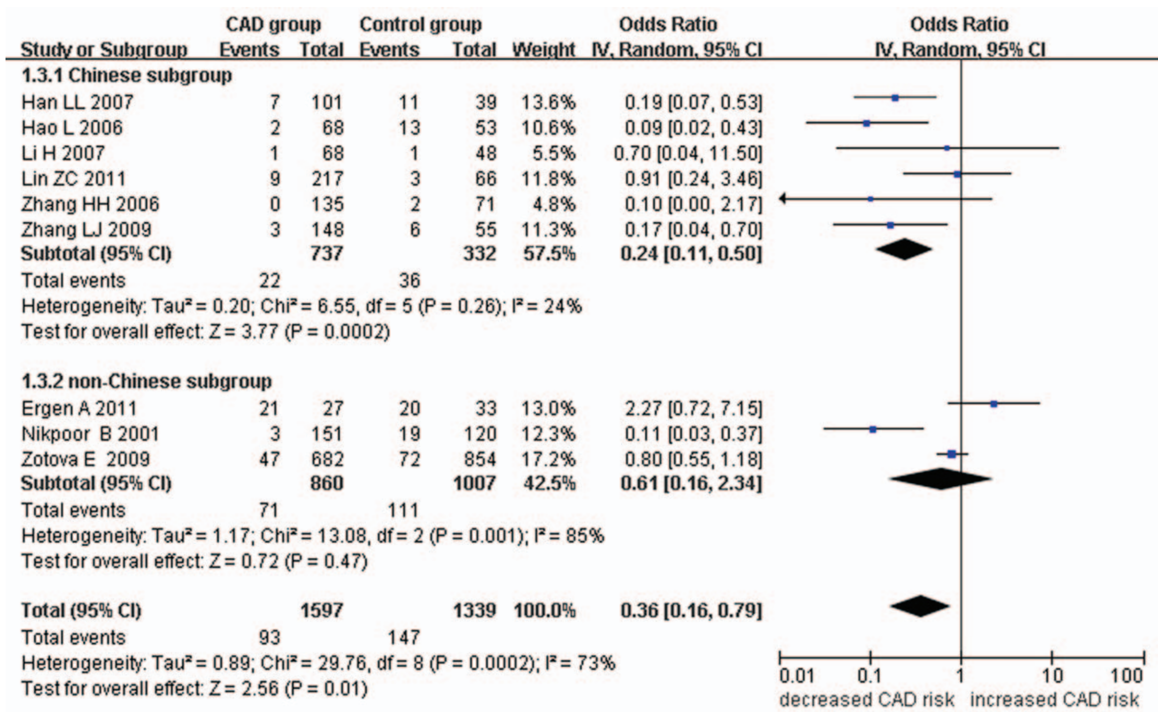

Figure 4. Forest plot of CAD associated with *MPO* -463G/A gene polymorphism stratified by ethnicity under a homozygous genetic model (AA vs GG). A= adenine, CAD=coronary artery disease, G=guanine, MPO=myeloperoxidase.

