Life Sciences 232 (2019) 116646

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

A meta-analysis on relationship between paraoxonase 1 polymorphisms and atherosclerotic cardiovascular diseases

Qinghua Zeng, Juan Zeng*

Center of General Practice, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, Sichuan, China

ARTICLE INFO

Keywords:
Paraoxonase 1 (*PON1*)
Polymorphisms
Atherosclerotic cardiovascular diseases (ASCVD)
Meta-analysis

ABSTRACT

Background: Some previous studies already explored associations between paraoxonase 1 (*PON1*) polymorphisms and atherosclerotic cardiovascular diseases (ASCVD), with conflicting findings. Here, we aimed to better analyze the relationship between *PON1* polymorphisms and ASCVD in a larger combined population by performing a meta-analysis.

Methods: We searched Pubmed, Embase and Web of Science for related articles. We calculated odds ratio (OR) and 95% confidence interval (CI) to estimate whether there are genetic associations between *PON1* polymorphisms and ASCVD.

Results: One hundred and nine studies were included for this meta-analysis. The *PON1* rs854560 (17,220 cases and 18,570 controls, recessive comparison: OR = 0.83, 95%CI 0.72–0.96) and rs662 (30,717 cases and 54,894 controls, dominant comparison: OR = 0.82, 95% CI 0.77–0.89; recessive comparison: OR = 1.17, 95% CI 1.07–1.28; allele comparison: OR = 0.85, 95% CI 0.81–0.90) polymorphisms were both found to be significantly associated with susceptibility to ASCVD in general population. Subgroup analyses by ethnicity revealed similar significant findings for rs854560 polymorphism only in East Asians, while similar positive findings for rs662 polymorphism were observed in Caucasians, East Asians and South Asians. Subgroup analyses by type of disease indicated that the significant findings for rs854560 polymorphism were mainly driven by the ischemic stroke (IS) subgroup, whereas the positive results for rs662 polymorphism were mainly driven by the coronary artery disease (CAD) subgroup.

Conclusions: In summary, this meta-analysis proved that *PON1* rs854560 polymorphism could be used to identify individual with elevated susceptibility to IS, whereas rs662 polymorphism could be used to identify individual with elevated susceptibility to CAD.

1. Introduction

Atherosclerotic cardiovascular diseases (ASCVD) usually manifest as coronary artery disease (CAD), ischemic stroke (IS) and peripheral arterial disease (PAD) [1]. It poses a huge threat to public health and is the leading cause of death all over the world [2]. Although the precise pathogenesis mechanism of ASCVD is still unrevealed, it was thought that genetic factors may contribute a lot to its development. First, the prevalence of ASCVD varies greatly across different populations [3], and difference in genetic components is likely to be one of reasons for this variation in disease prevalence. Second, previous genetic association studies showed that many genetic loci were significantly associated with an increased susceptibility to ASCVD [4–6]. Moreover, using the combination of these susceptible genetic loci to predict the risk of developing ASCVD in general population was also demonstrated to be effective and cost-saving [7].

Oxidative stress, featured by aggregation of superoxide free radicals, oxidation of membrane lipids and damage of DNA strands, is believed to be involved in the pathogenesis of ASCVD [8,9]. Paraoxonase 1 (PON1) is responsible for eliminating various toxins and metabolites [10]. Moreover, past pre-clinical studies demonstrated that PON1 could put down oxidative stress and relieve its associated cellular damage [11]. Consequently, it is possible that functional *PON1* polymorphisms, which could influence normal biological function of PON1, may also affect individual susceptibility to ASCVD.

In recent years, some investigations already studied potential associations between *PON1* polymorphisms and ASCVD. Nevertheless, the findings of these studies were not always consistent and the sample size

* Corresponding author at: Center of General Practice, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, No. 32 West Second Section First Ring Road, Chengdu 610027, Sichuan, China.
E-mail address: juanzeng6732@163.com (J. Zeng).

https://doi.org/10.1016/j.lfs.2019.116646
Received 28 June 2019; Received in revised form 8 July 2019; Accepted 9 July 2019
Available online 11 July 2019

