Original Article

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Paraoxonase 1 gene (Q192R) polymorphism confers susceptibility to coronary artery disease in type 2 diabetes patients: Evidence from case-control studies

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Summary **Numerous published studies have investigated the relationship between the paraoxonase 1 (*PON1*) gene Q192R (rs662) polymorphism and the risk of coronary artery disease (CAD) in type 2 diabetes mellitus (T2DM) patients. However, the results are still conflicting and inconclusive. Potentially eligible articles were searched for in related databases. Odds ratios (OR) with 95% confidence intervals (CI) were used to estimate the associations. Subgroup analysis was performed based on ethnicity. Ten case-control studies were included. A significant increase in the susceptibility for CAD in T2DM patients was found in the allelic model (OR = 1.49, $p < 0.001$), homozygote model (OR = 2.47, $p < 0.001$), heterozygote model (OR = 1.47, $p < 0.001$), dominant model (OR = 1.64, $p < 0.001$), and recessive model (OR = 1.74, $p = 0.001$). In subgroup analysis by ethnicity, a significant increase susceptibility was found in Asian populations in the allelic model (OR = 1.39, $p = 0.001$), homozygote model (OR = 2.15, $p = 0.002$), heterozygote model (OR = 1.37, $p = 0.006$), recessive model (OR = 1.65, $p = 0.012$), and dominant model (OR = 1.54, $p < 0.001$). A similar significant increase in susceptibility was found in Caucasian populations in the allelic model (OR = 1.75, $p = 0.002$), homozygote model (OR = 3.39, $p = 0.002$), recessive model (OR = 1.98, $p = 0.030$), heterozygote model (OR = 1.64, $p = 0.001$), and dominant model (OR = 1.83, $p < 0.001$). The results suggest that the *PON1* Q192R polymorphism is associated with a significantly increased risk of CAD in T2DM patients in both Asian and Caucasian populations.**

Keywords: *PON1*, coronary artery disease, type 2 diabetes mellitus, polymorphism, meta-analysis

1. Introduction

Diabetes mellitus along with insulin resistance, hypertension, and hyperlipidemia are closely associated with the development of coronary artery disease (CAD), which is reported to be one of the major causes of morbidity and mortality in certain developed countries (*1,2*). In addition to these traditional cardiovascular risk factors, a genetic predisposition is considered to have an important role in the development of CAD (*3*). Multiple genes are likely to be involved in the pathogenesis of CAD, including those with role in lipoprotein metabolism (*4*). Despite the fact that low- and high-density lipoprotein (LDL and HDL, respectively) cholesterol levels may be normal in patients with T2DM, lipoprotein glycation could be the reason for this abnormality (*5*). Therefore, genetic markers involved in lipoprotein metabolism and modification may be remarkably important in the development process of CAD in patients with T2DM.

Human PON1/arylesterase is an HDL-associated Ca^{2+} dependent glycoprotein (lactonase), which

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presents antioxidant and anti-atherogenic features through paraoxon hydrolysis (*6*). PON1 is an HDL-associated esterase that hydrolyses lipoperoxides. It acts as a protective factor against oxidative modifications of LDL, indicating that it may play a vital role in the prevention of the atherosclerotic process (*7*). The *PON1* gene, localized on chromosome 7q21.3, is 26,857 bp long containing 9 exons, and codes for a glycoprotein that is situated on the surface of HDLs and plays a significant role in preventing LDL oxidation (*8*). Human serum paraoxonase activity towards paraoxon presents varying interindividual mutations and underlies strict genetic control. The molecular basis of this mutation and declined PON1 activity is a polymorphism in the coding region of the gene, which leads to a glutamine (Gln)/arginine (Arg) amino acid substitution in position 192 (*9,10*). Recently, the presence of the Q192R (rs662) polymorphism in the *PON1* gene was announced to be an independent risk factor for CAD in patients with T2DM in various populations (*10-12*). However, studies on the relationship between the *PON1* rs662 polymorphism and CAD in T2DM patients have been inconsistent. A recent study performed in Egypt reported that the Arg allele of the *PON1* Q192R gene polymorphism is an independent risk factor for CAD in T2DM (*6*). A study from China reported that the R allele of the Q192R polymorphism is associated with coronary heart disease in Chinese Han T2DM patients (*11*). It was revealed that the most frequent genotype and allele of the 192 Gln/Arg polymorphism in the *PON1* gene in the Chinese Han population were QR and allele R, respectively. Conversely, genotype QQ and allele Q were the most frequent in the Caucasian populations (*12*). However, they also failed to show evidence of a positive association under the allele, homozygote, recessive, heterozygote, and dominant models (*7,12*). The present study was designed to explore the potential relationship between the *PON1* gene polymorphism and the risk of CAD in T2DM. Therefore, a meta-analysis was performed to conclude a more comprehensive estimation of the relationship between the *PON1* Q192R polymorphism and CAD susceptibility in T2DM.

2. Materials and Methods

2.1. *Search strategies*

The meta-analysis conducted adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (*13*). Four online electronic databases were used to identify relevant studies to include in the present meta-analysis (EMBASE, Web of Science, PubMed, and CBM) for studies published up to October 2, 2018. The following terms were used: (type 2 diabetics or type 2 diabetes mellitus or noninsulin-dependent diabetes mellitus or NIDDM or T2DM) and (coronary artery disease or coronary heart disease or CAD or CHD), (paraoxonase 1 or paraoxonase or PONA or 192 Gln/Arg or Gln^{192}-Arg or PON1 or Q192R or rs662), (polymorphism or SNP or single nucleotide polymorphism or alleles or mutation or variation or genotype). Publications listed in the references cited were also reviewed carefully to identify any potentially relevant studies. There was no limitation placed on languages in the searching process. Divergence regarding the inclusion of a unique paper was also resolved by consensus.

