Full text open access online (Since 2001)

PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330
Int J Hum Genet, 24(3): 258-266 (2024)
DOI: 10.31901/24566322.2024/24.03.889

Association Between the rs4880 Genetic Polymorphism of the Manganese Superoxide Dismutase 2 Gene and Coronary Artery Disease: A Meta-analysis of Case Control Studies

Long Chen[1,2,3], Yan Lin[1,2,3] and Jianna Zhang[1,2,3,*]

[1]Department of Emergency Medicine, West China Hospital, Sichuan University,West China School of Nursing, Sichuan University, China
[2]Institute of Disaster Medicine, Sichuan University, Sichuan, China
[3]Nursing Key Laboratory of Sichuan Province, Sichuan, China

KEYWORDS Antioxidative System. Atherosclerotic Cardiovascular Disease. Manganese Superoxide Dismutase 2 Gene. Oxidative Stress. Single Nucleotide Polymorphism

ABSTRACT Manganese superoxide dismutase 2 (MnSOD2) is pivotal for modulating oxidative stress in cells and is thought to be involved in the pathogenesis of coronary artery disease (CAD). The aim of this study was to determine the association of the MnSOD2 rs4880 polymorphism with the risk of CAD. Relevant studies were retrieved from the PubMed and Embase databases by applying predefined search strategies. A total of nine eligible studies were included in the final analysis. According to the pooled analysis of the association between the MnSOD2 rs4880 polymorphism and coronary artery diseases, there was no statistically significant association between rs4880 and the risk of CAD in the four genetic models, as the ORs were 1.03 (0.76-1.41) in the allele model, 0.97 (0.63-1.48) in the dominant model, 1.12 (0.78-1.60) in the recessive model and 1.17 (0.94-1.47) in the addictive model. The results suggested that the MnSOD2 rs4880 polymorphism was not associated with the risk of CAD.

INTRODUCTION

Coronary artery disease (CAD) is a common cardiovascular disease that is one of the leading causes of mortality and morbidity in both developed and developing countries. The classification of CAD includes chronic coronary syndrome (CCS) and acute coronary syndrome (ACS), of which myocardial infarction is the most severe clinical presentation (Knuuti et al. 2020). The formation of atherosclerotic plaques in coronary arteries is the essential pathophysiology of CAD, causing arterial stenosis and impaired blood and oxygen supplies to the heart muscle. Many traditional risk factors could contribute to the development and progression of CAD, including cigarette consumption, hyperlipidemia, obesity, hypertension and diabetes mellitus. Genetic factors also affect the occurrence of CAD. Family clustering of CAD was first reported early in the middle of the last century, and family history has been reported to be related to premature onset of CAD in relatives (Malakar et al. 2019). Many genetic variants have been found to increase the risk of or be responsible for the occurrence of CAD. For instance, mutations in the LDLR, APOB and PCSK9 genes cause familial hypercholesterolemia, which greatly increases the risk of CAD and the severity of arterial stenosis (Hobbs et al. 1990; Clarke et al. 2022).

In oxidative stress, the excessive generation of reactive oxygen species (ROS) cannot be neutralised by the body's innate antioxidant defence system, leading to tissue and cell injuries. Growing evidence has indicated that oxidative stress participates in the process of atherosclerosis and CAD (Kattoor et al. 2017). As one of the essential antioxidant systems in the vascular wall, superoxide dismutases (SODs), which can convert superoxide to hydrogen peroxide at the beginning of the ROS scavenging process, are important for atherosclerosis and CAD. SOD is classified into three isoforms based on its cellular distribution. SOD2 is mainly found in the mitochondrial matrix and also is known as manganese superoxide dismutase (MnSOD2) (Liu et al. 2022). Due to the generation of most cellular ROS in mitochondria, MnSOD2 has attracted much attention. Recent studies have reported that MnSOD2 plays a role in cardiovascular diseases. For instance, the overexpression of

[*]Address for correspondence:
Jianna Zhang,
Emergency Department of West China Hospital,
Sichuan University,
Guoxue Xiang #37, Chengdu, 610041,
Sichuan, People's Republic of China
Phone: 18980606994,
E-mail: 9318696@qq.com

MnSOD2 in brain tissues at specific locations could significantly decrease blood pressure in response to chronic infusion of angiotensin II (Case et al. 2017). MnSOD2 was also found to be involved in irisin-treated cardiomyocytes in anoxia/reoxygenation cell model (Wang et al. 2018).