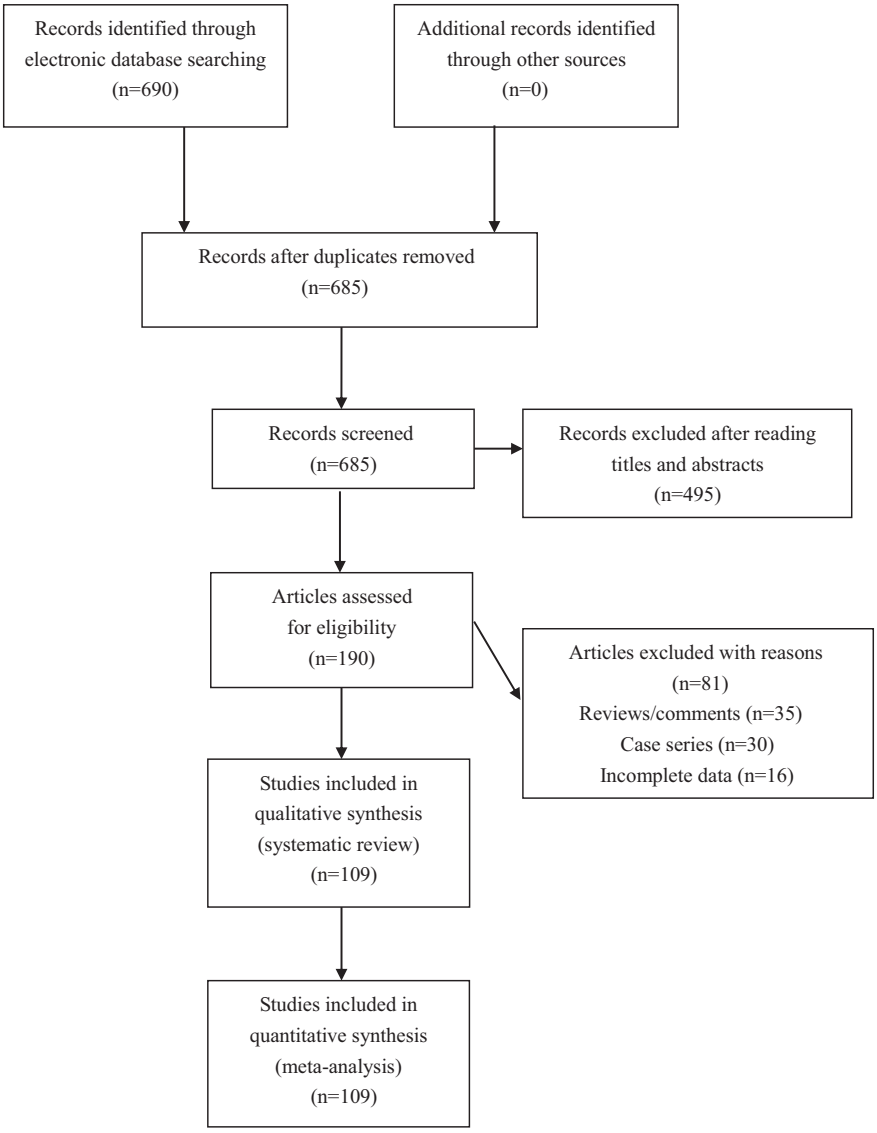

Fig. 1. Flowchart of study selection for the present study.

of each study was also statistically insufficient. In this meta-analysis, we aimed to better analyze the relationship between *PON1* polymorphisms and ASCVD in a larger combined population.

2. Materials and methods

This meta-analysis was written in accordance with PRISMA checklist [12]. We also created an Open Science Framework (osf.io) account to make this meta-analysis more publicly available.

2.1. Literature search and inclusion criteria

Eligible articles published before June 2019 were retrieved from PubMed, Web of Science, Embase and CNKI by using the following key words: “paraoxonase 1”, “paraoxonase-1”, “PON 1”, “PON-1”, “polymorphism”, “variant”, “variation”, “mutation”, “SNP”, “atherosclerosis”, “arteriosclerosis”, “coronary heart disease”, “coronary artery disease”, “angina pectoris”, “acute coronary syndrome”, “myocardial infarction”, “ischemic stroke”, “cerebral infarction”, “brain infarction”, “transient ischemic attack” and “peripheral arterial disease”. Additionally, we also checked the reference lists of all retrieved articles.

Inclusion criteria for this meta-analysis were as follows: (1) genetic association study about *PON1* polymorphisms and ASCVD in human beings; (2) providing distributions of genotypes in cases and controls; (3) available full text in English. We excluded studies when more than one of the following conditions was met: (1) studies that were not about *PON1* polymorphisms and ASCVD; (2) reviews or comments; (3) case reports or case series. If we found repeated publications by the same authors, only the most comprehensive study was included for this meta-analysis.

2.2. Data extraction and quality assessment

Following information was extracted by two authors: the last name of the first author and publication year, country of the principal investigator and ethnicity of study participants, type of disease, total sample size of each study and the distribution of *PON1* polymorphisms in cases and controls. We also calculated the probability value (p value) of Hardy-Weinberg equilibrium (HWE).

Newcastle-Ottawa scale (NOS) was used to evaluate the methodology quality of eligible studies [13]. The score of this scale ranged between zero and nine, if a study scored seven or more, we thought that the quality of this study was acceptable.

Data extraction and quality assessment were conducted by two

authors independently. We wrote to the corresponding authors for extra information when we thought that important information was missed.

2.3. Statistical analyses

Review Manager Version 5.3.3 was used in this meta-analysis for statistical analyses. We used the Z test to assess whether *PON1* polymorphisms were significantly associated with ASCVD, with the statistical significance p level set at 0.05. I^2 statistics were used to evaluate between-study heterogeneities. Random-effect models (DerSimonian-Laird method) were used if I^2 exceeded 50%. Otherwise, meta-analyses were conducted with fixed-effect models (Mantel-Haenszel method). We also conducted subgroup analyses by ethnicity of participants and type of disease. We tested the robustness of synthetic results in sensitivity analyses. We evaluated publication biases by funnel plots.

3. Results

3.1. Characteristics of included studies

Six hundred and ninety articles were identified by our comprehensive literature searching. One hundred and ninety articles were retrieved for eligibility assessment after exclusion of irrelevant and duplicate articles. Another thirty-five reviews and thirty case series were subsequently excluded, and sixteen other studies were excluded due to lack of essential data. Totally one hundred and nine eligible studies were ultimately included for this meta-analysis (Fig. 1). Table 1 presented essential data extracted from included studies.