2.2. *Inclusion and exclusion criteria*

All studies included were required to meet the following criteria: (1) studies focused on the role of the *PON1* Q192R polymorphism and the risk of CAD in T2DM; (2) studies with a case-control design; (3) control groups matched with type 2 diabetes patients without CAD; and (4) studies providing detailed genotype frequencies and the total number of cases and controls, especially the number of Q/Q, Q/R, and R/R genotypes in cases and controls groups. The exclusion criteria were: (1) the article was unrelated to the *PON1* rs662 polymorphism; (2) case reports, review article, comments, editorials, or meta-analysis; (3) basic experimental studies or animal studies; and (4) studies without available genotyping data.

2.3. *Data extraction*

Available data were collected and extracted from the included studies by 2 investigators independently, according to a preset data extraction table. Any divergences were resolved by consensus through discussion between all authors. The following detailed information was extracted from each study: surname of the first author, country where the study was carried out, population ethnicity of each study, publication year, source of control (hospital-based or population-based), and the genotype frequencies of the *PON1* rs662 polymorphism. Moreover, if the included paper failed to provide detailed information regarding the Hardy-Weinberg equilibrium (HWE), we further calculated the HWE and provided the related information.

2.4. *Quality assessment*

The quality of all eligible studies was assessed by 2 investigators independently according to a 9-star rating system, the Newcastle-Ottawa Scale (NOS) (*14*), which involve 3 broad aspects as follows: case and control group selection, exposure, and comparability of the groups. High, moderate, and low-quality studies were classified as a study with $\geq$ 7, 4-6, and $<$ 4 scores, respectively.

2.5. *Statistical analysis*

The association strength between the *PON1* Q192R (rs662) polymorphism and VAD risk in T2DM was calculated by odds ratios (OR) with a 95% CI. The pooled ORs were calculated for the allele model, dominant model, recessive model, heterozygote model, and homozygote model. The pooled ORs were measured using the *Z*-test. The HWE for a single study was measured using the χ^2 test, with $p < 0.05$ indicating a significant deviation. The ORs were summarized using either the random-effects model or the fixed effects model according to the heterogeneity assumption. The random effect model was used in the presence of substantial heterogeneity with $I^2 > 50\%$; otherwise, a fixed effect model was used (*15*). To further investigate the individual effect of a single study on the pooled results, sensitivity analysis was also conducted to confirm the stability of the results under all genetic models. We also omitted studies in which the genotype frequencies in the control groups deviated from the HWE. The presence of publication bias was assessed with Egger's funnel plot test, with $p < 0.05$ being considered to indicate statistical significance. All statistical analyses were performed with STATA 12.0 software (Stata Statistical software, College Station, TX, USA).

3. Results

3.1. *Characteristics of the included studies*

The initial search of related electronic databases yielded 98 studies according to the above comprehensive search strategy. A detailed flow chart of the study selection process is shown in Figure 1. After removing duplicate studies, 66 articles remained. A total of 45 obviously irrelevant studies were excluded after careful reading of the titles and abstracts. After the assessment of eligibility using full-text was conducted, 11 articles were excluded. After this procedure, we finally identified 10 relevant case-control studies (*6,7,9-12,16-*