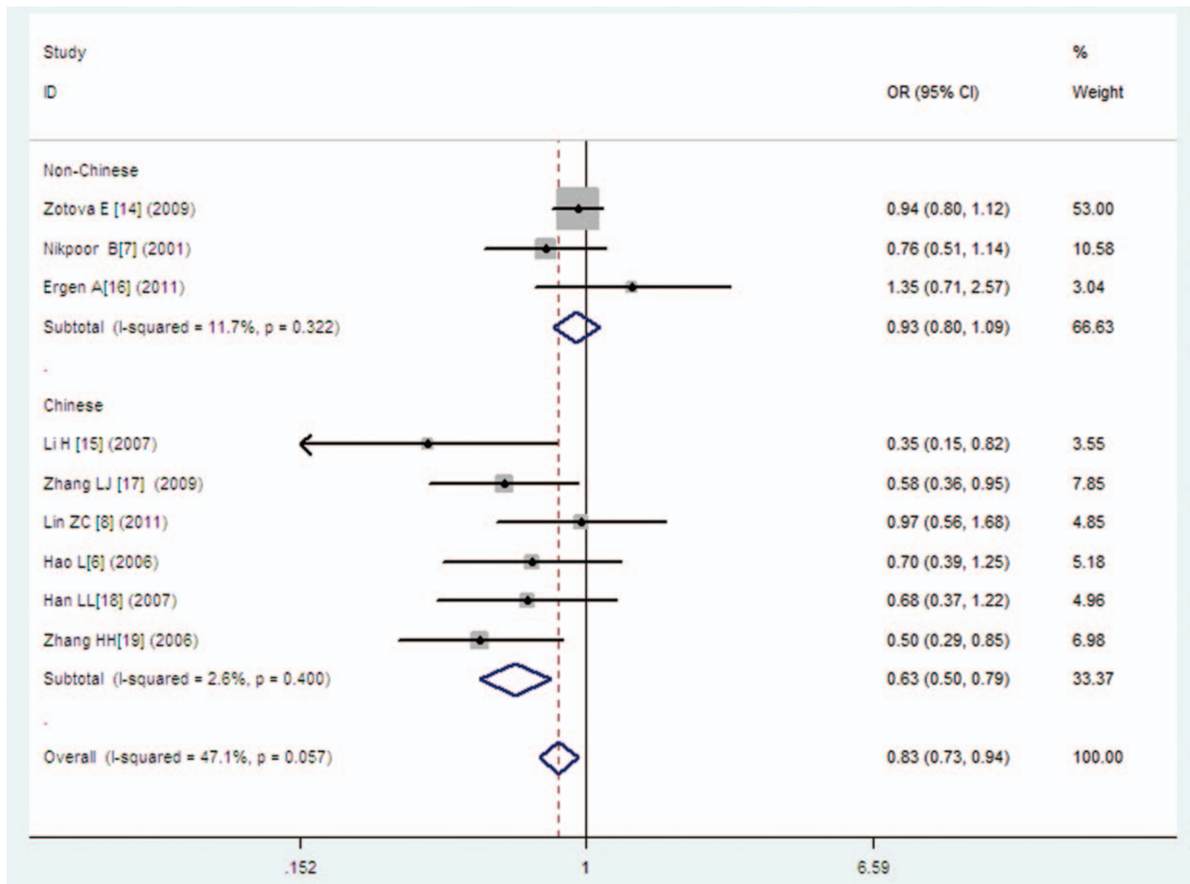

Figure 5. Forest plot of CAD associated with *MPO* -463G/A gene polymorphism stratified by ethnicity under a heterozygous genetic model (GA vs GG). A= adenine, CAD=coronary artery disease, G=guanine, MPO=myeloperoxidase.