3.2. Meta-analyses results

The *PON1* rs854560 (17,220 cases and 18,570 controls, recessive comparison: $p = 0.01$, OR = 0.83, 95%CI 0.72–0.96) and rs662 (30,717 cases and 54,894 controls, dominant comparison: $p < 0.0001$, OR = 0.82, 95%CI 0.77–0.89; recessive comparison: $p = 0.0005$, OR = 1.17, 95%CI 1.07–1.28; allele comparison: $p < 0.0001$, OR = 0.85, 95%CI 0.81–0.90) polymorphisms were both found to be significantly associated with susceptibility to ASCVD in general population. Subgroup analyses by ethnicity revealed similar significant findings for rs854560 polymorphism only in East Asians, but not in South Asians or Caucasians, while similar positive findings for rs662 polymorphism were observed in Caucasians, East Asians and South Asians. Subgroup analyses by type of disease indicated that the significant findings for rs854560 polymorphism were mainly driven by the IS subgroup, whereas the positive results for rs662 polymorphism were mainly driven by the CAD subgroup (Table 2).

3.3. Sensitivity analyses

We tested the effects of each study on meta-analysis results in sensitivity analyses. The meta-analysis results remained unchanged in sensitivity analyses, suggesting that our findings were statistically robust.

3.4. Publication biases

We evaluated publication biases by using funnel plots. We did not observe dissymmetry in any funnel plots, which indicated that the possibility that our meta-analysis results were affected by overt publication biases was low (Supplementary Fig. 1).

4. Discussion

In this meta-analysis, the combined results revealed that *PON1* rs854560 and rs662 polymorphisms were both significantly associated with susceptibility to ASCVD in certain populations. The significant findings for rs854560 polymorphism were mainly driven by the IS subgroup, whereas the positive results for rs662 polymorphism were mainly driven by the CAD subgroup. The meta-analysis results remained unchanged in sensitivity analyses, suggesting that our combined results were statistically robust.

There are few points that should be considered when interpreting our meta-analysis results. Firstly, pre-clinical studies proved that rs662 and rs854560 polymorphisms located in the coding region of *PON1* gene were both associated with altered enzymatic activity of PON1 [14]. So theoretically, it is possible that these two functional genetic variations may impact biological function of PON1, lead to excessive oxidative stress, and ultimately influence individual susceptibility to ASCVD. Considering the functional importance of these two polymorphisms, maybe our meta-analysis was still not statistically sufficient to detect the actual relationship between rs854560 polymorphism and ASCVD in subgroup analyses. So we call on further genetic association studies to confirm our findings, especially for rs854560 polymorphism. Secondly, as for evaluation of heterogeneities, we found that for two investigated polymorphisms, significant heterogeneities existed among included studies. Thus most of pooled analyses for these two polymorphisms were performed with REMs. But in further subgroup analyses, an obvious reduction of heterogeneity was found in East Asian, South Asian and IS subgroups, which suggested that differences in ethnic background and type of disease could somewhat explain observed heterogeneities between studies. The obvious heterogeneities existed between included studies for rs662 and rs854560 polymorphisms in combined analyses also indicated that the distribution of these polymorphisms varies greatly from population to population. Therefore, we should not generalize subgroup analyses results to a broader population. Thirdly, the aetiology of ASCVD is very complicated, consequently, we strongly recommend future studies to conduct haplotype analyses and investigate potential gene-gene interactions to more comprehensively explore the effects of genetics on disease susceptibility [15]. Fourthly, several recent meta-analyses also explored association between *PON1* polymorphisms and CAD or IS [16–19]. Nevertheless, many relevant articles were published in the past five years. So an update meta-analysis was feasible and the sample sizes of our combined analyses were also significantly larger than that of the previous studies. Moreover, previous meta-analyses usually focused on the most common investigated *PON1* polymorphism (rs662) or imposed strict restrictions on investigated populations, whereas we assessed relationship between two *PON1* polymorphisms and ASCVD without any restrictions on populations. So our work is a vital supplement to pre-existing literatures.

This meta-analysis has some limitations. First, our meta-analysis results were derived from unadjusted combined analyses, and failure to adjust for some crucial variables may impact the precision of our findings [20]. Second, environmental factors may also affect relationship between *PON1* polymorphisms and ASCVD. Regrettably, most of included studies only focus on genetic associations, so we could not conduct analyses regarding genetic-environmental interactions [21]. Thirdly, we did not search for grey literatures. So although we did not observe dissymmetry in any funnel plots, there is still possibility that publication biases may influence our meta-analysis results [22]. Fourthly, during literature searching, we did not find sufficient literatures to support combined analyses for other *PON1* polymorphisms. Since no any other *PON1* polymorphisms were studied by at least two eligible studies with regard to their associations with ASCVD, this meta-analysis only focus on relationship between two common *PON1* (rs662 and rs854560) polymorphisms and ASCVD.

In summary, this meta-analysis proved that *PON1* rs854560 polymorphism could be used to identify individual with elevated susceptibility to IS, whereas rs662 polymorphism could be used to identify individual with elevated susceptibility to CAD. However, further studies with larger sample sizes still need to verify our findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2019.116646.

Table 1
The characteristics of included studies for *PON1* polymorphisms and ASCVD.