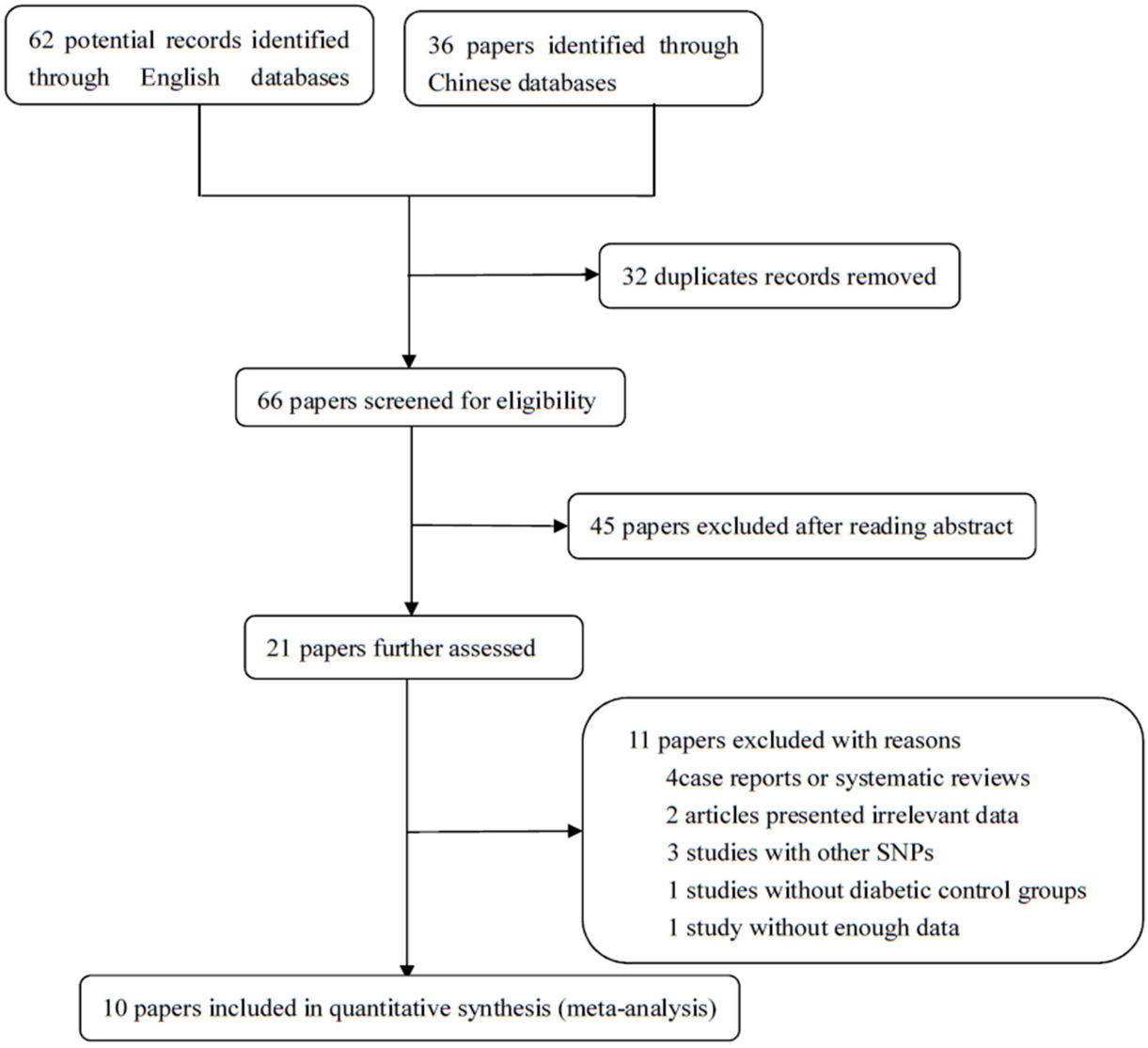

Figure 1. The detailed procedures for the literature search.

19). The control groups of 3 studies were recruited from population-based individuals, and the remaining 7 studies from hospital-based subjects. Four studies were conducted in Caucasian populations, and 6 among Asian populations. In 2 studies, the genotype frequency distribution in the control groups did not deviate from the HWE (*7,16*). The NOS results indicated that the 10 included studies were categorized as 'high quality'. Table 1 shows the detailed characteristics of the included studies.

Table 1. Characteristics of the studies included and genotype frequencies of the Q192R polymorphism in the *PON1* gene and coronary artery disease susceptibility in type 2 diabetes patients

Author	Year	Country	Ethnicity	Genotyping method	Source of control	HWE	NOS	Case			Control		
								QQ	QR	RR	QQ	QR	RR
Bhaskar	2011	India	Asian	PCR	HB	0.043	6	35	97	28	36	87	27
Shao	2014	China	Asian	DHPLC	HB	0.2971	6	19	95	88	31	78	68
Osei-Hyiaman	2001	China	Asian	PCR-SSCP	PB	0.1075	8	136	43	22	181	44	6
James	2000	France	Caucasian	Allele-specific hybridiza-tion	HB	0.1213	7	58	67	12	140	118	15
Ma	2003	China	Asian	PCR-RFLP	HB	0.2242	8	8	42	46	8	42	30
Gupta	2012	India	Asian	PCR and restriction diges-tion	PB	0.6147	7	78	159	63	81	126	43
Qian	2003	China	Asian	PCR	HB	< 0.001	7	9	75	41	20	85	16
Pfohl	1999	Germany	Caucasian	PCR	HB	0.8563	7	73	77	20	66	44	8
Elnoamany	2012	Egypt	Caucasian	PCR	PB	0.2899	7	15	14	19	27	14	4
Odawara	1997	UK	Caucasian	PCR	HB	0.2263	7	1	24	17	25	53	44

PCR, Polymerase Chain Reaction; HWE, Hardy-Weinberg Equilibrium; NOS, Newcastle-Ottawa Scale; RFLP, Restriction Fragment Length Polymorphism; HB, Hospital-Based; PB, Population-Based; PON1, paraoxonase 1; SSCP, Single strand conformational polymorphism; DHPLC, denaturing high performance liquid chromatography.