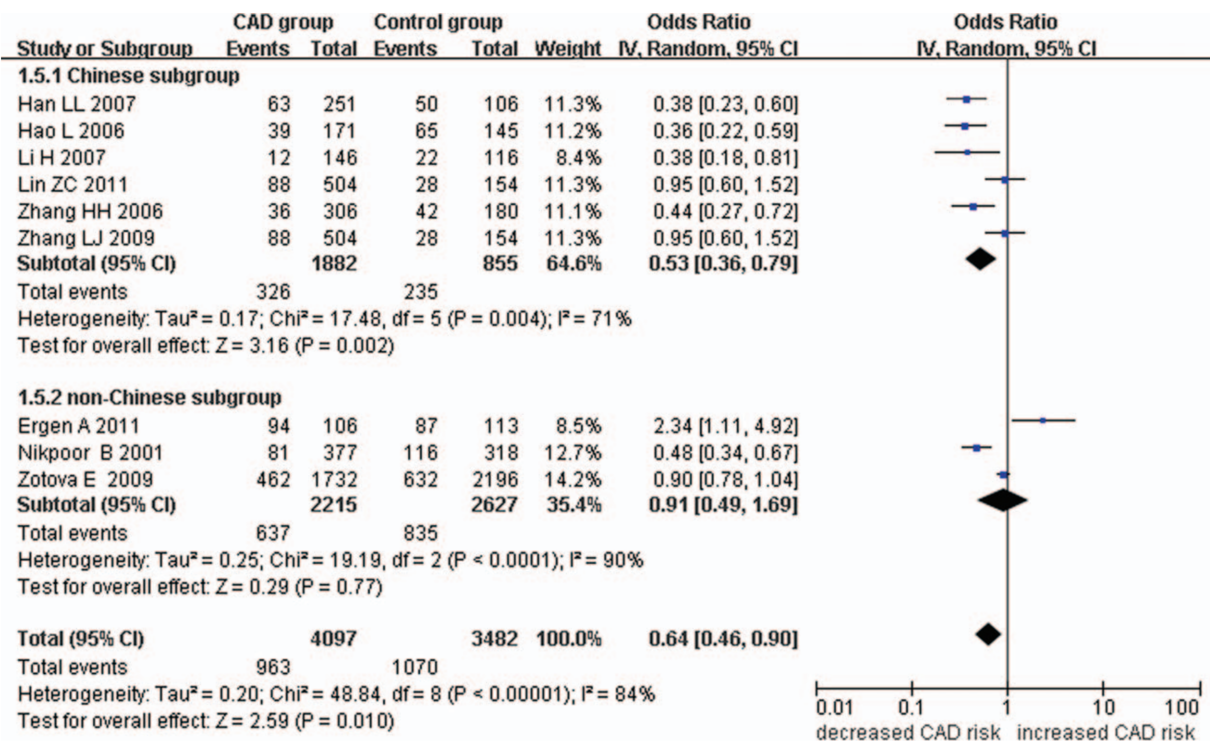

Figure 6. Forest plot of CAD associated with *MPO* -463G/A gene polymorphism stratified by ethnicity under an additive genetic model (total A vs total G). A = adenine, CAD = coronary artery disease, G = guanine, MPO = myeloperoxidase.

additive model when looking at the Chinese subgroup ($P_{heterogeneity} > 0.05$). In contrast, the non-Chinese subgroup still showed significant heterogeneity under the allelic, recessive, homozygous, and additive genetic models ($P_{heterogeneity} < 0.05$). This suggests ethnicity as a primary source of the heterogeneity in the current meta-analysis (Table 2, Figs. 1–6).

In the Chinese subgroup, a significant association between them was found under the allelic (OR: 0.58, 95% CI: 0.47–0.71, $P = 3.58 \times 10^{-7}$, $P_{heterogeneity} = 0.31$), recessive (OR: 0.29, 95% CI: 0.16–0.55, $P = 0.0001$, $P_{heterogeneity} = 0.38$), dominant (OR: 0.573, 95% CI: 0.452–0.725, $P = 3.48 \times 10^{-6}$, $P_{heterogeneity} = 0.37$), homozygous (OR: 0.24, 95% CI: 0.11–0.50, $P = 0.0002$, $P_{heterogeneity} = 0.26$), heterozygous (OR: 0.629, 95% CI: 0.498–0.793, $P = 9.23 \times 10^{-5}$, $P_{heterogeneity} = 0.40$), and additive genetic models (OR: 0.53, 95% CI: 0.36–0.79, $P = 0.002$, $P_{heterogeneity} = 0.004$).

In the non-Chinese subgroup, no significant association between them was found under the allelic (OR: 0. 85, 95% CI: 0.62–1.18, $P = 0.34$, $P_{heterogeneity} = 0.02$), recessive (OR: 0.58, 95% CI: 0.24–1.41, $P = 0.23$, $P_{heterogeneity} = 0.01$), dominant (OR: 0.883, 95% CI: 0.642–1.213, $P = 0.441$, $P_{heterogeneity} = 0.09$), homozygous (OR: 0.61, 95% CI: 0.16–2.34, $P = 0.47$, $P_{heterogeneity} = 0.001$), heterozygous (OR: 0.934, 95% CI: 0.803–1.086, $P = 0.377$, $P_{heterogeneity} = 0.322$), and additive genetic models (OR: 0.91, 95% CI: 0.49–1.69, $P = 0.77$, $P_{heterogeneity} < 0.0001$).

3.3. Bias diagnostics

The publication bias of the individual studies was evaluated by the funnel plot and Egger test. No visual publication bias was detected in the funnel plot under the allelic genetic model (Fig. 7). No statistically significant difference was detected in the Egger test that implies no publication bias in the present meta-analysis existed by using additive genetic model (T = -2.08, $P = 0.076$) (Fig. 8).