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P*-value for HWE	NOS score
					Cases controls			
L55M (rs854560)					LL/LM/MM			
Ahmad 2012	India	South Asian	CAD	204/178	NA	NA	NA	7
Arca 2002	Italy	Caucasian	CAD	387/178	156/171/60	76/81/21	0.934	8
Aydin 2009	Turkey	Caucasian	CAD	221/136	92/103/26	42/45/49	< 0.001	8
Birjmohun 2009	The Netherlands	Caucasian	CAD	1050/2064	424/486/140	869/932/263	0.595	8
Bounafaa 2015	Morocco	African	ACS	205/100	76/105/24	52/42/6	0.513	7
Campo 2004	Italy	Caucasian	AS	124/84	54/55/15	38/35/11	0.517	7
Can Demirdöğen 2008	Turkey	Caucasian	IS	108/78	54/41/13	34/30/14	0.119	8
Cascarbi 1999	Poland	Caucasian	CAD	964/971	433/416/114	436/435/100	0.578	7
Chen 2017	China	East Asian	CAD	165/79	29/81/55	11/24/44	0.019	8
Chi 2006	China	East Asian	CAD	262/100	197/65/0	99/1/0	0.960	7
Demirdöğen 2009	Turkey	Caucasian	IS	172/105	83/68/21	44/42/19	0.120	8
El-Lebedy 2014	Egypt	Caucasian	AS	66/50	12/32/22	7/14/29	0.031	7
Ferré 2002	Spain	Caucasian	CAD	215/215	78/107/30	86/91/38	0.110	8
Gardemann 2000	Germany	Caucasian	CAD	1750/535	724/791/235	222/245/68	0.975	8
Grubisa 2013	Serbia	Caucasian	AS	60/100	20/36/4	45/46/9	0.569	7
Gupta 2011	India	South Asian	CAD	350/300	247/99/4	193/101/6	0.080	8
Han 2013	China	East Asian	AS	371/222	281/88/2	178/42/2	0.782	7
Huang 2006	China	East Asian	CI	153/153	148/5/0	143/10/0	0.676	7
Imai 2000	Japan	East Asian	CAD	208/431	179/28/1	371/55/5	0.078	7
Iwanicka 2017	Poland	Caucasian	CAD	232/221	96/103/33	94/109/18	0.078	8
Jarvik 2000	USA	Mixed	AS	106/106	40/55/11	42/51/13	0.680	7
Kallel 2010	Tunisia	Caucasian	MI	310/375	139/135/36	147/178/50	0.736	8
Kaman 2009	Turkey	Caucasian	CAD	277/92	123/123/31	30/43/19	0.620	8
Kang 2013	China	East Asian	CAD	515/536	491/24/0	515/19/2	< 0.0001	8
Kerkeni 2006	France	Caucasian	CAD	100/120	57/37/6	64/53/3	0.036	8
Koubaa 2009	Tunisia	Caucasian	ACS	91/118	46/35/10	69/45/4	0.302	8
Lakshmy 2010	India	South Asian	MI	124/154	80/41/3	88/63/3	0.028	8
Lazaros 2010	Greece	Caucasian	IS	178/181	73/90/15	79/83/19	0.683	8
Likidlilid 2010	Thailand	East Asian	CAD	106/103	97/9/0	101/2/0	0.921	8
Liu 2014	China	East Asian	CAD	792/864	709/79/4	759/98/7	0.059	8
Liu 2014	China	East Asian	CAD	400/400	355/42/3	360/39/1	0.958	8
Mackness 2019	Spain	Caucasian	CAD	410/274	146/219/45	102/146/26	0.010	8
Martinelli 2004	Italy	Caucasian	MI	618/272	224/305/89	99/126/47	0.527	7
Martinelli 2005	Italy	Caucasian	CAD	642/273	237/321/84	100/128/45	0.709	7
Martinelli 2009	Italy	Caucasian	MI	200/100	72/95/33	41/48/11	0.583	7
Martínez-Salazar 2018	Mexico	Mixed	IS	29/28	20/5/4	19/8/1	0.890	7
Mukamal 2009	USA	Mixed	MI	232/467	102/104/26	190/214/63	0.823	8
Oliveira 2004	Brazil	Mixed	CAD	351/379	165/167/19	151/183/45	0.354	8
Ozkök 2008	Turkey	Caucasian	CAD	139/119	51/65/23	32/40/47	< 0.001	8
Ranade 2005	USA	Mixed	IS	81/2535	31/45/5	1015/1199/321	0.255	8
Rejeb 2013	Tunisia	Caucasian	CAD	212/104	82/89/41	30/42/32	0.050	8
Rios 2007	Brazil	African	CAD	148/127	73/50/25	60/46/21	0.024	8
Rios 2007	Brazil	Caucasian	CAD	296/141	74/95/127	41/48/52	< 0.001	8
Rodríguez-Esparragón 2005	Spain	Caucasian	CAD	275/303	NA	NA	NA	7
Rodríguez-Esparragón 2017	Spain	Caucasian	IS	127/170	50/64/13	59/90/21	0.135	8
Saeed 2007	Pakistan	South Asian	MI	201/350	127/68/6	209/130/11	0.084	8
Salonen 1999	Finland	Caucasian	MI	55/110	20/22/13	45/54/11	0.370	7
Sanghera 1998	USA	South Asian	CAD	119/181	111/8/0	168/13/0	0.616	7
Sanghera 1998	USA	East Asian	CAD	114/183	71/40/3	119/54/10	0.248	7
Schiavon 2007	Italy	Caucasian	IS	126/92	55/61/10	43/39/10	0.796	8
Sen-Banerjee 2000	USA	Mixed	MI	492/518	267/195/30	288/188/42	0.153	8
Sesal 2009	Turkey	Caucasian	CAD	53/26	NA	NA	NA	7
Shin 2008	Korea	East Asian	IS	350/242	317/33/0	215/27/0	0.358	8
Taşkiran 2009	Turkey	Caucasian	CAD	120/102	56/56/8	67/30/5	0.498	7
Tobin 2004	UK	Caucasian	MI	547/505	221/240/86	204/235/66	0.896	7
Troughton 2008	UK	Caucasian	CAD	246/433	111/107/29	184/191/58	0.452	8
Ueno 2003	Japan	East Asian	CI	112/106	93/16/3	98/8/0	0.686	7
Voetsch 2002	USA	Mixed	IS	118/118	53/55/10	56/48/14	0.457	8
Watzinger 2002	Austria	Caucasian	CAD	43/260	27/12/4	104/116/40	0.419	7
Zama 1997	Japan	East Asian	CAD	75/115	65/10/0	94/21/0	0.281	8
Zhang 2013	China	East Asian	IS	337/498	307/29/1	459/38/1	0.819	7
Zhou 2009	China	East Asian	CAD	86/90	72/11/3	73/10/7	< 0.001	7
Q192R (rs662)					QQ/QR/RR			
Agirbasli 2011	Turkey	Caucasian	CAD	90/90	48/29/13	54/25/11	0.008	8
Ahmad 2012	India	South Asian	CAD	204/178	NA	NA	NA	7
Alharbi 2017	Saudi Arabia	South Asian	AS	100/100	40/48/12	57/36/7	0.689	7
Antikainen 1996	Finland	Caucasian	CAD	380/169	211/140/29	87/75/7	0.061	7
Aubó 2000	Spain	Caucasian	MI	156/310	84/60/12	154/123/33	0.261	7
Aydin 2009	Turkey	Caucasian	CAD	218/131	48/114/56	61/47/23	0.013	8
Aynacioglu 2000	Turkey	Caucasian	CAD	96/105	35/50/11	51/43/11	0.668	7