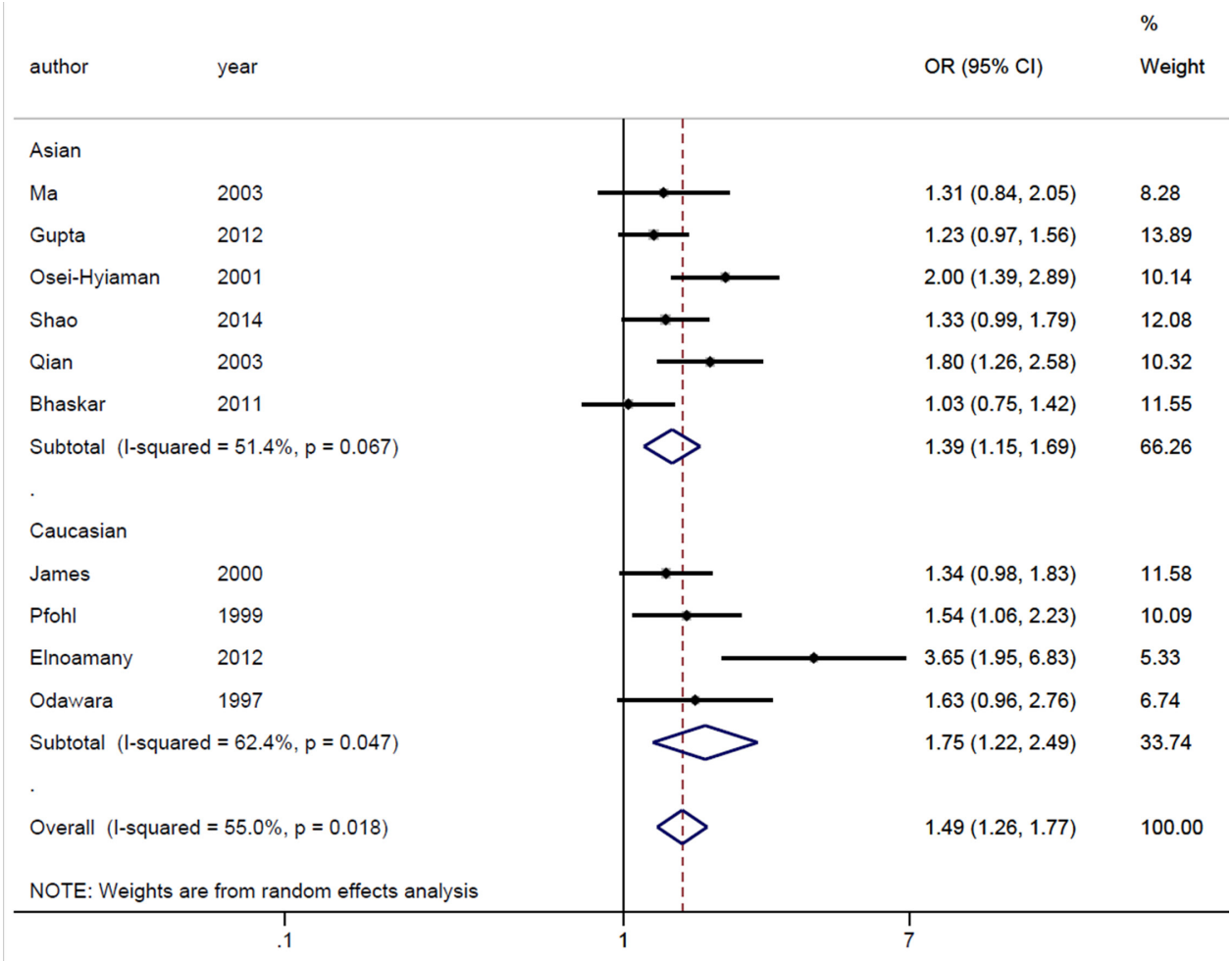

Figure 2. Forest plot for the association between the *PON1* Q192R polymorphism and coronary artery disease susceptibility in type 2 diabetes patients by ethnicity under the allelic model.