Moreover, a study demonstrated that reducing MnSOD2 activity increases cardiac fibrosis and has a negative effect on heart function (Loch et al. 2009).

It has been reported that one of the most studied mutants of MnSOD2 (rs4880, c.47C>T, Ala16Val) might compromise the activity of antioxidant defence against reactive oxygen species (ROS) (Shimoda-Matsubayashi et al. 1996) and is associated with many diseases, such as stroke (Yadav and Yadav 2014), renal diseases (Abbasi et al. 2018; Jerotic et al. 2019) and cardiogenic shock (Charniot et al. 2011). However, the association of MnSOD2 rs4880 polymorphisms with coronary artery disease is controversial. Therefore, the researchers conducted this meta-analysis to investigate the relationship between MnSOD2 rs4880 polymorphisms and coronary artery disease.

MATERIALS AND METHODS

Search Strategy

To identify relevant studies exploring the association between MnSOD2 rs4880 polymorphisms and CAD, the researchers conducted literature searches up to January 2023 in two databases, PubMed and Embase, using the main keywords as "superoxide dismutase", "MnSOD", "polymorphisms", "Val16Ala", "rs4880" and "coronary artery disease", without language or publication date limitations. Articles on irrelevant topics or on other SODs were discarded. The bibliographies of relevant studies or reviews were scrutinised to avoid omissions.

Study Inclusion Criteria

The subjects included in this meta-analysis were patients with coronary artery disease (CAD), myocardial infarction (MI) or acute coronary syndrome (ACS), although there was a slight difference in disease definitions among the studies. Control subjects were defined as healthy individuals or patients without documented evidence of CAD according to specific studies. All retrieved studies were independently reviewed by two investigators to determine whether they were eligible for inclusion in this meta-analysis. When there were disagreements, a third investigator was consulted to reach a consensus after comprehensive discussions. The included studies met the following criteria:

1. were case-control studies or cohort studies with both CAD patients and unrelated non-CAD patients as defined
2. had detailed genotype data of interest for both CAD patients and non-CAD patients.

Studies of the following exclusion criteria were also removed:

1. studies that did not meet the previously mentioned inclusion criteria
2. literature and systematic reviews, meta-analyses, book chapters, guidelines, case reports, and case series
3. studies conducted on animals or cells.

Data Extraction

Using a predesigned form with the same format, two investigators independently performed the process of data extraction. The information extracted from the studies included the name of the first author, the year of publication, the study country, the definitions and characteristics of the case and control populations, and most importantly, the genotypes of different populations.

Statistical Analysis

The p-value of Hardy-Weinberg equilibrium (HWE) was calculated using the chi-square test in the control group of each study, and <0.05 indicated deviation from Hardy-Weinberg equilibrium. Pooled odds ratios (ORs) with the corresponding 95 percent confidence intervals (CIs) were measured to evaluate the association between MnSOD2 Val16Ala polymorphisms and CAD under four different inherited models, namely, the allele model (T allele versus C allele), dominant model (TT+TC versus CC), recessive model (TT versus TC+CC) and addictive model (TT+CC versus TC). Subgroup analysis was performed stratified by ethnicity, CAD subtype and control selection method. The Q test and I^2 statistic were used to detect heterogeneity between studies. If I^2>50% and p<0.05, a random effect model (REM) was adopted

as the pooling method, otherwise, a fixed effect model (FEM) was used. Meta-regression was further carried out to explore the possible sources of heterogeneity between studies. Begg's test and Egger's test were used to evaluate publication bias. Sensitivity analysis was performed by sequentially omitting individual studies to examine the consistency of the results. The statistical analyses described above were performed using RStudio software (version 1.2.1578). A p-value (two-tailed) <0.05 was considered to indicate statistical significance.

RESULTS

A total of 800 and 405 citations from PubMed and Embase respectively, were retrieved by applying the above mentioned search strategies. After 196 duplicates were removed, citations were further screened by glancing over titles and abstracts. Then, the remaining 24 studies were read to determine whether they were eligible for inclusion in the analysis. Finally, nine eligible studies (Chi et al. 2006; Fujimoto et al. 2008; Katakami et al. 2010; Chen et al. 2012; Souiden et al. 2016; Abdelrauf et al. 2017; Yeh et al. 2018; Decharatchakul et al. 2019; Yari et al. 2021) with a total of 7,486 subjects were included in the final analysis of the association between the MnSOD2 rs4880 polymorphism and coronary artery disease. The process of study selection is summarised in Figure 1.