(*continued on next page*)

Table 1 (*continued*)

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P*-value for HWE	NOS score
					Cases controls			
L55M (rs854560)					LL/LM/MM			
Balcerzyk 2008	Poland	Caucasian	CAD	178/180	107/64/7	86/71/23	0.175	8
Baum 2006	China	East Asian	MI	231/310	102/91/38	110/135/65	0.052	8
Baum 2006	China	East Asian	IS	242/310	91/119/32	110/135/65	0.052	8
Bayrak 2012	Turkey	Caucasian	CAD	102/106	48/47/7	55/46/5	0.231	7
Bhaskar 2011	India	South Asian	CAD	250/120	65/140/45	40/66/14	0.091	7
Birjmohun 2009	The Netherlands	Caucasian	CAD	1055/2116	548/415/92	1092/847/177	0.481	8
Bounafaa 2015	Morocco	African	ACS	205/100	105/65/35	57/39/4	0.397	7
Campo 2004	Italy	Caucasian	AS	124/84	58/56/10	39/37/8	0.856	7
Can Demirdöğen 2008	Turkey	Caucasian	IS	108/78	48/42/18	31/40/7	0.241	8
Cascarbi 1999	Poland	Caucasian	CAD	963/971	512/387/64	511/389/71	0.797	7
Chen 2013	Taiwan	East Asian	CAD	213/162	64/78/71	44/84/34	0.602	8
Chen 2017	China	East Asian	CAD	165/79	75/70/20	52/18/9	0.002	8
Cozzi 2013	Italy	Caucasian	AS	42/63	24/14/4	33/26/4	0.707	7
Demirdöğen 2009	Turkey	Caucasian	IS	172/105	77/74/21	46/50/9	0.370	8
Deshpande 2013	India	South Asian	CAD	249/243	85/114/50	89/118/36	0.759	8
El-Lebedy 2014	Egypt	Caucasian	AS	66/50	21/36/9	33/12/5	0.033	7
Fallah 2010	Iran	South Asian	CAD	145/157	42/71/32	73/66/18	0.602	7
Ferré 2002	Spain	Caucasian	CAD	215/215	105/87/23	106/93/16	0.473	8
Gardemann 2000	Germany	Caucasian	CAD	1750/535	869/748/133	279/216/40	0.839	8
Gluba 2010	Poland	Caucasian	MI	275/139	132/118/25	89/40/10	0.077	7
Grubisa 2013	Serbia	Caucasian	AS	60/100	33/22/5	53/39/8	0.826	7
Gu 2013	China	East Asian	AS	539/536	222/243/74	216/252/68	0.678	7
Gupta 2011	India	South Asian	CAD	350/300	127/170/53	168/108/24	0.264	8
Guxens 2008	Spain	Caucasian	MI	746/1796	NA	NA	NA	7
Han 2013	China	East Asian	AS	688/1226	296/328/64	560/524/142	0.251	7
Hassan 2013	Saudi Arabia	South Asian	CAD	121/108	40/57/24	60/37/11	0.154	8
Herrmann 1996	France	Caucasian	MI	701/642	362/265/74	307/268/67	0.455	7
Huang 2006	China	East Asian	CI	153/153	53/79/21	56/82/15	0.055	7
Imai 2000	Japan	East Asian	CAD	208/431	179/28/1	371/55/5	0.078	7
Ito 2002	Japan	East Asian	CAD	214/212	21/109/84	45/109/58	0.639	7
Jarvik 2000	USA	Mixed	AS	106/106	55/43/8	50/48/8	0.444	7
Juan 2017	China	East Asian	IS	1007/1151	362/513/132	458/559/134	0.062	7
Kallel 2010	Tunisia	Caucasian	MI	310/375	129/127/54	191/143/41	0.075	8
Kaman 2009	Turkey	Caucasian	CAD	277/92	117/114/46	43/41/8	0.686	8