4. Discussion

Our meta-analysis on the relationship between *MPO* gene -463G/A polymorphism and CAD found significant correlation under allelic (OR: 0.68), recessive (OR: 0.41), dominant (OR:

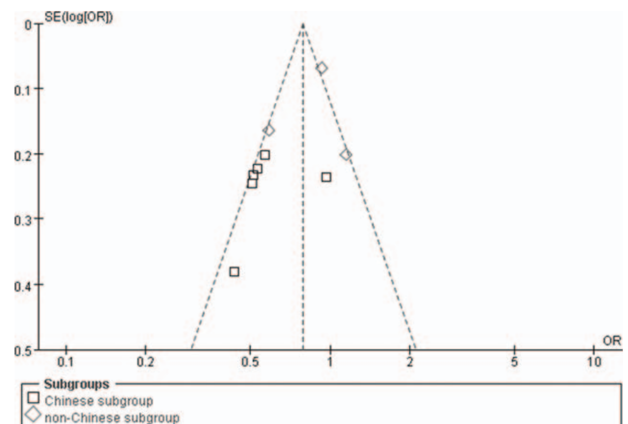

Figure 7. Funnel plot for studies of CAD associated with *MPO* -463G/A gene polymorphism under an allelic genetic model (distribution of A allelic frequency of *MPO* gene). The horizontal and vertical axis correspond to the OR and confidence limits. A = adenine, CAD = coronary artery disease, G = guanine, MPO = myeloperoxidase, OR = odds ratio, SE = standard error.

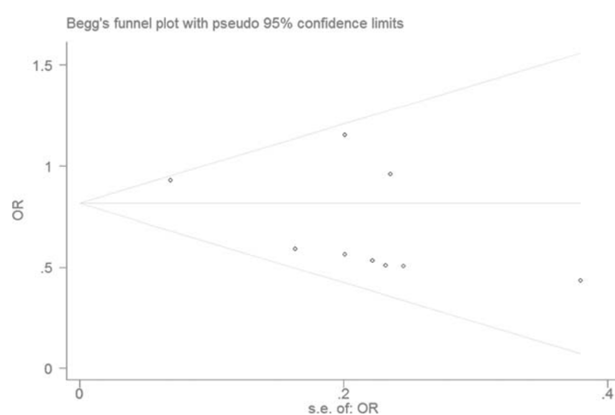

Figure 8. Begg funnel plot for studies of the association of CAD associated *MPO* -463G/A gene polymorphism under an additive genetic model (total A vs total G). The horizontal and vertical axis correspond to the OR and confidence limits. A=adenine, CAD=coronary artery disease, G=guanine, MPO=myeloperoxidase, OR=odds ratio, SE=standard error.

0.682), homozygous (OR: 0.36), heterozygous (OR: 0.832), and additive genetic models (OR: 0.64) in the whole population. When we focused our analysis to the Chinese subgroup, the correlation grew stronger with lower ORs under all genetic models: allelic (OR: 0.58), recessive (OR: 0.29), dominant (OR: 0.573), homozygous (OR: 0.24), heterozygous (OR: 0.629), and additive (OR: 0.53). In the non-Chinese subgroup, we found no significant correlation under allelic (OR: 0. 85), recessive (OR: 0.58), dominant (OR: 0.883), homozygous (OR: 0.61), heterozygous (OR: 0.934), and additive genetic models (OR: 0.91). Summarily, our data suggest that the *MPO* gene -463G/A polymorphism is associated with CAD susceptibility, particularly in the Chinese population with the A allele of *MPO* gene -463G/A polymorphism playing a protective role in the disease process.

MPO is an essential part of the host immune response, but its expression is closely linked to atherosclerotic formation. It is used clinically as a marker for local inflammation in the coronary artery and has even demonstrated to be an independent marker for myocardial infarction.[23,24] High plasma MPO levels are also correlated with cardiovascular events such as ACS and heart failure.[25]

The primary reaction catalyzed by MPO is the formation of cytotoxic hypochlorous acid. This is the signature reaction that powers the "respiratory burst" of neutrophils. The oxidation of tyrosine is also an important reaction catalyzed by MPO. MPO could translate L-tyrosine to cheese ammonia acyl and acquire hydrogen through Diallyl heartland of methyl groups of the polyunsaturated fatty acid and launch the lipid peroxidation by forming the tyrosine cross-link in the protein.