Characteristics of the Included Studies

Of the nine studies, seven were conducted in Asia, and two were conducted in Africa, as presented in Table 1. There were more male subjects in all included studies due to higher prevalence rate in males than in females. The average age ranged from 53 to 71. The diagnostic criteria of patients in four studies (Chi et al. 2006; Yeh et al. 2018; Decharatchakul et al. 2019; Yari et al. 2021) were at least 50 percent stenosis of the coronary artery confirmed by coronary angiography, one study (Fujimoto et al. 2008) was 75 percent, and the remaining studies were performed according to hospital records, past medical history or clinical manifestations. Five studies (Katakami et al. 2010; Chen et al. 2012; Yeh et al. 2018; Decharatchakul et al. 2019; Yari et al. 2021) were hospital-based. Two studies (Katakami et al. 2010; Chen et al. 2012) focused on the diabetes population. The genotype distributions in the control group of all nine included studies were consistent with HWE. The MnSOD2 rs4880 polymorphism genotype distributions of each study are shown in Table 2.

Meta-analysis Results

Pooled analysis revealed no statistically significant associations between MnSOD2 rs4880 polymorphisms and coronary artery diseases ac-

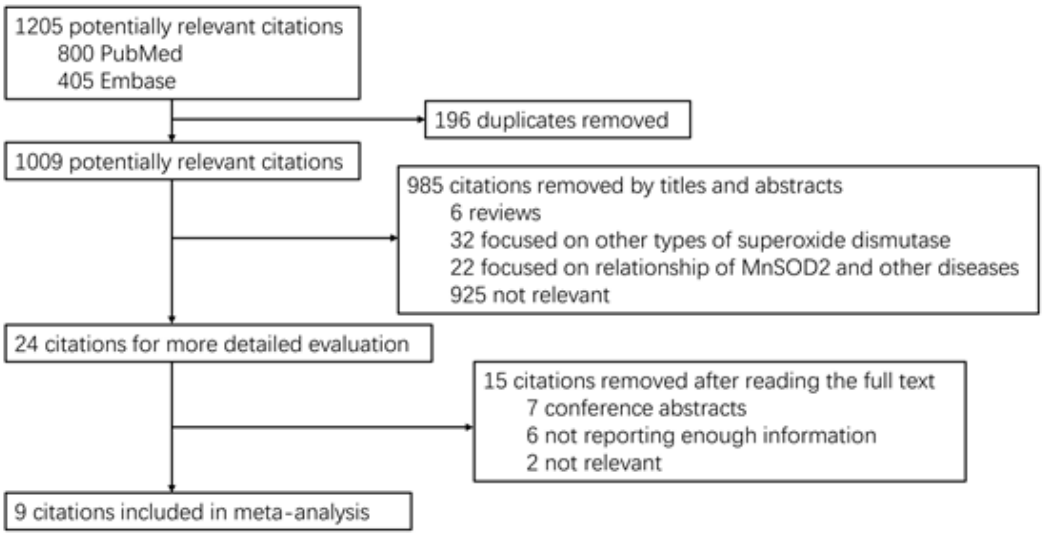

Fig. 1. Workflow of the study selection process

Table 1: Characteristics of the included studies

First author	*Year*	*Country*	*Definition of cases*	*Control selection*	*Sample size (case/control)*	*Age (case/control)*	*Male (%) (case/control)*
Abolfazl Yari	2021	Iranian	CAD, defined as a significant luminal narrowing (50% or more) in at least one main coronary artery.	hospital-based	250/250	53.5±6.9/53.0±5.9	56.4/51.6
Nisa Decharatchakul	2019	Thailand	CAD, at least one of the main coronary arteries e”50% luminal stenosis	hospital-based	225/164	61.0±9.2/61.0±9.2	68.9/44.5
Hseng-Long Yeh	2018	China	CAD, at least one of the main coronary arteries e”50% luminal stenosis	hospital-based	481/228	64.8±12.2/58.1±12.6	73.6/63.9
Lobna M Abdelrauf	2017	Egypt	AMI, defined as clinical presentation with ECG changes and/or elevated biochemical markers	healthy subjects	100/100	NS	55/60
Yosra Souiden	2016	Tunisia	ACS, defined as clinical presentation with ECG changes and/or elevated biochemical markers	healthy subjects	164/203	63.0±11.9/60.6±12.3	59.2/58.6
Hong Chen	2011	China	CAD in DM patients, defined as having a history of myocardial infarction, angina or coronary-artery bypass grafting	hospital-based	85/83	71.4±1.1/65.6±1.0	58.8/47.0
Naoto Katakami	2010	Japan	MI in DM patients, evaluated by clinical records, characteristic ECG changes, and coronary angiography and echocardio-graphy	hospital-based	226/3593	62.2±9.4/59.5±10.5	64.2/60.6
Hajime Fujimoto	2007	Japan	CAD and AMI, at least one of the main coronary arteries >75% luminal stenosis	healthy subjects	498/627	66.4+8.9/57.4+9.2	76.1/71.3
DS Chi	2006	China	CAD, defined as at least one of the main coronary arteries >50% luminal stenosis or met WHO diagnositic criteria of CAD	healthy subjects	161/100	66.4±10.2/66.6±6.4	50.9/53.0