Kang 2013	China	East Asian	CAD	515/537	71/214/230	76/222/239	0.039	8
Kerkeni 2006	France	Caucasian	CAD	100/119	62/31/7	80/35/4	0.943	8
Ko 1998	Taiwan	East Asian	CAD	218/218	25/102/91	30/96/92	0.538	8
Koch 2001	Germany	Caucasian	IS	149/241	79/64/6	127/99/15	0.457	8
Kotur-Stevuljevic 2006	Serbia	Caucasian	CAD	113/148	68/32/13	81/50/17	0.040	7
Koubaa 2009	Tunisia	Caucasian	ACS	91/118	49/36/6	74/39/5	0.961	8
Lakshmy 2010	India	South Asian	MI	124/221	42/70/12	108/100/13	0.102	8
Lazaros 2010	Greece	Caucasian	IS	178/181	100/71/7	94/79/8	0.086	8
Li 2005	USA	Mixed	MI	154/154	27/66/61	31/73/50	0.644	7
Likidlilid 2010	Thailand	East Asian	CAD	161/103	27/84/98	24/36/43	0.005	8
Liu 2010	China	East Asian	IS	131/135	16/54/61	27/63/45	0.563	8
Liu 2014	China	East Asian	CAD	792/864	110/405/277	164/452/248	0.098	8
Liu 2014	China	East Asian	CAD	400/400	47/205/148	71/212/117	0.138	8
Lopez-mejias 2014	Spain	Caucasian	AS	333/252	172/136/25	125/98/29	0.152	7
Luu 2011	USA	Caucasian	CAD	1429/8501	719/569/141	4236/3564/701	0.204	7
Luu 2011	USA	African	CAD	440/2009	48/186/206	371/1432/1347	< 0.001	7
Luu 2011	USA	Caucasian	IS	327/9603	168/135/24	4787/3998/818	0.681	7
Luu 2011	USA	African	IS	267/3323	39/119/109	380/1499/1444	0.762	7
Mackness 2019	Spain	Caucasian	CAD	410/274	206/172/32	155/97/22	0.222	8
Mahrooz 2014	Iran	South Asian	IS	82/90	NA	NA	NA	7
Man 2010	China	East Asian	IS	191/162	22/95/74	34/75/53	0.436	8
Martinelli 2004	Italy	Caucasian	MI	618/272	313/245/60	136/117/19	0.359	7
Martinelli 2005	Italy	Caucasian	CAD	642/273	326/254/62	135/118/20	0.400	7
Martinelli 2009	Italy	Caucasian	MI	200/100	102/85/13	49/40/11	0.516	7
Martínez-Salazar 2018	Mexico	Mixed	IS	29/28	8/12/9	6/14/8	0.978	7
Masud 2011	Pakistan	South Asian	CAD	129/101	NA	NA	NA	7
Mohamed 2010	Egypt	Caucasian	CAD	150/50	18/56/76	23/17/10	0.056	7
Mukamal 2009	USA	Mixed	MI	233/465	118/97/18	241/177/47	0.091	8
Oliveira 2004	Brazil	Mixed	CAD	351/376	166/152/33	160/174/42	0.605	8
Ombres 1998	Italy	Caucasian	CAD	310/162	144/139/27	82/62/18	0.236	7
Osei-Hyiaman 2001	Japan	East Asian	CAD	201/231	136/43/22	181/44/6	0.107	7
Ozkök 2008	Turkey	Caucasian	CAD	139/119	36/72/31	59/46/14	0.286	8
Pati 1998	India	South Asian	CAD	120/80	30/70/20	60/12/8	< 0.001	7
Pfohl 1999	Germany	Caucasian	CAD	170/118	73/77/20	66/44/8	0.856	7
Rahman 2015	Egypt	Caucasian	MI	102/72	39/50/13	48/18/6	0.040	7
Ranade 2005	USA	Mixed	IS	81/2547	25/45/11	1328/985/214	0.104	8
Rejeb 2013	Tunisia	Caucasian	CAD	212/104	86/91/35	49/39/16	0.090	8