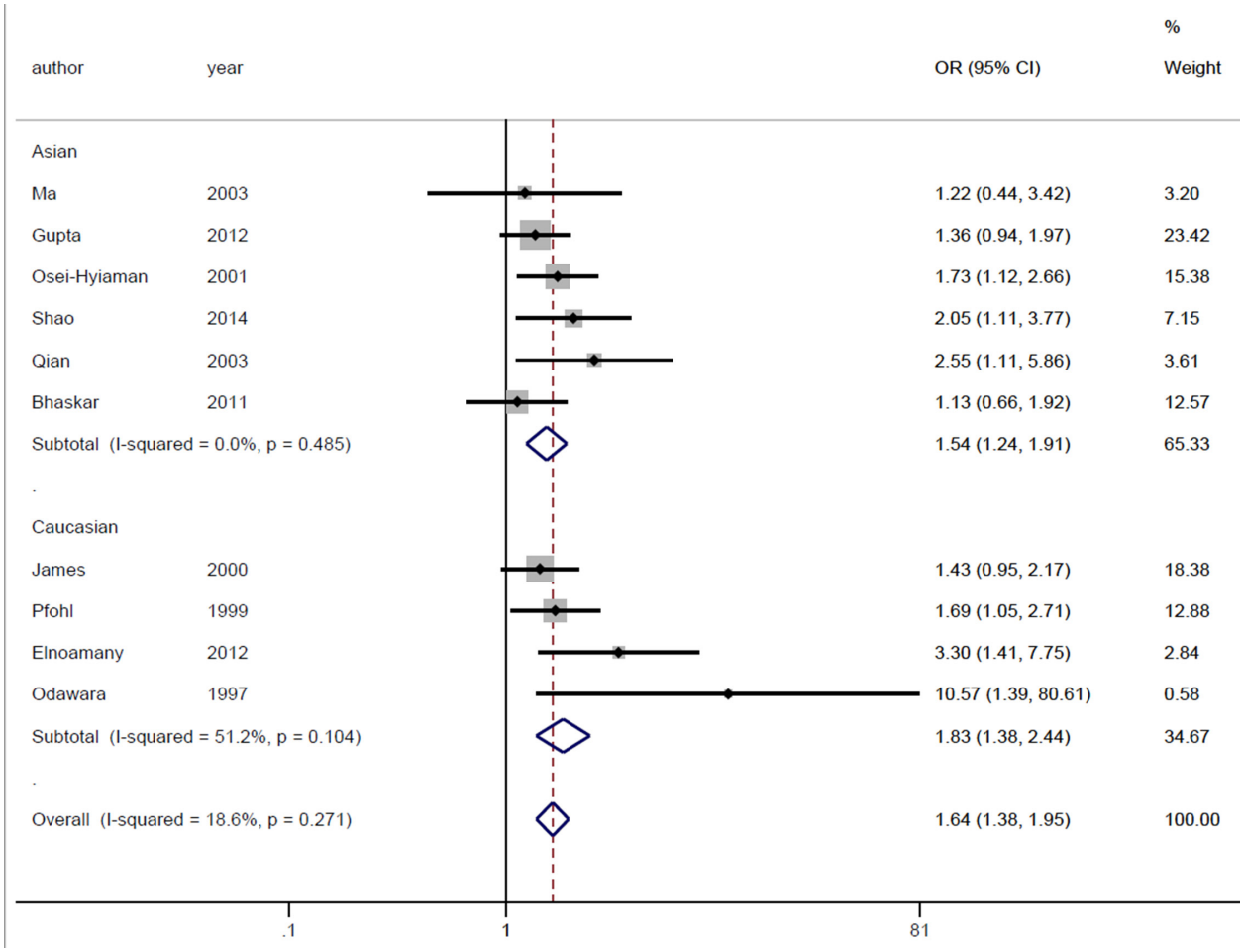

Figure 3. Forest plot for the association between the *PON1* Q192R polymorphism and coronary artery disease susceptibility in type 2 diabetes patients by ethnicity under the dominant model.

3.2. *Main meta-analysis results*

Ten case-control studies were included, reporting a total of 1,481 cases of CAD in T2DM patients and 1,567 T2DM patients without CAD. A significant increase in the susceptibility for CAD in T2DM patients was found in the allele model (R *vs.* Q: OR = 1.49, 95% CI: 1.26-1.77, $p < 0.001$), heterozygote model (QR *vs.* QQ: OR = 1.47, 95% CI: 1.22-1.76, $p < 0.001$), homozygote model (RR *vs.* QQ: OR = 2.47, 95% CI: 1.64-3.71, $p < 0.001$), dominant model (RR + RQ *vs.* QQ: OR = 1.64, 95% CI: 1.38-1.95, $p < 0.001$), and recessive model (RR *vs.* RQ + QQ: OR = 1.74, 95% CI: 1.26-2.39, $p = 0.001$). In the subgroup analysis by ethnicity, a significant increase in the susceptibility CAD in T2DM was found in Asian populations in the allele model (OR = 1.39, 95% CI: 1.15-1.69, $p = 0.001$), homozygote model (OR = 2.15, 95% CI: 1.31-3.51, $p = 0.002$), heterozygote model (OR = 1.37, 95% CI: 1.09-1.73, $p = 0.006$), recessive model (OR = 1.65, 95% CI: 1.11-2.45, $p = 0.012$), and dominant model (OR = 1.54, 95% CI: 1.24-1.91, $p < 0.001$) (Figures 2-6). A similar significant increase in susceptibility was found in Caucasian populations in the allele model (OR = 1.75, 95% CI: 1.22-2.49, $p = 0.002$), homozygote model (OR = 3.39, 95% CI: 1.58-7.27, $p = 0.002$), recessive model (OR = 1.98, 95% CI: 1.07-3.65, $p = 0.030$), heterozygote model (OR = 1.64, 95% CI: 1.21-2.21, $p = 0.001$), and dominant model (OR = 1.83, 95% CI: 1.38-1.95, $p < 0.001$). Subgroup analysis by source of control also yielded positive results in hospital-based population (R *vs.* Q: OR = 1.37, 95% CI: 1.20-1.57, $p < 0.001$; RR *vs.* QQ: OR = 2.16, 95% CI: 1.38-3.36, $p = 0.001$; QR *vs.* QQ: OR = 1.55, 95% CI: 1.23-1.96, $p < 0.001$; RR + RQ *vs.* QQ: OR = 1.65, 95% CI: 1.31-2.06, $p < 0.001$; RR *vs.* RQ + QQ: OR = 1.49, 95% CI: 1.12-2.00, $p = 0.007$) and population-based individuals (R *vs.* Q: OR = 1.96, 95% CI: 1.12-3.42, $p = 0.018$; RR *vs.* QQ: OR = 3.59, 95% CI: 1.21-10.61, $p = 0.021$; QR *vs.* QQ: OR = 1.34, 95% CI: 1.01-1.79, $p = 0.044$; RR + RQ *vs.* QQ: OR = 1.63, 95% CI: 1.25-2.13, $p < 0.001$; RR *vs.* RQ + QQ: OR = 3.11, 95% CI: 1.01-9.57, $p = 0.048$) (Table 2).