Table 2: MnSOD2 rs4880 polymorphism genotype distributions of each study population

First author	*Year*	*CAD*			*non-CADp for HWE (control)*			*p ror*	*Newcastle -Ottawa*
		Val/Val (TT)	*Val/Ala (TC)*	*Ala/Ala (CC)*	*Val/Val (TT)*	*Val/Ala (TC)*	*Ala/Ala (CC)*	*HWE Control*	*Scale(NOS)*
Abolfazl Yari	2021	65	130	55	78	118	54	0.940	*****
sa Decharatchakul	2019	129	82	14	91	62	11	0.920	*****
Hseng-Long Yeh	2018	352	83	12	181	27	2	0.388	*****
Lobna M Abdelrauf	2017	49	31	20	21	42	37	0.168	*****
Yosra Souiden	2016	54	71	39	49	101	53	0.948	******
Hong Chen	2011	65	18	2	66	17	0	0.299	*****
Naoto Katakami	2010	176	46	4	2712	827	54	0.314	****
Hajime Fujimoto	2007	389	103	6	431	182	14	0.305	*****
DS Chi	2006	7	51	103	9	48	43	0.393	******

cording to the allele model (OR 1.03, 95% CI 0.76-1.41), dominant model (OR 0.97, 95% CI 0.63-1.48), recessive model (OR 1.12, 95% CI 0.78-1.60), or additive model (OR 1.17, 95% CI 0.94-1.47), as shown in Table 3 and Figure 2. However, in the subgroup analysis of MI, significant associations of MnSOD2 rs4880 polymorphisms with CAD were found in all four inherited models of allele (OR 1.67, 95% CI 1.09-2.55), dominant (OR 1.43, 95% CI 1.00-2.04), recessive (OR 1.96, 95% CI 1.16-3.32) and additive (OR 1.41, 95% CI 1.13-1.76) models. It is worth noting that the subgroup analysis of studies with healthy subjects as control groups showed a significant association between MnSOD2 rs4880 polymorphisms and CAD in the addictive model, and the heterogeneity decreased to zero.

Conspicuous heterogeneity existed across studies, as indicated by the Q test and I^2 statistic >50 percent. To explore the origins of heterogeneity, the researchers undertook a panel of subgroup analyses as described above and sensitivity analysis. As shown in Table 3, despite being stratified by ethnicity, subtypes of CAD and methods of control group selection, heterogeneity across studies seemed to remain. Sensitivity analysis confirmed the validity of the pooled meta-analysis results but could not identify a single study that contributed prominent heterogeneity to the results, as shown in Figure 3. Meta-regression was conducted with year of publication, country, sex ratio, age and control selection as variables, and none of those variables could explain the high heterogeneity among studies.

Publication bias was not detected in the pooled analysis, as evaluated by applying Begg's test (z=-1.4846, p=0.14) and Egger's test (t=-1.1592, p=0.29), despite the relatively limited number of included articles. These results indicated that there was no significant publication bias in this meta-analysis.

DISCUSSION

The present study aimed to investigate whether MnSOD2 polymorphisms are associated with CAD. The results of the pooled meta-analysis suggested that MnSOD2 rs4880 polymorphisms were not statistically significantly associated with CAD. However, it might be a risk factor for myocardial infarction, as indicated in subgroup analyses.