(*continued on next page*)

Table 1 (*continued*)

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotype distribution		*P*-value for HWE	NOS score
					Cases controls			
L55M (rs854560)					LL/LM/MM			
Rios 2007	Brazil	Caucasian	CAD	296/141	128/113/55	71/47/23	0.003	8
Rios 2007	Brazil	African	CAD	148/125	58/49/41	39/55/31	0.193	8
Rodríguez-Esparragón 2005	Spain	Caucasian	CAD	304/315	NA	NA	NA	7
Rodríguez-Esparragón 2017	Spain	Caucasian	IS	129/174	63/62/4	84/72/18	0.660	8
Ruiz 1995	Switzerland	Caucasian	CAD	171/263	91/71/9	147/108/8	0.024	7
Saeed 2007	Pakistan	South Asian	MI	203/349	75/102/26	166/137/46	0.041	8
Sanghera 1998	USA	South Asian	CAD	114/175	30/70/14	84/73/18	0.717	7
Sanghera 1998	USA	East Asian	CAD	116/142	17/56/43	27/67/48	0.675	7
Scacchi 2003	Italy	Caucasian	CAD	200/181	123/62/15	112/61/8	0.933	7
Schiavon 2007	Italy	Caucasian	IS	126/92	58/56/12	44/36/12	0.293	8
Sen-Banerjee 2000	USA	Mixed	MI	492/518	230/257/5	279/226/13	< 0.001	8
Sentí 2001	Spain	Caucasian	MI	930/1031	489/289/152	532/337/162	< 0.001	7
Serrato 1995	USA	Mixed	CAD	223/247	68/115/40	120/99/28	0.276	7
Sesal 2009	Turkey	Caucasian	CAD	53/26	NA	NA	NA	7
Shabana 2018	Pakistan	South Asian	CAD	219/404	84/84/51	118/175/111	0.007	8
Shin 2008	Korea	East Asian	IS	350/242	156/194/0	103/139/0	< 0.001	8
Su 2005	China	East Asian	CAD	184/239	24/75/85	40/116/83	0.961	7
Suehiro 1996	Japan	East Asian	CAD	134/252	20/67/47	34/124/94	0.492	7
Taşkiran 2009	Turkey	Caucasian	CAD	120/102	67/48/5	64/36/2	0.227	7
Tobin 2004	UK	Caucasian	MI	547/505	291/206/50	261/210/34	0.342	7
Topić 2001	Croatia	Caucasian	IS	56/124	28/23/5	58/61/5	0.023	7
Ueno 2003	Japan	East Asian	CI	112/106	22/40/50	24/37/45	0.005	7
Vaisi-Raygani 2011	Iran	South Asian	CAD	280/134	NA	NA	NA	7
Voetsch 2002	USA	Mixed	IS	118/118	36/63/19	50/62/6	0.017	8
Wang 2002	China	East Asian	CAD	474/495	80/218/176	52/230/193	0.177	7
Wang 2003	China	East Asian	CAD	39/74	5/22/12	28/37/9	0.544	7
Watzinger 2002	Austria	Caucasian	CAD	43/260	20/22/1	147/96/17	0.804	7
Xing 2009	China	East Asian	CAD	128/110	29/68/31	22/54/34	0.947	8
Zama 1997	Japan	East Asian	CAD	75/115	39/33/3	37/61/17	0.314	8
Zhang 2013	China	East Asian	IS	507/489	204/217/86	207/208/74	0.072	7
Zuliani 2002	Italy	Caucasian	AS	60/161	38/14/8	34/108/19	< 0.001	7

Abbreviations: ASCVD, Atherosclerotic cardiovascular diseases; AS, Atherosclerosis; CAD, Coronary artery disease; ACS, Acute coronary syndrome; MI, Myocardial infarction; IS, Ischemic stroke; CI, Cerebral infarction; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; NA, Not available.

Authors' contributions

Qinghua Zeng and Juan Zeng conceived of the study, participated in its design. Qinghua Zeng and Juan Zeng conducted the systematic literature review. Qinghua Zeng and Juan Zeng performed data analyses. Qinghua Zeng and Juan Zeng drafted the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgments

None.

Funding

None.

Table 2
Meta-analysis results for *PON1* polymorphisms and ASCVD.

Polymorphisms	Population	Sample size	Dominant comparison	Recessive comparison	Over-dominant comparison	Allele comparison
			P value OR (95% CI)	*P* value OR (95% CI)	*P* value OR (95% CI)	*P* value OR (95% CI)
L55M (rs854560)	Overall	17,220/18570	0.95 1.00 (0.95–1.05)	**0.01 0.83 (0.72–0.96)**	0.05 1.05 (1.00–1.10)	0.11 1.05 (0.99–1.12)
	Caucasian	10,414/8907	0.74 1.01 (0.95–1.07)	0.14 0.88 (0.74–1.04)	0.29 1.03 (0.97–1.10)	0.18 1.06 (0.97–1.14)
	East Asian	4046/4122	0.47 0.92 (0.74–1.15)	**0.001 0.52 (0.35–0.77)**	0.11 1.22 (0.96–1.54)	0.88 0.98 (0.78–1.23)
	South Asian	998/1163	0.21 1.13 (0.93–1.36)	0.65 0.85 (0.42–1.73)	**0.04 0.80 (0.65–0.99)**	0.05 1.20 (1.00–1.44)
	CAD	14,602/13702	0.73 1.01 (0.96–1.07)	0.10 0.87 (0.73–1.03)	0.26 1.03 (0.98–1.09)	0.15 1.06 (0.98–1.14)
	IS	1891/4306	0.91 1.01 (0.86–1.18)	**0.03 0.73 (0.55–0.97)**	0.26 1.10 (0.94–1.28)	0.29 1.07 (0.94–1.21)
Q192R (rs662)	Overall	30,717/54894	< **0.0001 0.82 (0.77–0.89)**	**0.0005 1.17 (1.07–1.28)**	0.09 1.06 (0.99–1.14)	< **0.0001 0.85 (0.81–0.90)**
	Caucasian	16,792/32534	**0.03 0.90 (0.82–0.99)**	**0.001 1.14 (1.05–1.23)**	0.32 1.04 (0.96–1.13)	**0.001 0.89 (0.83–0.96)**
	East Asian	7700/8258	**0.04 0.87 (0.76–0.99)**	**0.01 1.19 (1.04–1.37)**	0.91 1.00 (0.94–1.07)	**0.04 0.90 (0.82–0.99)**
	South Asian	2690/2760	< **0.0001 0.54 (0.41–0.70)**	**0.0003 1.38 (1.16–1.64)**	**0.003 1.54 (1.16–2.04)**	**0.0002 0.67 (0.54–0.83)**
	CAD	24,084/32764	< **0.0001 0.78 (0.72–0.86)**	**0.0006 1.21 (1.09–1.36)**	0.05 1.09 (1.00–1.19)	< **0.0001 0.83 (0.77–0.89)**
	IS	4515/19452	0.06 0.92 (0.85–1.00)	0.27 1.06 (0.95–1.19)	0.40 1.03 (0.96–1.12)	0.17 0.94 (0.86–1.03)

Abbreviations: ASCVD, Atherosclerotic cardiovascular diseases; CAD, Coronary artery disease; IS, Ischemic stroke; OR, Odds ratio; CI, Confidence interval; NA, Not available.
The values in bold represent there is statistically significant differences between cases and controls.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Ethical statement

This article does not contain any studies with human participants or animals performed by any of the authors, thus ethical approval and informed consent are not required.