Although MPO is an important component of the innate immune response, MPO-derived oxidative agents (hypochlorous acid, 3-chloration tyrosine, cheese ammonia acyl, and nitrotyrosine) can be produced in excess, resulting in oxidative stress and tissue damage. Hypochlorous acid is capable of degrading proteoglycan and decreasing the adhesion between extracellular matrix and endothelial cells, ultimately causing shearing of endothelial cells from the vessel wall and impaired endothelial function.[26]

MPO can also attenuate the fibrous cap of atherosclerotic plaques and enlarge their lipids centers, making them more prone to rupture. MPO-generated nitric oxide (NO) derivatives can also launch pathological incidents in the AS cascades. MPO could take advantage of the NO with the protective factor as the substrate, as well as produce various potential causing atherosclerosis factors. These elements are associated with the vulnerability of endothelium dysfunction and foam cells depositing in the atheromatous plaque.[27]

Lastly, MPO is a key enzyme in oxidizing both low and high-density lipoprotein (LDL/HDL). High levels of LDL, the main carrier of cholesterol through the body, are primary factor in atherosclerosis. Research shows that in order to promote the vascular disease process, LDL must be oxidatively modified to form oxidized LDL (ox-LDL).[28] Ox-LDL damages the artery intima and induces expression of endothelial adhesion molecules, colony-stimulating factors, vascular smooth muscle growth factors, and monocyte chemotaxis protein-1. The ox-LDL also induces the transformation of smooth muscle cells and monocytes to foam cells that accumulate under the endothelial cells and form the fatty streaks.

Fourth, MPO also promotes the HDL oxidation, and influences reverse cholesterol transport. HDL interactions with vascular endothelial cells are seen to be protective of vascular function by transporting redundant cellular cholesterol to the liver tissue. Thus, it could inhibit the platelet activation, increase the NO synthesis and release, and adjust the adhesion molecules expression in the endothelial cells and the endothelin secretion.[29] One study found that hypochlorous acid produced from MPO could oxidize apolipoprotein A-I (apo A-I) and cause reduced reverse cholesterol transport.[30] Its underlying possible mechanism is that MPO could influence the reaction of apo A-I and scavenger receptor B I.[31]

Despite the limitations of the current meta-analysis, we hope that this study will offer other researchers a comprehensive and improved perspective on the relationship between the *MPO* gene -436G/A polymorphism and CAD over past meta-analyses. Although the study performed by Chang et al[32] in 2013 found a significant correlation between the gene polymorphism and CAD, the small data set limited the conclusions that could be drawn from it. By combining data from 9 studies, in contrast to the 5 of Chang, we hope to provide a more comprehensive perspective. In 2014, Chen et al[33] also found a significant correlation. They found that the A allele of *MPO* -463G/A gene polymorphism is associated with decreased risk of CAD except in the Europeans. Deviation of these studies, which were also used in the works of Yin et al,[20] Li et al,[21] and Chen et al,[22] limits their objectivity. Work produced by Tang et al[34] in 2013 also included studies that were not at HWE.[21,22] In addition, the individual study by Du et al[35] was carried out by the similar author group to the study by Wu et al.[36] Hence, their results were not as accurate as that from the current meta-analysis.

In addition to the inevitable measurement errors, the large-scale researches on the relationship between CAD and *MPO* gene -463G/A polymorphism are still needed. Inevitably, plasma MPO levels are influenced by other genetic polymorphisms, such as the *MPO* gene -129A/G polymorphism and environmental factors, such as ethnicity, smoke, hypertension, hyperlipidemia, and diabetes mellitus.

5. Conclusions

The present meta-analysis indicates that the *MPO* gene -463G allele might increase CAD risk, especially in the Chinese population. It is our hope that the conclusion assists researchers in the search for an individualized treatment for CAD and that

future studies will build upon this study to further elucidate this important area of research.

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