Table 3: Results of pooled and subgroup analyses in 4 applied inherited models

		Inherited model	*OR (95% CI)*	*P value*	*I^2(%)*	*FEM/REM*
Pooled Analysis		Allele	1.03 (0.76-1.41)	0.837	84	REM
		Dominant	0.97 (0.63-1.48)	0.884	65	REM
		Recessive	1.12 (0.78 -1.60)	0.545	78	REM
		Addictive	1.17 (0.94-1.47)	0.167	60	REM
Subgroup Analysis Ethnicity	Asia	Allele	0.89 (0.67-1.20)	0.457	81	REM
		Dominant	0.79 (0.50-1.24)	0.304	51	REM
		Recessive	0.94 (0.70-1.28)	0.707	72	REM
		Addictive	1.11 (0.84-1.47)	0.444	68	REM
	Non-Asia	Allele	1.75 (0.88-3.45)	0.110	86	REM
		Dominant	1.58 (0.78-3.22)	0.208	69	REM
		Recessive	2.30 (1.00-5.29)	0.050	79	REM
		Addictive	1.40 (1.00-1.95)	0.053	0.0	FEM
Subtypes of CAD	MI	Allele	1.67 (1.09-2.55)	0.018	81	REM
		Dominant	1.43 (1.00-2.04)	0.047	38	FEM
		Recessive	1.96 (1.16-3.32)	0.012	79	REM
		Addictive	1.41 (1.13-1.76)	0.013	40	FEM
	Non-MI	Allele	0.90 (0.58-1.40)	0.636	80	REM
		Dominant	0.73 (0.54-0.97)	0.028	50	FEM
		Recessive	0.93 (0.58-1.49)	0.750	74	REM
		Addictive	1.16 (0.76-1.76)	0.492	74	REM
Control Selection	Hospital-based	Allele	0.92(0.79-1.06)	0.240	43	FEM
		Dominant	0.89 (0.63-1.24)	0.484	0	FEM
		Recessive	0.90 (0.75-1.09)	0.280	40	FEM
		Addictive	0.94 (0.78-1.12)	0.485	19	FEM
	Healthy subjects	Allele	1.26 (0.74-2.15)	0.397	91	REM
		Dominant	1.16 (0.53-2.53)	0.707	85	REM
		Recessive	1.60 (0.95-2.70)	0.079	76	REM
		Addictive	1.56 (1.25-1.90)	“ÿ0.001	0	FEM

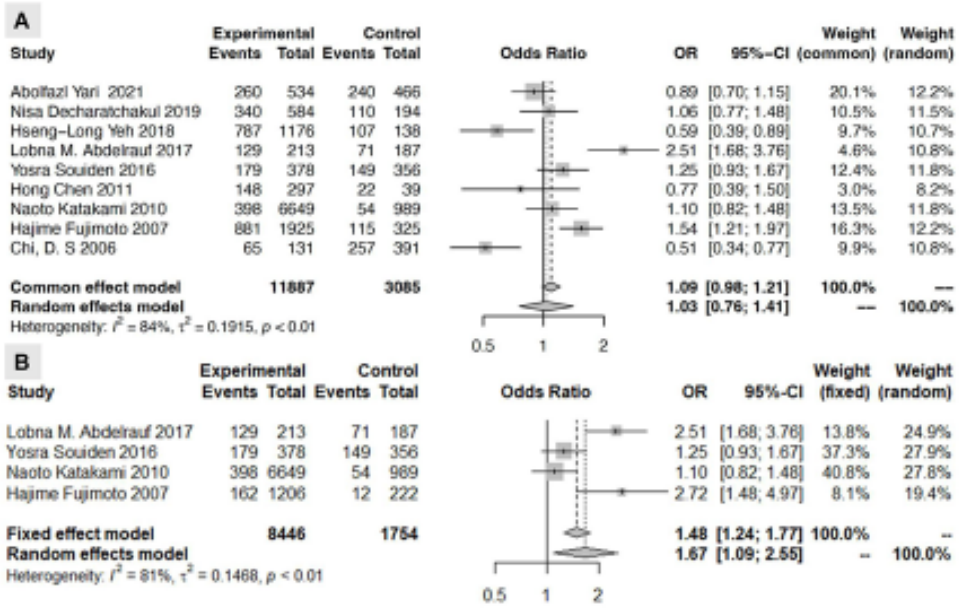

Fig. 2. Forest plots of the allele model. A is forest plot of the pooled meta-analysis of the allele model; B is the forest plot of the MI subgroup analysis of the allele model