References

[1] A. Rognoni, C. Cavallino, A. Veia, S. Bacchini, R. Rosso, M. Facchini, G.G. Secco, A. Lupi, F. Nardi, F. Rametta, A.S. Bongo, Pathophysiology of atherosclerotic plaque development, Cardiovasc. Hematol. Agents Med. Chem. 13 (2015) 10–13.

[2] P. Libby, P.M. Ridker, G.K. Hansson, Progress and challenges in translating the biology of atherosclerosis, Nature. 473 (2011) 317–325.

[3] W. Herrington, B. Lacey, P. Sherliker, J. Armitage, S. Lewington, Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease, Circ. Res. 118 (2016) 535–546.

[4] X. Chen, S. Li, Y. Yang, X. Yang, Y. Liu, Y. Liu, W. Hu, L. Jin, X. Wang, Genome-wide association study validation identifies novel loci for atherosclerotic cardiovascular disease, J. Thromb. Haemost. 10 (2012) 1508–1514.

[5] P. van der Harst, N. Verweij, Identification of 64 novel genetic loci provides an expanded view on the genetic architecture of coronary artery disease, Circ. Res. 122 (2018) 433–443.

[6] NINDS Stroke Genetics Network (SiGN), International Stroke Genetics Consortium (ISGC), Loci associated with ischaemic stroke and its subtypes (SiGN): a genome-wide association study, Lancet Neurol. 15 (2016) 174–184.

[7] B. Mayer, J. Erdmann, H. Schunkert, Genetics and heritability of coronary artery disease and myocardial infarction, Clin. Res. Cardiol. 96 (2007) 1–7.

[8] F. Violi, L. Loffredo, R. Carnevale, P. Pignatelli, D. Pastori, Atherothrombosis and oxidative stress: mechanisms and management in elderly, Antioxid. Redox Signal. 27 (2017) 1083–1124.

[9] P. Pignatelli, D. Menichelli, D. Pastori, F. Violi, Oxidative stress and cardiovascular disease: new insights, Kardiol. Pol. 76 (2018) 713–722.

[10] N. Shunmoogam, P. Naidoo, R. Chilton, Paraoxonase (PON)-1: a brief overview on genetics, structure, polymorphisms and clinical relevance, Vasc. Health Risk Manag. 14 (2018) 137–143.

[11] H.L. Li, D.P. Liu, C.C. Liang, Paraoxonase gene polymorphisms, oxidative stress, and diseases, J Mol Med (Berl). 81 (2003) 766–779.

[12] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (2009) 264–269.

[13] A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur. J. Epidemiol. 25 (2010) 603–605.

[14] S.P. Deakin, R.W. James, Genetic and environmental factors modulating serum concentrations and activities of the antioxidant enzyme paraoxonase-1, Clin Sci (Lond). 107 (2004) 435–447.

[15] A. Nishi, D.A. Milner Jr., E.L. Giovannucci, R. Nishihara, A.S. Tan, I. Kawachi, S. Ogino, Integration of molecular pathology, epidemiology and social science for global precision medicine, Expert. Rev. Mol. Diagn. 16 (2016) 11–23.

[16] Zhang Z, Ou J, Cai P, Niu B, Li J. Association between the PON1 Q192R polymorphism and coronary heart disease in Chinese: a meta-analysis. Medicine (Baltimore). 2018; 97: e11151.

[17] F. Rodríguez-Esparragón, J.C. López-Fernández, N. Buset-Ríos, M.A. García-Bello, E. Hernández-Velazquez, L. Cappiello, J.C. Rodríguez-Pérez, Paraoxonase 1 and 2 gene variants and the ischemic stroke risk in Gran Canaria population: an association study and meta-analysis, Int J Neurosci. 127 (2017) 191–198.

[18] H. Liu, P. Xia, M. Liu, X.M. Ji, H.B. Sun, L. Tao, Q.W. Mu, PON gene polymorphisms and ischaemic stroke: a systematic review and meta analysis, Int. J. Stroke 8 (2013) 111–123.

[19] D.A. Lawlor, I.N. Day, T.R. Gaunt, L.J. Hinks, P.J. Briggs, M. Kiessling, N. Timpson, G.D. Smith, S. Ebrahim, The association of the PON1 Q192R polymorphism with coronary heart disease: findings from the British Women's heart and health cohort study and a meta-analysis, BMC Genet. 5 (2004) 17.

[20] X. Xie, X. Shi, M. Liu, The roles of TLR gene polymorphisms in atherosclerosis: a systematic review and meta-analysis of 35,317 subjects, Scand. J. Immunol. 86 (2017) 50–58.

[21] Liu A, Wan A, Feng A, Rui R, Zhou B. ICAM-1 gene rs5498 polymorphism decreases the risk of coronary artery disease. Medicine (Baltimore). 2018; 97: e12523.

[22] Z. Luo, Z. Lu, I. Muhammad, Y. Chen, Q. Chen, J. Zhang, Y. Song, Associations of the MTHFR rs1801133 polymorphism with coronary artery disease and lipid levels: a systematic review and updated meta-analysis, Lipids Health Dis. 17 (2018) 191.