3.3. *Sensitivity analysis*

Sensitivity analysis was conducted to investigate the potential influence of a single individual study on the combined OR by eliminating studies one by one in all models. The sensitivity analysis results revealed that no individual study significantly affected the combined

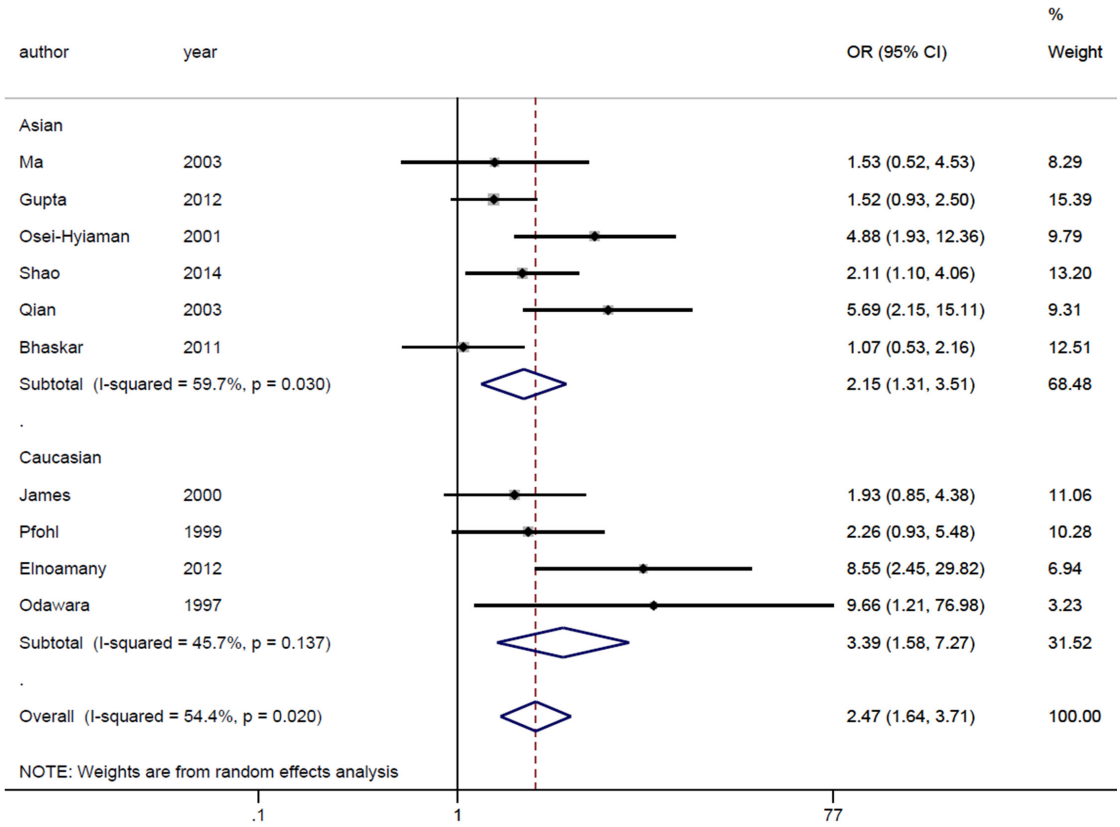

Figure 4. Forest plot for the association between the *PON1* Q192R polymorphism and coronary artery disease susceptibility in type 2 diabetes patients by ethnicity under the recessive model.