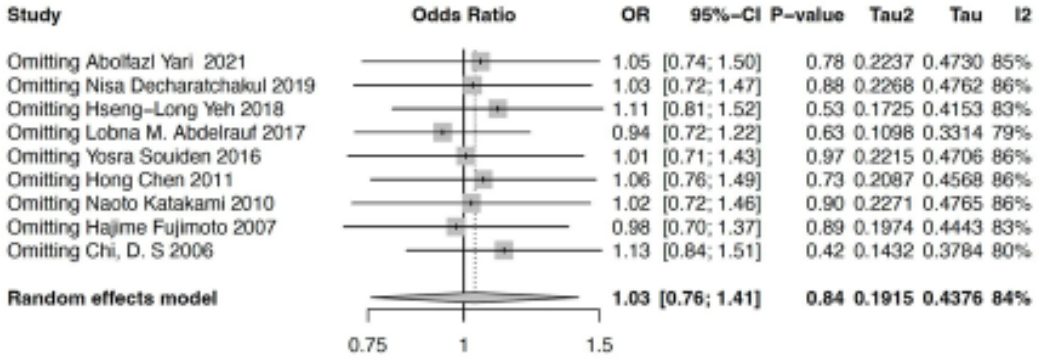

Fig. 3. Sensitivity analysis of pooled meta-analysis

Many studies have proven that oxidative stress plays an essential role in the pathogenesis and progression of atherosclerosis and coronary heart disease (Glass and Witztum 2001; Harrison et al. 2003; Dubois-Deruy et al. 2020), mainly by impairing the endothelial function of coronary arteries. Oxidative stress can reduce the production and availability of nitric oxide in endothelial cells, causing vasoconstriction, platelet aggregation and vascular smooth muscle cell proliferation, which eventually leads to atherosclerosis. Moreover, under the overproduction of reactive oxygen species, the oxidative modification of lipids and apolipoprotein B (Apo B) of low-density lipoprotein also acts as the initial factor of atherosclerosis (Glass and Witztum 2001), recruitment of leukocytes and macrophages and transition of smooth muscle cells in the vascular wall (Harrison et al. 2003; Kattoor et al. 2017). ROS in the body maintain balance through fine regulation of their production and elimination. MnSOD2, an important first-line antioxidative enzyme, is essential for eliminating ROS and could be a protective factor against atherosclerosis and coronary artery disease.

Although the Ala16Val variant of MnSOD2 was previously reported to impact its transportation to mitochondria and thus might affect its antioxidative function (Shimoda-Matsubayashi et al. 1996), it was not found to be associated with total antioxidant capacity (Abbasi et al. 2018) or SOD activity (Karahalil et al. 2011). An included study revealed that MnSOD activity was not significantly different in the cytosol of leukocytes but was significantly different in mitochondria between the non-valine/valine genotype and the valine/valine genotype (Fujimoto et al. 2008). Another study focused on extracellular superoxide dismutase activity revealed that vascular SOD activity was reduced in CAD patients but increased in young hypercholesterolemic individuals (Landmesser et al. 2000). These factors indicate the complexity of the oxidative and antioxidative systems in the pathogenesis of certain diseases. In contrast with conflicting results reported in previous studies (Chi et al. 2006; Fujimoto et al. 2008; Souiden et al. 2016; Yeh et al. 2018), the pooled analysis of the present study suggested that MnSOD2 rs4880 was not associated with CAD. In the four applied inherited models, there was only a possible difference in the addictive models (p=0.066). However, a subgroup analysis stratified by myocardial infarction showed a significant association between MnSOD2 rs4880 and MI. Although it is a subtype of CAD, MI, as the most severe manifestation of this disease, exhibits a different pathophysiological process than other subtypes. Compared with chronic atherosclerosis, MI is a relatively acute process initiated by the rupture of atherosclerotic plaques, and ROS production by macrophages and smooth muscle cells might be more critical than that by endothelial cells in maintaining plaque stability (Rajagopalan et al. 1996; Kobayashi et al. 2003). The valine variant of MnSOD2 polymorphisms in macrophages was previously reported to exacerbate oxLOL-induced apoptosis in vitro (Fujimoto et al. 2008). These differences could partly explain the different meta-analysis results of CAD and MI patients.

CONCLUSION

Although oxidative stress participates in the development of atherosclerosis and coronary heart

disease and manganese superoxide dismutase plays a pivotal role in the antioxidative system, the meta-analysis results suggested that the rs4880 heart disease.

RECOMMENDATIONS

Due to apparent heterogeneity across the included studies and the relatively small sample size, more investigations, including population investigations on a larger scale with standardised and unified protocols and experiments with drugs specifically targeting enhanced MnSOD2 activity in the heart, should be performed in the future to settle this dispute.

LIMITATIONS

Several limitations exist in this meta-analysis. Only nine studies were included in this analysis, and heterogeneity across studies was not identified. This could impact the reliability and validity of this meta-analysis, and additional studies with larger sample sizes are needed to confirm the findings of the analysis. In addition, the researchers did not consider other risk factors for CAD, such as environmental and genetic factors, pharmaceuticals and lifestyles.

ACKNOWLEDGEMENT

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

No competing interests were reported.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

Long Chen wrote the main manuscript text. Long Chen and Yan Lin prepared figures and tables and revised the manuscript. Chen Long and Jianna Zhang discussed and formed the idea of this study. Jianna Zhang provided the support for the research and edited the manuscript. All authors reviewed the manuscript.

REFERENCES

Abbasi M, Daneshpour MS, Hedayati M, Mottaghi A et al. 2018. The relationship between MnSOD Val16Ala gene polymorphism and the level of serum total antioxidant capacity with the risk of chronic kidney disease in type 2 diabetic patients: A nested case-control study in the Tehran lipid glucose study. *Nutr Metab (Lond)*, 15: 25.

Abdelrauf LM, Abdel Rahman MF, Abdel-Maksoud SM et al. 2017. Association of manganese superoxide dismutase Ala16Val polymorphism in the incidence of acute myocardial infarction in the Egyptians. *J Genet Eng Biotechnol*, 15: 415-418.

Case AJ, Tian J, Zimmerman MC 2017. Increased mitochondrial superoxide in the brain, but not periphery, sensitizes mice to angiotensin II-mediated hypertension. *Redox Biol*, 11: 82-90.

Charniot JC, Sutton A, Bonnefont-Rousselot D et al. 2011. Manganese superoxide dismutase dimorphism relationship with severity and prognosis in cardiogenic shock due to dilated cardiomyopathy. *Free Radic Res*, 45: 379-88.

Chen H, Yu M, Li M, Zhao R, Zhu Q et al. 2012. Polymorphic variations in manganese superoxide dismutase (Mn-SOD), glutathione peroxidase-1 (GPX1), and catalase (CAT) contribute to elevated plasma triglyceride levels in Chinese patients with type 2 diabetes or diabetic cardiovascular disease. *Mol Cell Biochem*, 363: 85-91.

Chi DS, Ling WH, Ma J, Xia M et al. 2006. Study of the association between paraoxonase1 55 Met/Leu, paraoxonase2 148 Ala/Gly and manganese superoxide dismutase (MnSOD) 9 Ala/Val genetic polymorphisms and coronary heart disease. *Zhonghua Liu Xing Bing Xue Za Zhi*, 27: 808-813.

Clarke SL, Tcheandjieu C, Hilliard AT, Lee KM et al. 2022. Coronary artery disease risk of familial hypercholesterolemia genetic variants independent of clinically observed longitudinal cholesterol exposure. *Circ Genom Precis Med*, 15: e003501.

Decharatchakul N, Settasatian C, Settasatian N, Komanasin N et al. 2019. Association of genetic polymorphisms in SOD2, SOD3, GPX3, and GSTT1 with hypertriglyceridemia and low HDL-C level in subjects with high risk of coronary artery disease. *PeerJ*, 7: e7407.

Dubois-Deruy E, Peugnet V, Turkieh A, Pinet F 2020. Oxidative stress in cardiovascular diseases. *Antioxidants (Basel)*, 9(9): 864.

Fujimoto H, Taguchi JI, Imai Y, Ayabe S et al. 2008. Manganese superoxide dismutase polymorphism affects the oxidized low-density lipoprotein-induced apoptosis of macrophages and coronary artery disease. *European Heart Journal*, 29: 1267-1274.

Glass CK, Witztum JL 2001. Atherosclerosis. the road ahead. *Cell*, 104: 503-16.

Harrison D, Griendling KK, Landmesser U et al. 2003. Role of oxidative stress in atherosclerosis. *Am J Cardiol*, 91: 7a-11a.