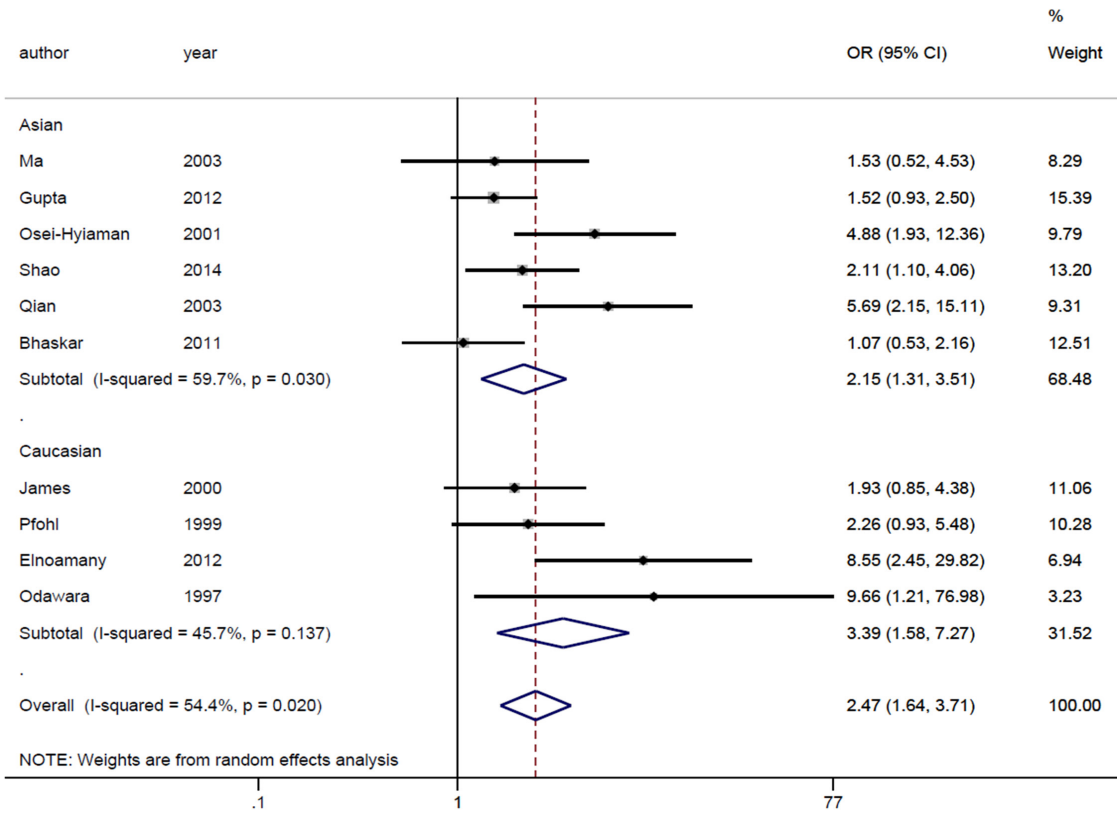

Figure 5. Forest plot for the association between the *PON1* Q192R polymorphism and coronary artery disease susceptibility in type 2 diabetes patients by ethnicity under the homozygous model.

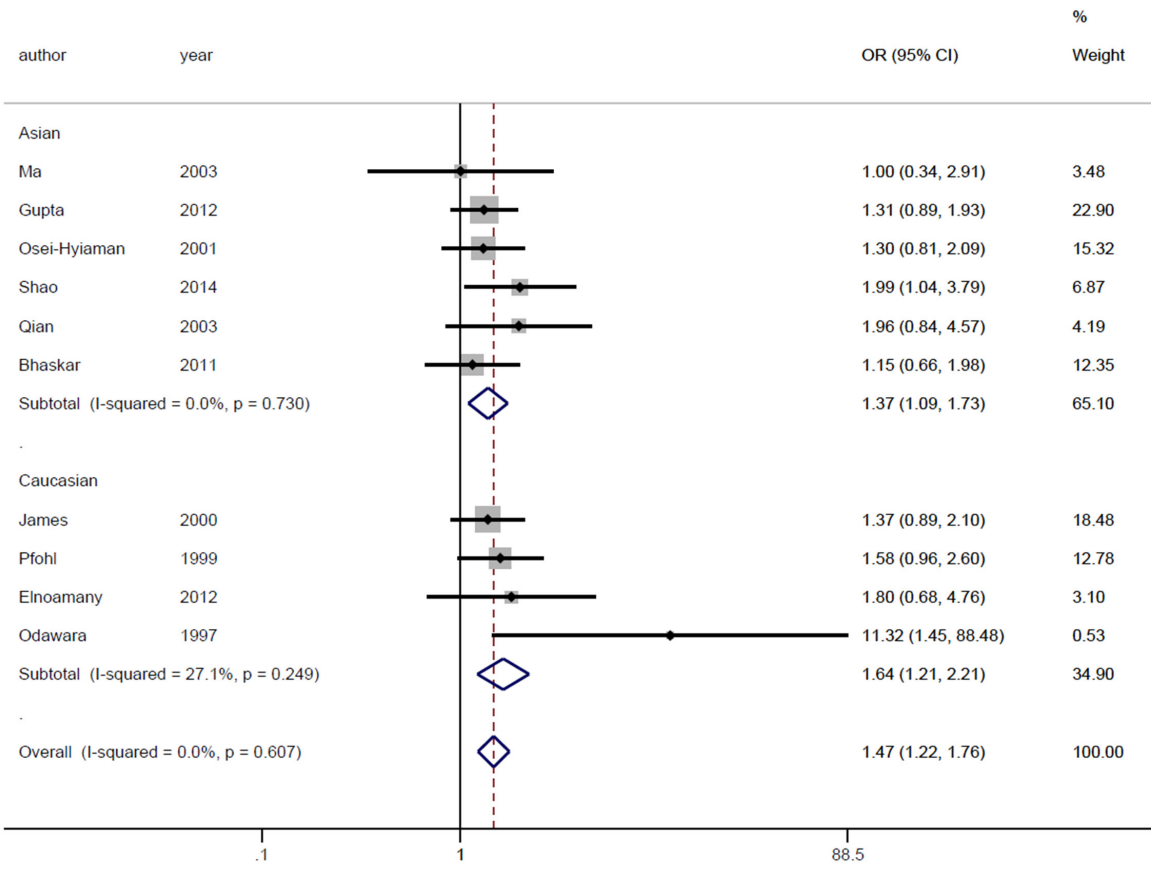

Figure 6. Forest plot for the association between *PON1* the Q192R polymorphism and coronary artery disease susceptibility in type 2 diabetes patients by ethnicity under the heterozygote model.

Table 2. Meta-analysis of the association between the *PON1* Q192R polymorphism and susceptibility of coronary artery disease in type 2 diabetes patients