Hobbs HH, Russell DW, Brown MS, Goldstein JL 1990. The LDL receptor locus in familial hypercholesterolemia: Mutational analysis of a membrane protein. *Annu Rev Genet*, 24: 133-70.

Jerotic D, Matic M, Suvakov S, Vucicevic K et al. 2019. Association of Nrf2, SOD2 and GPX1 Polymorphisms with biomarkers of oxidative distress and survival in end-stage renal disease patients. *Toxins (Basel)*, 11(7): 431.

Karahalil B, Kesimci E, Emerce E, Gumus T, Kanbak O 2011. The impact of OGG1, MTH1 and MnSOD gene polymorphisms on 8-hydroxy-2'-deoxyguanosine and cellular superoxide dismutase activity in myocardial ischemia-reperfusion. *Mol Biol Rep*, 38: 2427-2435.

Katakami N, Kaneto H, Matsuoka TA, Takahara M et al. 2010. Accumulation of gene polymorphisms related to oxidative stress is associated with myocardial infarction in Japanese type 2 diabetic patients. *Atherosclerosis*, 212: 534-538.

Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL 2017. Oxidative Stress in Atherosclerosis. *Curr Atheroscler Rep*, 19: 42.

Knuuti J, Wijns W, Saraste A, Capodanno D et al. 2020. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*, 41: 407-477.

Kobayashi S, Inoue N, Ohashi Y, Terashima M et al. 2003. Interaction of oxidative stress and inflammatory response in coronary plaque instability: important role of C-reactive protein. *Arterioscler Thromb Vasc Biol*, 23: 1398-404.

Landmesser U, Merten R, Spiekermann S, Büttner K et al. 2000. Vascular extracellular superoxide dismutase activity in patients with coronary artery disease: relation to endothelium-dependent vasodilation. *Circulation*, 101: 2264-70.

Liu M, Sun X, Chen B, Dai R, Xi Z, Xu H 2022. Insights into manganese superoxide dismutase and human diseases. *Int J Mol Sci*, 23(24): 15893.

Loch T, Vakhrusheva O, Piotrowska I, Ziolkowski W et al. 2009. Different extent of cardiac malfunction and resistance to oxidative stress in heterozygous and homozygous manganese-dependent superoxide dismutase-mutant mice. *Cardiovasc Res*, 82: 448-57.

Malakar AK, Choudhury D, Halder B, Paul P et al. 2019. A review on coronary artery disease, its risk factors, and therapeutics. *J Cell Physiol*, 234: 16812-16823.

Rajagopalan S, Meng XP, Ramasamy S, Harrison DG, Galis ZS 1996. Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. *J Clin Invest*, 98: 2572-2579.

Shimoda-Matsubayashi S, Matsumine H, Kobayashi T, Nakagawa-Hattori Y, Shimizu Y, Mizuno Y 1996. Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene. A predictive evidence for conformational change to influence mitochondrial transport and a study of allelic association in Parkinson's disease. *Biochem Biophys Res Commun*, 226(2): 561-565. doi: 10.1006/bbrc.1996.1394.

Souiden Y, Mallouli H, Meskhi S, Chaabouni Y, Rebai A et al. 2016. MnSOD and GPx1 polymorphism relationship with coronary heart disease risk and severity. *Biol Res*, 49: 22.

Wang Z, Chen K, Han Y, Zhu H, Zhou X et al. 2018. Irisin protects heart against ischemia-reperfusion injury through a SOD2-dependent mitochondria mechanism. *J Cardiovasc Pharmacol*, 72: 259-269.

Yadav RK, Yadav R 2014. Association of SOD2 (rs4880) gene polymorphism, plasma lipid and lipoprotein with stroke. *Clinical Chemistry and Laboratory Medicine*, 52: S1360.

Yari A, Saleh-Gohari N, Mirzaee M, Hashemi F, Saeidi K 2021. A study of associations between rs9349379 (PHACTR1), rs2891168 (CDKN2B-AS), rs11838776 (COL4A2) and rs4880 (SOD2) polymorphic variants and coronary artery disease in Iranian population. *Biochemical Genetics*, 60(1): 106-126.

Yeh HL, Kuo LT, Sung FC, Yeh CC 2018. Association between polymorphisms of antioxidant gene (MnSOD, CAT, and GPx1) and risk of coronary artery disease. *Biomed Res Int*, 2018: 5086869.

Paper received for publication in January, 2024
Paper accepted for publication in April, 2024