Subgroup analysis	Study number	OR	95% CI	$P_{(Z-t)}$	I^2 (%)	$P_{(Q-t)}$	Model
R *vs*. Q	10	1.49	1.26-1.77	< 0.001	55	0.018	Random
Asian	6	1.39	1.15-1.69	0.001	51.4	0.067	Random
Caucasian	4	1.75	1.22-2.49	0.002	62.4	0.047	Random
HB	7	1.37	1.20-1.57	< 0.001	3.3	0.4	Fixed
PB	3	1.96	1.12-3.42	0.018	84.2	0.002	Random
RR *vs*. QQ	10	2.47	1.64-3.71	< 0.001	54.4	0.002	Random
Asian	6	2.15	1.31-3.51	0.002	59.7	0.003	Random
Caucasian	4	3.39	1.58-7.27	0.002	45.7	0.137	Fixed
HB	7	2.16	1.38-3.36	0.001	40.4	0.122	Fixed
PB	3	3.59	1.21-10.61	0.021	78.9	0.009	Random
QR *vs*. QQ	10	1.47	1.22-1.76	< 0.001	0	0.607	Fixed
Asian	6	1.37	1.09-1.73	0.006	0	0.73	Fixed
Caucasian	4	1.64	1.21-2.21	0.001	27.1	0.249	Fixed
HB	7	1.55	1.23-1.96	< 0.001	9	0.36	Fixed
PB	3	1.34	1.01-1.79	0.044	0	0.827	Fixed
RR+RQ *vs*. QQ	10	1.64	1.38-1.95	< 0.001	18.6	0.271	Fixed
Asian	6	1.54	1.24-1.91	< 0.001	0	0.485	Fixed
Caucasian	4	1.83	1.38-1.95	< 0.001	51.2	0.104	Random
HB	7	1.65	1.31-2.06	< 0.001	19.9	0.278	Fixed
PB	3	1.63	1.25-2.13	< 0.001	44.3	0.166	Fixed
RR *vs*. RQ+QQ	10	1.74	1.26-2.39	0.001	57.8	0.011	Random
Asian	6	1.65	1.11-2.45	0.012	65.7	0.012	Random
Caucasian	4	1.98	1.07-3.65	0.03	50.6	0.108	Random
HB	7	1.49	1.12-2.00	0.007	32.7	0.178	Fixed
PB	3	3.11	1.01-9.57	0.048	82.2	0.004	Random

OR, odds ratios; CI, confidence intervals; $P_{(Z-t)}$ value for association test; $P_{(Q-t)}$ value for heterogeneity test; HB, Hospital-Based; PB, Population-based.

ORs under any genetic *PON1* rs662 polymorphism model (data not shown), which indicated the robustness and reliability of the results. Sensitivity analyses were further performed by sequentially leaving out the studies that were not consistent with the balance of HWE. The recalculated results remained statistically significant for the *PON1* rs662 polymorphism and CAD risk in T2DM under any of the genetic models (data not shown).

3.4. *Publication bias*

Substantial asymmetry was observed in 4 genetic models by visual inspection of the Begg's funnel plots. In quantitative analysis, no evidence of publication bias was observed in the heterozygote model ($p = 0.051$); however, substantial asymmetry was noted in the other models ($p = 0.032$ for the dominant model, $p = 0.026$ for the allelic model, $p = 0.023$ for the recessive model, and $p = 0.024$ for the homozygous model) (figures not shown).

4. Discussion

Peroxidation of LDL plays a key role in the process of atherogenesis (*20*). Enzymes associated with HDL particles, including PON1, can cleave oxidized lipids from LDL. HDL diminishes the accumulation of lipid peroxides in LDL generally owing to PONA activity (*21*). It was reported that PON1 activity is reduced in patients with CAD and in patients with T2DM (*19,22-24*). The reason for the decreased PON1 activity in these studies could be owed to the increased glycation of HDL cholesterol particles. The predisposition to CAD is determined by a combination of environmental and genetic factors. A single study lacks enough statistical power to confirm the relationship between *PON1* rs662 and the risk of CAD in T2DM owing to the limited sample size. In order to clarify the relationship between these two entities, a comprehensive meta-analysis with a large sample size was performed to identify the associations. To our knowledge, this is the first meta-analysis to reveal that the *PON1* Q192R polymorphism is associated with a significantly increased risk of CAD in T2DM in both Asian and Caucasian populations.

For T2DM patients, the functional role of PONA is more profoundly essential than in non-diabetes individuals. Chronic persistent hyperglycemia results in considerable modification in the protein structure and function, primarily caused by the non-enzymatic glycation of amino acid residues (*5*). Furthermore, LDL cholesterol along with glycated apolipoprotein-B100 interacts with the vascular endothelium and platelets, resulting in elevated production of thromboxanes hence reducing thrombolytic prostaglandins (*25,26*). On the other hand, glycated LDL cholesterol is more readily oxidized, leading to enhanced macrophage uptake by the scavenger receptor pathway (*27*).

It has been revealed that diabetes mellitus patients are at a rising risk for oxidative stress (*28*). The reason may partly be due to features of the diabetic state, markedly hyperglycemia and increased level of glycosylation end products. In accordance with diabetes mellitus, smoking is a well-established risk factor for CAD in which oxidative mechanisms play a significant role. An elevated number of free radicals and their by-products is observed in smokers from lipid peroxidation of oxidized LDL particles compared with non-smokers (*29*).

However, some limitations should be considered when interpreting the results. First, some confounding factors addressed across the various studies, such as age, gender, smoking, family history, and eating habits may have influenced the reliability of the results. Second, 2 studies were not in agreement with HWE; the pooled ORs were not materially altered in the sensitivity analysis. Furthermore, even though we performed a comprehensive literature search, publication bias still remains a problem. Last, owing to the limited studies in certain subgroups, some conclusions should be interpreted with caution in the subgroup analysis. Further prospective studies in a larger population of various races are still required to confirm these findings.

5. Conclusion

In summary, the present meta-analysis results provide strong evidence that the *PON1* Q192R polymorphism is associated with a significantly increased risk of CAD in T2DM patients in both Asian and Caucasian populations.

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